Clinical Practice Guideline for Care in Pregnancy and Puerperium

NOTE:

It has been 5 years since the publication of this Clinical Practice Guideline and it is subject to updating.

The recommendations included should be considered with caution taking into account that it is pending evaluate its validity.

CLINICAL PRACTICE GUIDELINES IN THE SPANISH NHS
MINISTRY OF HEALTH, SOCIAL SERVICES AND EQUALITY

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

RED ESPAÑOLA DE AGENCIAS DE EVALUACIÓN DE TECNOLOGÍAS Y PRESTACIONES DEL SISTEMA NACIONAL DE SALUD

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JUNTA DE ANDALUCIA CONSEJERÍA DE IGUALDAD, SALUD Y POLÍTICAS SOCIALES

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This CPG is an aid to decision making in healthcare. The compliance of this guide is not mandatory, nor does it replace the clinical judgement of the healthcare personnel.

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Presentation

Documenting the variability in clinical practice, analyse its causes and adopt strategies aimed at eliminating it, have proven to be initiatives that promote safe and effective decision-making by health professionals, being patient-centred and shared by them. Such strategies include preparing Clinical Practice Guidelines (CPG), "a set of recommendations based on a systematic review of the evidence and the assessment of the risks and benefits of different alternatives in order to optimize health care patients."

The priorities of the Ministry of Health, Social Services and Equality, include continuing to promote the development and use of reports from health technology assess ment and CPGs, consolidating the Network of Agencies for Health Technology Assessment and Performance of National Health and the GuíaSalud Project.

Pregnancy or gestation is defined as a period during which the embryo develops and grows inside the mother's body and whose duration ranges from egg fertilisation until birth.

This CPG aims to answer clinical questions concerning this process and has the mission to offer the various professionals involved in both primary care and hospital care, guidelines for quality care to women during pregnancy and after childbirth, besides dealing with different aspects of the newborn.

This guide is the result of work carried out by a large group of professionals from different Autonomous Communities, who represent all the disciplines involved in the care of the reproductive process. Women belonging to associations involved in promoting adequate care before, during and after childbirth have also participated in its elaboration. Prestigious professionals belonging to the corresponding scientific societies have performed the external review process.

In the Directorate General of Public Health, Quality and Innovation, we are very satisfied with the work done and hope this guide allows making secure and efficient decisions, improve the quality of health care. We place women and children as main protagonists of such a unique event as well as important which is giving life and delivering it.

M. MERCEDES VINUESA SEBASTIÁN

Director General of Public Health, Quality and Innovation

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Spanish Society for Family and Community Medicine (SEMFyC)

Spanish Society of Gynaecology and Obstetrics (SEGO)

Spanish Society of Neonatology (SEN)

Federation of Spanish Midwives Associations (FAME)

"Vía Láctea"Association

"El Parto es Nuestro" Association

Members of these societies have taken part in the auditory, expert collaboration and external review of this CPG.

Declaration of interest: All members of the Working Group, as well as those who have participated in the expert collaboration and external review, have made the declaration of interest as appears in Appendix 1.

Key Questions

PRECONCEPTION VISIT

1. What is the aim and what should be the content of a preconception visit?

CARE DURING PREGNANCY

Visits and monitoring during pregnancy

Organisation of prenatal care

2. What professionals should provide prenatal care?

Visits and monitoring during pregnancy

3. Does the number of monitoring visits during pregnancy influence the health outcomes of the mother and / or the newborn?
4. What should be the content of the medical record?
5. What is the purpose of the routine examination of the body mass index (BMI) and weight watching, measurement of blood pressure, breast and gynaecological exploration in early pregnancy? What is the purpose of universal screening for hypertensive disorders [measurement of blood pressure (BP) and test strips] and in on what stage of pregnancy should it be done? What is the purpose of universal screening for cervical cancer and on what stage of pregnancy should it be done?
6. What is the purpose of determining the plasma urea level in a biochemical test?
7. What is the purpose of determining the plasma creatinine level in a biochemical test?
8. What is the purpose of determining the plasma uric acid level in a biochemical test?
9. What is the purpose of universal screening for syphilis in pregnant women and at what stage of pregnancy should it be done?
10. What is the purpose of universal screening for Chagas disease in pregnant women and at what stage of pregnancy should it be done?
11. What is the purpose of universal screening for chlamydia in pregnant women and at what stage of pregnancy should it be done?
12. What is the purpose of universal screening for bacterial vaginosis in asymptomatic pregnant women and at what stage of pregnancy should it be done?
13. What is the purpose of universal screening for rubella in pregnant women and at what stage of pregnancy should it be done?
14. What is the purpose of universal screening for toxoplasma infection in pregnant women and at what stage of pregnancy should it be done?
15. What is the purpose of universal screening for varicella in pregnant women and at what stage of pregnancy should it be done?
16. What is the purpose of universal screening for cytomegalovirus in pregnant women and at what stage of pregnancy should it be done?
17. What is the purpose of universal screening for hepatitis Bvirus in pregnant women and at what stage of pregnancy should it be done?

18. What is the purpose of universal screening for hepatitis C in pregnant women and at what stage of pregnancy should it be done?
19. What is the purpose of universal screening for group B streptococcus in pregnant women and at what stage of pregnancy should it be done?
20. What is the purpose of universal screening for human immunodeficiency virus (HIV) in pregnant women and at what stage of pregnancy should it be done?
21. What is the purpose of universal screening for symptomatic bacteraemia in pregnant women and at what stage of pregnancy should it be done?
22. What is the purpose of universal screening for anaemia and at what stage of pregnancy should it be done?
23. What is the purpose of determining the level of ferritin in a biochemical test?
24. What is the purpose of universal screening for Rh incompatibility and at what stage of pregnancy should it be done?
25. Which is the most effective and appropriate guideline for the anti-D prophylaxis in the prevention against Rh sensitisation?
26. What is the purpose of universal screening for thyroid disease and at what stage of pregnancy should it be done?
27. What is the most suitable screening method for gestational diabetes testing? At what stage of pregnancy should gestational diabetes screening be done? What are the appropriate criteria to consider a pregnant woman gestational diabetic?
28. What is the purpose of universal screening for risk of preterm delivery and at what stage of pregnancy should it be done?
29. Is it beneficial to make a birth plan during pregnancy?

Ultrasound scanning and prenatal diagnosis

30. In what week of pregnancy should the ultrasound scans be carried out? Is any complication during the performance of ultrasound scans referred?
31. What information from the ultrasound scans should be provided? How and when should this information be provided?
32. What is the performance of the combined test for chromosomal screening versus performing invasive tests?

Control of foetal growth and wellbeing

33. Is the symphysis-fundal height (SFH) measurement useful to predict foetal growth control?
34. What is the benefit of the Doppler study of uterine artery and umbilical artery in low risk pregnancies?
35. Are routine cardiotocography checks needed for the prenatal assessment of foetal wellbeing? If so, in what week of pregnancy?

Vaccines during pregnancy

36. What vaccines are indicated and which are contraindicated during pregnancy?

Lifestyles during pregnancy

Eating Habits

37. Are specific indications on eating habits and diet during pregnancy necessary?
38. What are the recommendations for dietary intake during pregnancy?
39. With a varied diet, are micronutrient needs as iron, vitamins or iodine covered?

Pharmacological supplementation of nutrients

40. What is the effect of iron prophylaxis in women during pregnancy?
41. Is a pharmacological iodine supplementation necessary during pregnancy?
42. Is a pharmacological folic acid supplementation necessary during pregnancy?
43. Is a pharmacological vitamin complex supplementation necessary during pregnancy?
44. How safe are food supplements (omega3 fatty acids) during pregnancy?

Medication during pregnancy

45. What widely used drugs are safe during pregnancy?

Alcohol and smoking during pregnancy

46. What are the consequences of drinking alcohol during pregnancy?
47. Are there programs to reduce alcohol consumption targeting pregnant women?
48. What are the consequences of active and passive smoking during pregnancy?
49. Are there specific smoking cessation programs targeting pregnant women?

Exercise during pregnancy

50. Is it necessary to perform physical exercise or sport in certain circumstances during pregnancy?

Psychological changes of pregnancy. Psychosocial stress and affective disorders

51. What are the tools with better performance in the detection of mental disorders during pregnancy?

Sexuality

52. Is sexual activity related to the occurrence of problems during pregnancy? Is sexual activity related to the appearance of labour contractions?

Travelling

53. What recommendations are required during pregnancy for women who want to travel?

Managing common problems during pregnancy

54. What is the effect of interventions for the treatment of nausea and vomiting during pregnancy?
55. What is the effect of interventions to prevent or treat heartburn during pregnancy?
56. What is the effect of interventions for the prevention or relief of constipation during pregnancy?
57. What is the effect of interventions for the prevention or relief of haemorrhoids during pregnancy?

58. What is the effect of interventions for the prevention or treatment of low back pain during pregnancy?

59. What is the effect of interventions for the prevention or treatment of low back pain during pregnancy?

Managing breech pregnancy from week 35

60. What interventions have shown a benefit to attempt a successful external cephalic version?

61. What are the ideal conditions to perform a cephalic external version?

62. What is the ideal time to attempt a cephalic external version?

Preparation for birth

63. How effective is conducting education programs for preparing birth?

Managing pregnancy from week 41

64. What is the most appropriate obstetric management of pregnancy from week 41?

CARE DURING PUERPERIUM

Hospital care during puerperium

65. What checks and care are most suitable for the newborn during hospitalisation?

66. What checks and care are most suitable for the mother during hospitalisation?

67. Which specialist is most suitable for the control of hospital care during puerperium?

68. What are the benefits of non-separation and mother-infant rooming-in during the hospital puerperium period for maternal and neonatal health? What are the benefits of bedding-in in mother's bed during the hospital puerperium period for maternal and neonatal health?

Discharge and advice on care during the puerperium

69. What are the benefits and safety of early discharge?

70. What is the appropriate information and recommended care provided at the time of hospital discharge? What are the warning signs related to the mother and the newborn, which must be provided at discharge?

Monitoring visits during the puerperium in primary care

71. What are the appropriate checks during the puerperium in primary care, and at what time and place should these be made? Who is the ideal professional to assist during the puerperium in primary care?

Managing common problems in the puerperium

72. What is the benefit of the treatments for perineal pain?

73. What is the benefit of the treatments for post-dural puncture headache?

74. What is the benefit of the treatments for low back pain post-dural puncture?

75. What is the benefit of the treatments for constipation?

76. What is the benefit of the rehabilitation of the pelvic floor muscles during the puerperium?

Contraception during the puerperium

77. At what point can a contraceptive treatment after delivery be started?
78. What special considerations should be made after delivery by type of birth control?

Mental health during the puerperium

79. What are the tools with better performance in the detection of mental disorders during the puerperium?
80. Does the contact of the mother with other mother networks and support groups reduce the risk of mental problems and postpartum depression?

Breastfeeding

81. What practices favour the establishment of breastfeeding during the puerperium?
82. What practices help to maintain breastfeeding during the puerperium?
83. What is the most appropriate treatment for the cracks in the nipple, breast engorgement and mastitis?

Levels of evidence and grades of recommendation

<table>
<tr><th colspan="4">Rating the quality of evidence in the GRADE system</th></tr>
<tr><th>Quality of scientific evidence</th><th>Design study</th><th>Reduce quality if</th><th>Increase quality if</th></tr>
<tr><td>High</td><td>RCT</td><td rowspan="4">In design: Important (-1)
Very important (-2)
Inconsistency (-1)

Direct evidence:
Some uncertainty (-1)
A lot of uncertainty about evidence being direct (-2)

Inaccurate data (-1)

Biased reporting:
High probability of (-1)</td><td rowspan="4">Association:
• Scientific evidence of a strong association (RR> 2 to<0.5 based on unconfounded observational studies) (+1).
• Scientific evidence of a very strong association (RR> 5 or <0.2 based on unbiased studies) (+2)

Dose-response gradient (+1)

All potential confounding factorsmay have reduced the observed effect (+1)</td></tr>
<tr><td>Moderate</td><td></td></tr>
<tr><td>Low</td><td>Observational studies</td></tr>
<tr><td>Very Low</td><td>meta Other types design</td></tr>
</table>

<table>
<tr><th colspan="3">Implications of the strength of recommendation in the GRADE system</th></tr>
<tr><th colspan="3">Implications of a strong recommendation</th></tr>
<tr><th>Women</th><th>Clinical</th><th>Managers / Planners</th></tr>
<tr><td>The vast majority of people would agree with the recommended action and only a small proportion would not.</td><td>Most women should receive there commended intervention.</td><td>The recommendation can be adopted as health policy in most situations.</td></tr>
<tr><th colspan="3">Implications of a weak recommendation:</th></tr>
<tr><th>Women</th><th>Clinical</th><th>Managers / Planners</th></tr>
<tr><td>Most people would agree with the recommended action but a significant number of them do not.</td><td>Recognizes that different options would be appropriate for different women and the physician has to help each patient to reach the decision consistent with their values and preferences.</td><td>There is an important need for debate and participation of interest groups.</td></tr>
</table>

Recommendations

Preconception visit

Chronic Diseases	
√	Women planning a pregnancy and who suffer some chronic disease should be informed on the possible impact on the course of their disease and prenatal outcomes. A detailed anamnesis should be carried out to identify all potential risks and plan the pregnancy properly. In some cases of women with diabetes, epilepsy, hypothyroidism or other chronic diseases, it may be necessary at early pregnancy to re-evaluate the usual treatment by the attending physician.
√	Women planning pregnancy, who are overweight or obese (IMC≥25 kg / m^2) and with more than one additional risk factor for diabetes (including a history of gestational diabetes) should to undergo screening to detect pre-diabetes and diabetes type 2.
√	In women planning pregnancy and who are diabetic, glycaemic control should be optimized to achieve, before pregnancy, the best control possible.
√	Women planning pregnancy and suffering from high blood pressure (HBP) should have their chronic antihypertensive medication reviewed to check if it should be modified.
√	Women planning pregnancy and suffering from epilepsy should have their medication reviewed to check if it should be modified or suspended before pregnancy and start supplementation with folic acid (5 mg / day) at least one month before conception and keep up to 12 weeks after gestation.
Reproductive history	
√	Reproductive history should be evaluated in all women planning pregnancy
√	History of preterm labour and control the possible causes of recurrence before the next pregnancy should be evaluated in women planning pregnancy
√	Women planning pregnancy and with a history of repeated abortions (over three reproductive losses according to the British College of Obstetrics and Gynaecology) should undergo a study to identify possible causes and assess their treatment.
√	Women planning pregnancy and with a history of stillbirth should complete a study of the possible causes and change the possible associated risk factors.
√	Women planning pregnancy and with a history of caesarean section should be adviced about waiting at least 18 months until the next delivery.
Infectious Diseases	
√	Women planning pregnancy and who are not immunised against hepatitis B should be vaccinated before pregnancy.
√	Women planning pregnancy and who are at high risk of hepatitis C virus (HCV) infection should undergo screening for hepatitis C to provide information about the possible risks of vertical transmission.

√	Women planning pregnancy and who are not immunised against rubella should be vaccinated before pregnancy with the measles-mumps-rubella (MMR) vaccine and take precautions to avoid pregnancy during the 28 days following vaccination.
√	Women planning pregnancy should be adviced about the appropriate measures to prevent infection with Toxoplasma gondii during pregnancy.
Nutrition	
√	Women planning pregnancy should be adviced about a nutrient-rich balanced diet.
√	Women planning pregnancy should be adviced about taking iodized salt.
√	Women planning pregnancy and having a body mass index ≥25 kg / m 2 or ≤18 kg/m 2 should be provided information and dietary advice as well recommendations on physical activity.
Drug abuse	
√	Women planning pregnancy should undergo a detailed anamnesis on the consumption of tobacco , alcohol, drugs and other psychoactive substances.
√	Women planning pregnancy and who smoke or consume alcohol, should be adviced about giving up these habits and be provided with cessation measures.
√	Women planning pregnancy and who are drug users, should be adviced about quitting this habit and be provided with dishabituation measures.
Educational and health promotion measures	
√	Women planning pregnancy should be adviced about doing exercise on a regular basis.
Pharmacological supplements	
√	Women planning pregnancy should take a daily supplementation with 0.4 mg of folic acid for at least one or two months prior to conception. In women with a history of neural tube defects, who have had a child with a neural tube defect previously, are diabetic or are taking anticonvulsants, should take a daily supplementation with 5 mg of folic acid.
√	Women planning pregnancy should not be systematically administered a daily iodine supplementation.
√	Women planning pregnancy should not be systematically administered a daily multivitamin supplementation in order to avoid neural tube defects.

Care during pregnancy

Organisation of prenatal care

Strong	It is recommended that prenatal care in pregnancies without complications are provided by midwives and family physician , with the participation of other health professionals in primary care teams and the support of the corresponding obstetric unit.
√	Scheduled prenatal visits in pregnancies without complications should be coordinated by midwives.

Visits and monitoring during pregnancy

Number of visits	
Weak	We suggest a monitoring program of between 6 and 9 visits for women at low risk of complications during pregnancy or childbirth.
Content of medical history	
Strong	We recommend that at the first prenatal visit an anamnesis be made by recording the information in a structured medical history in order to assess the overall status of women and to identify possible risk factors.
√	The medical history should be updated during every follow-up pregnancy visit.
√	All information should be registered and shared in a computerised medical record to facilitate the integration of all levels of health care (primary and hospital).
Usefulness of routine screening of Body Mass Index (BMI), weight monitoring, measurement of blood pressure and breast and pelvic examination during pregnancy. Usefulness of universal screening for hypertensive disorders and cervical cancer.	
Strong	It is recommended to calculate the BMI at the first prenatal visit, to identify those women who require weight gain monitoring during pregnancy.
Strong	Blood pressure should be measured at each prenatal visit to detect the risk of preeclampsia.
Weak	We suggest not carrying out a mammary exploration as a screening of breast cancer, or to promote breastfeeding or identify potential difficulties in breastfeeding.
Weak	We suggest not developing a gynaecological exploration during prenatal visits in order to predict the likelihood of a preterm delivery or detect any gynaecological pathology.
Weak	We suggest not developing a pelvimetry in order to assess the need for caesarean section in women with a baby with cephalic presentation at term.
Weak	We suggest not performing vaginal examinations or Hamilton's manoeuvre as a routine procedure in women with an uncomplicated pregnancy before term and who have no indication of completion of pregnancy.
Weak	We suggest not performing a cervical smear at the first prenatal visit to assess the risk of cervical cancer.
√	The smear should be delayed up to 6 or 8 weeks after childbirth in women with a history of negative smears and who should undergo a new screening test, except in cases where there is doubt about the monitoring of screening by woman or when more than 5 years have passed since the last smear.
Weak	We suggest the determination of proteinuria at each prenatal visit to detect the risk of preeclampsia.
√	Individualised assessment of weight during pregnancy should be performed avoiding routine weights in all prenatal visits.

Biochemical useful parameters during pregnancy	
Weak	We suggest not determining the level of blood urea routinely in pregnant women.

Weak	We suggest not determining the level of creatinine in blood on the initial biochemical assay to control the risk of hypertension during pregnancy in women with no risk of complications during pregnancy.
√	The level of serum uric acid should be determined in the blood test carried out in the second trimester as a warning sign of preeclampsia in normotensive women.
Screening for infections during pregnancy	
Weak	We suggest a routine syphilis screening to all pregnant women at the first prenatal visit.
√	Since syphilis-screening tests may produce false positive results, appropriate diagnostic protocols should be used.
Strong	We recommend thatscreening for Chagas disease be offered at the first prenatal visit for all those women originating or having spent time in an endemic area.
Weak	We suggest not performing a systematic chlamydia screening to all pregnant women.
Weak	We recommend offering a chlamydia screening for asymptomatic pregnant women who are at risk of sexually transmitted infections.
Weak	We suggest not performing routine screening for bacterial vaginosis to all pregnant women.
Strong	We recommend that a screening of rubella is offered to pregnant women at the first prenatal visit to assess immunity to rubella and provide vaccination as soon as possible in the postpartum of unimmunised women.
Weak	We suggest not offering screening for toxoplasma infection to all pregnant women.
√	Women should be informed about dietary and hygienic measures aimed at reducing the risk of toxoplasma infection.
√	During pregnancy, in the anamnesis, a varicella screening should be carried out by reviewing the personal medical history of varicella of women, in order to avoid contact with anyone who has chickenpox in the case of not being immunised, and to consult with a health professional in case of contact.
√	Pregnant women who are seronegative to the varicella zoster virus should be warned to avoid contact with anyone who has chickenpox, and to consult with a health professional in case of contact.
Strong	Screening for cytomegalovirus should not be carried out during pregnancy.
Weak	We suggest that women are informed of hygienic measures aimed at avoiding exposure to saliva and urine, which may contain cytomegalovirus.
Strong	Hepatitis B screening should be provided to all pregnant women at their first visit.
√	In those cases where the pregnant woman presents antigen HBsAg (+),she should be referred to the corresponding healthcare service in order to study whether she is an asymptomatic carrier or has a chronic liver disease, and thus establish a treatment if is appropriate and program a monitoring schedule.
Strong	A universal screening for hepatitis C virus (HCV) should not be carried out in pregnant women.

√	Evaluating the performance of screening for hepatitis C in women considered at risk for HCV infection should be carried out: history of intravenous drug using, receiving blood transfusions, having undergone a transplant before the 90s, Human Immunodeficiency Virus (HIV) positive women, HBV carriers with a history of endoscopic interventions or haemodialysis, or having a partner with HCV infection.
Weak	We suggest a universal screening for group B streptococcal colonization between weeks 35 and 37 of gestation to reduce the risk of neonatal sepsis.
Strong	Universal HIV screening should be provided in the first prenatal visit.
√	We suggest repeating the determination of the last blood test during pregnancy in women at risk of HIV infection.
Strong	We recommend performing a urine culture for all pregnant women at the first prenatal visit to detect the presence of asymptomatic bacteraemia and prevent the risk of upper urinary tract infection and low birth weight.
Screening for anaemia during pregnancy	
Weak	We suggest a universal screening for anaemia in pregnant women during the first prenatal visit.
√	The universal screening for anaemia should be repeated in pregnant women after 28 weeks of gestation.
√	The diagnosis of anaemia in pregnancy should be set when the haemoglobin is below 11 g / dl in the first trimester, less than 10.5 g / dl in the second and less than 11 g / dl in the third trimester.
Strong	We recommend determining the level of serum ferritin to confirm a questionable diagnosis of iron deficiency anaemia.
Screening for Rh isoimmunisation	
Strong	A screening for Rh compatibility, ABO blood group and irregular antibodies should be performed to all pregnant women at the first prenatal visit.
Strong	The determination of anti-Rh antibodies should be determined to Rh negative pregnant women with Rh incompatibility between weeks 24 and 28 of gestation.
Anti-D prophylaxis	
Strong	Routine prenatal prophylaxis with an administration of 300 µg (1,500 IU) of anti-D immunoglobulin should be offered to unsensitised Rh-negative pregnant women to reduce the risk of sensitisation.
Strong	The prenatal prophylaxis should be administered as a single dose between weeks 28 to 30 of gestation to unsensitised Rh-negative women.
Strong	A single dose of anti-D immunoglobulin should be administered within 72 hours of any episode of potential sensitisation (abortion, ectopic pregnancy, partial molar pregnancy, chorial biopsy, amniocentesis, cordocentesis, External Cephalic Version –ECV-.)
Strong	Additional doses of anti-D immunoglobulin should be administered if a feto-maternalhaemorrhage of 10 to 15 mL occurs.
Strong	Prophylaxis with 300 micrograms (1,500 IU) of anti-D immunoglobulin should be administered to Rh-negative unsensitised women whose newborn (NB) is Rh positive during the first 72 hours of postpartum.

Screening for hypothyroidism	
√	A screening of thyroid function should be carried out at the first visit in pregnant women with risk factors for thyroid dysfunction: women over 30, women with a family history of thyroid disease, women with a history of thyroid disease, women with DM type 1 or other autoimmune disorders, women with a history of repeated abortions, irradiation of head or neck, on levothyroxine replacement therapy or who live in areas that are presumably deficient in iodine.
Screening for gestational diabetes	
√	In those cases of pregnant women without risk of complications, the following risk factors for gestational diabetes should be measured during the first visits of pregnancy: BMI ≥ 30 kg / m2, history of macrosomic children with ≥4,5 kg birth weight, history of gestational diabetes, or family history of diabetes in first grade.
√	Screening for gestational diabetes should be carried out in the first trimester in women with a history of gestational diabetes.
√	The screening should be repeated between weeks 24 and 28 of gestation in those women in whom any of the risk factors for gestational diabetes with a negative result in the first trimester screening, or a positive result and a normal glucose curve.
√	The O'Sullivan test should be carried out between weeks 24 to 28 as a screening test, after having informed women about the characteristics of the test.
Screening for risk of preterm delivery	
Weak	We suggest not performing an ultrasound determination of the length of the cervix routinely.
Weak	We suggest not determing routinely ultrasound cervical tunnelling to all pregnant women without previous signs or symptoms of preterm delivery.
Delivery and birth plan	
Weak	We suggest offering to pregnant women the chance to develop a delivery and birth plan from week 28, which allows to know their preferences.
√	The delivery and birth plan should be sent to the hospital and incorporated into the medical record so that those professionals attending childbirth know the desires of women and can plan childbirth together.

Ultrasound examination and prenatal diagnosis

Chronology	
Strong	Two scans should be performed during pregnancy in women with no risk factors.
Strong	A first scan should be carried out at the end of the first trimester (11 -13 + 6) and the second one, around week 20.
Weak	We suggest not carring out a routine ultrasound during the third trimester of pregnancy.
Information	
√	Before each ultrasound examination women should be informed about the characteristics and objectives of the test as well as the limitations of ultrasound, checking that the woman has understood the information provided.

√	Women should be informed about the purpose and implications of the pathological findings of ultrasound to facilitate informed decision-making, as well as the limitations of routine ultrasound examinations.
Screening for chromosome disorders	
Strong	A combined test (maternal age, nuchal translucency measurement, PAPP-A and free β-hCG fraction) should be recommended between weeks 11 and 13 + 6 to determine the risk of Down syndrome.
Strong	A quadruple test between weeks 13+0 and 17+0 should be offered only to those pregnant women who could not be screened during the first trimester.

Control of foetal growth and wellbeing

Measurement of fundal height	
Weak	We suggest carring out the measurement of fundal height during prenatal visits from week 24 of gestation as part of the interventions to assess foetal growth.
Doppler study of uterine artery	
Weak	We suggest not performing routinely in pregnancies at low risk of developing complications Doppler utero-placental and umbilical / foetal studies .
Cardiotocography	
Weak	We suggest not performing foetal monitoring by cardiotocography before week 40 of gestation in pregnant women without risk of complications.

Vaccines during pregnancy

√	Healthcare professionals should provide information to women about the risks certain vaccine-preventable diseases pose to the foetus and the newborn. The vaccination schedule should be checked and the benefits of vaccination discussed by the health professional together with the woman during prenatal visits.
Strong	The attenuated influenza vaccine, or vaccines against rubella, mumps, measles and varicella should not be administered during pregnancy as they are contraindicated.
Strong	The administration of inactivated influenza vaccine should be provided during the flu season to all pregnant women during any stage of pregnancy.
Strong	The diphtheria and tetanus vaccine should be administered for those pregnant women who do not have a complete vaccination regimen, avoiding them during the first trimester of pregnancy.
Strong	In the case of pregnant women in whom there is no data of immunisation against rubella, a dose of the MMR postpartum vaccine should be offered, assessing the benefits and risks during the breastfeeding period.
Strong	In pregnant women in whom there is no data of immunisation against varicella, the first dose of the vaccine should be administered as soon the pregnancy ends and, whenever possible, before being discharged from hospital. The second dose of vaccine should be given between 4 and 8 weeks after the first dose.

Lifestyles during pregnancy

Eating habits

Specific measures	
Weak	We suggest providing of nutritional advice to pregnant women in order to follow a balanced diet and adjust an adequate caloric intake to the needs of the pregnancy.
Weak	We suggest providing advice about a balanced protein-energy diet to those pregnant women to whom an insufficient dietary intake has been identified.
Weak	We suggest not recommending routinely a diet with high protein or isocaloric content to pregnant women.
Weak	We suggest recommending a protein-energy restriction to overweight pregnant women, or those who have gained excessive weight during pregnancy (> 570 g per week).
Micronutrients in the diet	
Weak	We suggest carring out an assessment of the dietary habits of pregnant women at the first contact with health professionals. This assessment should estimate the daily food intake in order to quantify its nutritional value, and this way be able to inform women about a proper diet for their needs and about the advisability of supplementing the diet.

Pharmacological Supplementation of nutrients

Pharmacological iron supplementation	
Weak	We suggest administering iron supplementation routinely to pregnant women.
Pharmacological iodine supplementation	
Weak	We suggest administering a pharmacological supplementation with potassium iodide at a dose of 200 mg / day during pregnancy to women who do not meet the recommended daily intake of iodine in their diet (3 servings of milk and dairy products + 2 g of iodized salt).
Pharmacological folic acid supplementation	
Strong	A daily supplementation at a dose of 0.4 mg / day (400 mg / day) of folic acid should be administered during the first twelve weeks of pregnancy.
√	In patients using AEDs (antiepilepticdrugs), a daily dose of 5 mg is recommended regardless of the type of antiepileptic used.
Pharmacological multivitamin supplementation	
√	Pregnant women should be informed to avoid taking vitamin A supplements in doses higher than 2,500 IU or 750 mcg due to their teratogenicity.
√	Women should not take multivitamin supplements during pregnancy.

Medication during pregnancy

√	During pregnancy, the least amount of drugs should be prescribed and the lowest possible dose, limiting its use to those circumstances in which the expected benefits to the mother and foetus outweigh the known risks to the foetus.

Alcohol and smoking during pregnancy

Weak	We suggest that women who are pregnant or planning pregnancy do not consume alcohol.
√	Women should be informed that excessive drinking during pregnancy (defined as more than 5 units or 7.5 standard drinks on a single occasion) is a risk to the foetus.
Strong	Women who decide to consume alcohol during pregnancy, should avoid drinking more than one unit of alcohol a day (equivalent to half a pint of beer, or 25 ml of liquor or a 125 ml glass of wine).
Weak	We suggest implementing some sort of measure aimed at reducing alcohol consumption in women where hazardous drinking is detected during pregnancy
Strong	Pregnant women should be strongly recommended to give up smoking.
Strong	Women planning pregnancy should be recommended to give up smoking completely.
Strong	Pregnant women who smoke should be provided detailed information about the effects of smoking on their health and that of the foetus, as well as the benefits of giving it up.
Strong	Pregnant women who smoke should be provided measures based on education and motivation (including participation in smoking cessation programs) to give up smoking.
Weak	For pregnant women who do not want to give up smoking and do not accept non-pharmacological interventions we suggest providing information on the risks and benefits of nicotine replacement based therapies (NRT).

Exercise during pregnancy

√	Individualised advice on starting or maintaining physical activity as well as its intensity, duration and frequency should be provided.
√	Pregnant women should be informed of the potential dangers of certain activities during pregnancy, for example, contact sports, high impact sports and racquet sports that may involve risk of abdominal trauma; falls or excessive joint stress as well as diving can cause problems at birth and provoke the decompression illness (DCI) of the foetus.

Psychological changes of pregnancy. Psychosocial stress and affective disorders

Weak	We suggest carring out a screening of the psychosocial status of the pregnant woman when there is suspicion of a material factor that may affect the course of pregnancy or postpartum.
√	Health professionals should be alert to the signs and symptoms of domestic violence during pregnancy, asking women about possible abuse in an environment where they feel safe, at least at the first prenatal visit, on a quarterly basis and in the postpartum visit.

Sexuality

Weak	We suggest providing information to pregnant women and their partners about the possibility of having sexual relations regularly during pregnancy because these are not associated with any risk to the foetus.

Travelling

√	An assessment of the potential risks arising from a trip should be carried out depending on the mother's circumstances and the point of the pregnancy when she wishes to go.
√	When the pregnant woman states that she would like to travel, she should be advised of the possible restrictions for pregnant women established by travel companies.
√	When the pregnant woman states that she would like to travel, she should be informed about the increased risk of venous thromboembolism in long-distance travels.

Managing common problems during pregnancy

Nausea and vomiting

Weak	We suggest administering of pyridoxine treatment for relief of nausea and vomiting during the early stages of pregnancy.
Weak	We suggest administering antihistamines (dimenhydrinate and meclizine), ginger and / or sessions of acupressure or acupuncture as therapeutic alternatives to pyridoxine for the relief of nausea and vomiting during the early stages of pregnancy.
Weak	We suggest using phenothiazines (thiethylperazine) as the last therapeutic option for the relief of nausea and vomiting during the early stages of pregnancy.

Heartburn

√	Pregnant women with heartburn should be informed on changes in their lifestyle and their diet.
Weak	We suggest the use of antacids in pregnant women to relieve heartburn.
Weak	We suggest combining ranitidine (H2 receptor antagonist) with antacids if heartburn persists after a treatment with antacids alone.

Constipation and haemorrhoids

Weak	For pregnant women suffering from constipation we suggest increasing the intake of foods high in fiber to foster stool frequency.
Weak	Pregnant women suffering from constipation may consider the use of laxatives that increase faecal bolus volume as first-line laxatives intensify intestinal motility.

Varicose veins

Weak	We suggest providing information to women about that varicose veins are common during pregnancy, and that the use of compression stockings can help improve the symptoms, but does not ensure prevention.
Weak	We suggest administering rutoside (troxerutine) orally to those pregnant women with venous insufficiency to relieve their symptoms.

Haemorrhoids

Weak	We suggest the use of rutosides (troxerutine) orally for the treatment of symptomatic haemorrhoids grade 1 and 2 in pregnant women.

Low back pain

Weak	We suggest the performance of water exercises and other individualised exercise programs for pregnant women , as well as therapeutic massages to relieve low back pain during pregnancy.

Management of breech pregnancy from week 35

Weak	We suggest administering ECV to those pregnant women with the baby in breech presentation at term gestation (37 weeks) and no contraindications to the procedure in order to reduce breech presentations and caesarean deliveries for this presentation.
Weak	We suggest the administration of tocolytic drugs prior to attempt ECV in those pregnant women with singleton breech presentation who have accepted the realization of ECV.
Weak	We suggest not performing an attempting an ECV before term (37 weeks) to those pregnant women with the baby in breech presentation.
√	The following conditions which have shown to have a bearing on the success of external cephalic version should be taken into account: multiparity, no fitting of the baby in breech presentation, relaxed uterus, palpable foetal head, weight of mother under 65 kg and subsequent ecographic criteria of posterior placental location, complete breech position and amniotic fluid index >10.

Preparation for birth

√	All pregnant women and their partners should be offered the opportunity to participate in a program of preparation for the birth in order to acquire knowledge and pregnancy-related skills, childbirth, care of the postpartum period, the newborn and during the breastfeeding period.

Management of pregnancy from week 41

Weak	We suggest offering to pregnant women the chance to induce labour at the time deemed most appropriate from the week before reaching weeks 41 and 42 of gestation, after reporting on the benefits and risks of induction.

Care during puerperium

Hospital care during puerperium

Postnatal checks and care of the newborn during hospital stay	
Strong	A single physical examination of the newborn in the first 24 hours of birth should be carried out in order to identify complications that may require specialised care.
√	The baby should be identified correctly from the time of umbilical cord ligation and possible separation of the mother and newborn should be avoided. Before carrying out any physical separation between the mother and the baby, a system of identification should be placed with the personal information of both, which should be visible throughout the hospital stay.

Strong	The umbilical cord should be cleaned with soap and water, dried afterwards and covered with clean dressings that must be changed frequently, and the diaper should be changed after bowel movements or urinations by the baby, in order to keep the cord dry and clean. This care should be performed until the umbilical cord falls following the aseptic and hygiene hand washing measures. This care should start only when the contact between the mother and her newborn is finished.
Strong	After birth, babies should be administered an intramuscular dose of 1 mg of vitamin K to prevent haemorrhage caused by a deficiency of this vitamin.
√	When parents do not accept the intramuscular administration of vitamin K, an oral regimen of 2 mg at birth should be administered, followed in partially or total breastfed babies by a weekly dose of 1 mg until the 12th week of life.
Strong	The administration of a topical antibiotic is recommended in the newborn after birth to reduce the risk of neonatal conjunctivitis.
√	Erythromycin ointment at 0.5% or tetracycline ointment at 1%, in a single-format should be used to increase the safety of the procedure.
√	The newborn should not be separated from his / her mother only for administering vitamin K or antibiotic eye drops, respecting the time of skin contact with his / her mother for this procedure.
Checks and care of the mother during the hospital puerperium period	
√	The checks and care provided to the mother during the hospital puerperium period are aimed at identifying signs that may warn of possible complications, providing care to facilitate recovery of the birth process and promoting self-care and baby care, especially regarding food and hygiene, as well as promoting the bond between the mother and the baby.
Qualified professional to control the hospital puerperium period	
Strong	Hospital care and postnatal care for mothers and their babies should be coordinated and delivered by a midwife, identifying those cases that may require additional or specialised care
Benefits of non-separation and co-sleeping during the hospital puerperium period	
Strong	Healthy babies should be placed immediately after birth, on the abdomen or breast of their mother and skin-to-skin contact should be maintained.
√	During the first two hours of life,skin-to-skin contact should be supervised by a health professional in order to identify any potential complications in the babies.
Weak	We suggest that mothers with healthy newborns, during the nights of hospital stay during the puerperium, ask to have the newborn asleep in a cradle attached (sidecar type) to the mother's bed.

Discharge and advice on care during the puerperium

Benefits of early discharge	
Weak	We suggest providing hospital discharge within 48 hours to those women whose babies were born at term without complications, when provided a proper monitoring can be ensured.

Adequate information and warning signs at discharge	
Weak	We suggest encouraging parents to take part in educational activities after birth, specifically targeting at their own training on issues related to health, development and relationship with their babies.
√	During hospitalisation after birth, health professionals should take advantage of routine contacts with mothers and their partners to offer useful information on baby care and warning signs in the mother or baby. Mothers and their partners should be encouraged to take this time to answer questions and express any concerns related to the care of their babies.
√	Prior to discharge, the mothers and their partners should be provided with informational materials that offer them answers to possible doubts about infant care.

Control visits during the puerperium

Controls and skilled professionals during the puerperium period in primary care	
Strong	Ensuring continuity of care for women and babies after hospital discharge should be provided by using a model of care where the midwife coordinates the actions of the various professionals involved in the care for mothers, newborns and their families.
√	Prior to discharge the first appointment with the midwife or the Primary Care Centre should be set for the third or fourth day of life of the newborn.
√	A minimum of two visits in the first 40 days after hospital discharge should be offered, the first between 24 to 48 hours after discharge, and another one at the end of the quarantine.
√	Women should be offered the possibility of conducting home visits after discharge according to their circumstances and the evolution and characteristics of their pregnancy and childbirth. These visits are aimed at providing advice and assistance on care for women and newborns.
√	Those women who do not wish to receive home visits, should be offered the possibility to attend visits to a primary care centre or hospital for an overall assessment of their health and that of the newborn and to receive the necessary advice.
√	During each puerperium visit, the emotional status of women, their family and social support and coping strategies developed to address situations of daily life, should be explored. Likewise any emotional or attitude change should be assessed with them and their partners.

Managing common problems during the puerperium

Treatments for perineal pain	
Weak	We suggest administering a dose of oral paracetamol (of 500-1000 mg every 8 to 12 hours) for perineal pain after childbirth.
Weak	We suggest administering rectal diclofenac analgesia for perineal pain during the first 48 hours after childbirth.
Weak	We suggest not treating perineal pain after childbirth with topical anaesthetics.
Weak	We suggest using localized cooling treatment (ice pack and cold gel pads) as second line treatment for perineal pain after childbirth.
Treatments for post-LP headache	
√	Women with persistent headache after epidural analgesia should be referred to the appropriate anaesthesiology service for proper assessment and treatment.

Weak	We suggest not administering intramuscular adrenocorticotropic hormone (ACTH), oral caffeine or subcutaneous sumatriptan for the treatment of post-LP headache.
Weak	We suggest not administering an epidural blood patch for the treatment of post-LP headache as first-line treatment.
Treatments for low back pain	
√	Women with low back pain after childbirth should receive the same therapeutic treatments as the general population.
Treatments for constipation	
Strong	Women with constipation in the puerperium period should be offered advice to reinforce the intake of natural fiber and fluids in their diet.
Strong	An osmotic or intestinal motility stimulant should be administered to women in whom constipation persists despite an increased intake of natural fibers and liquid laxative.
Benefits of rehabilitation of the pelvic floor muscles	
Weak	We suggest that women starting the practice of pelvic floor exercises whilst preparing for childbirth to reduce the risk of urinary incontinence after delivery.
Weak	We suggest carring out a training program of pelvic floor muscles in women with urinary or faecal incontinence after childbirth.

Contraception

Contraception methods	
√	Health professionals should promote during the puerperium, visits where aspects regarding contraceptive advice and experience of sexuality issues at this stage can be dealt with women and their partners.
√	The "Medical Eligibility Criteria for Contraceptive Use", created by the World Health Organisation (WHO) should be referred to in order to identify the most appropriate choice of contraceptive method according to the characteristics and medical history of each woman.
Strong	Women planning their future pregnancies, and who do not maintain exclusive breastfeeding should be informed about the need for contraception and the introduction of the method that best suits their situation, starting 21 days after childbirth.
Weak	In women with no risk of transmitting or acquiring a sexually transmitted infection, the lactational amenorrhea method (LAM) might apply until 6 months after childbirth if amenorrhea persists and exclusive breastfeeding is done.

Mental health in the puerperium

Tools for detecting mental disorders during the puerperium	
Weak	We suggest, after childbirth, asking to women the following question during the visits to identify the possibility of puerperal depression: "During the last month, have you often worried because you felt down, depressed or hopeless?" "During the last month, have you been worried because you often felt that you had little interest in activities and that these did not provide you any pleasure?"

Weak	We suggest not continuing with the diagnosis of postpartum depression if she says 'no' to the previous questions.
Strong	The Edinburgh Postnatal Depression Scale (EPDS, Appendix 5) should be used to confirm the diagnosis of postpartum depression in women who have answered 'yes' to the previous questions.
√	A score of over 12 points in the EPDS should be taken as a reference point for the diagnosis of postpardum depression
Weak	We suggest the use of the EPDS scale in the first six weeks after childbirth to ensure that the risk of depression in women is correctly discriminated.
Support groups during the puerperium	
√	Puerperium support groups should be created in primary care, offering psychological support during the period and enhancing the acquisition of knowledge and skills that have already been worked on in preparation for childbirth groups during the pregnancy.

Breastfeeding

Practices to foster the establishment of breastfeeding	
Strong	All pregnant women should be provided with information and support for the establishment of breastfeeding.
Practices to encourage the maintenance of breastfeeding	
Strong	All mothers should be offered support in order to maintain the duration and exclusivity of breastfeeding in the long term. Should this support be provided, it is preferable to be done individually following the 10 steps recommended by the Initiative for a more Human Birth and Lactation Care (BFHI).
Weak	We suggest providing information to mothers about the materials and educational activities available to promote breastfeeding.
Treatment of complications during breastfeeding	
Weak	We suggest using an antibiotic treatment and maintenance of breastfeeding with frequent voiding to solve infectious mastitis.
Weak	We suggest encouraging to Women to start breastfeeding as soon as possible to prevent complications such as engorgement or pain and injury to the nipple.
Weak	We suggest providing advice to omen with breast engorgement aboutbreastfeeding their babies frequently and on a continuous basis, with the possibility of performing massages in the breast and stimulate it for milk to be ejected manually.
Weak	We suggest offering educational activities on the position of the mother and baby during breastfeeding, signs of proper latch and effective signs of milk transfer.
Weak	We suggest using warm compresses after breastfeeding for those women who breastfeed with pain or nipple lesions.
√	At least one observation of breastfeeding should be done before hospital discharge to check it is done properly, and if there are any complications such as engorgement, sore and cracked nipple to help correct the difficulties in latching of the baby.

1. Introduction

As emphasized by the National Strategy for Sexual and Reproductive Health of the Ministry of Health, Social Services and Equality, the Observatory of Women's Health and the General Department of Quality and Cohesion to which it belongs, no effort has been spared from its creation to improve aspects related to equity regarding access and quality of care in the reproductive process.

During pregnancy, the care provided to pregnant women should be consistent with the care of a physiological and natural process, and therefore, should be based on care for its normal development, on the use of appropriate technology and on the recognition of the important role of women themselves when making decisions that affect them. Respect for the natural evolution of pregnancy should mark all health care and any intervention must be assessed to be applied only if it has demonstrated benefit and is in accordance with the needs and desires of each woman. Quality care for pregnant women should involve an efficient monitoring process, conducting visits, tests and evidence-based procedures, the involvement of users and proper coordination of primary and hospital care. During the puerperium, healthcare should have continuity and maintain the same high level of care.

The essence of this guide is to highlight that pregnancy is a normal physiological process and as such, any intervention performed must have known benefits and be acceptable to the pregnant woman. This guide has been developed with the aim of providing both information about the best clinical practice for referral care of all pregnant women, and extensive information on care during pregnancy and uncomplicated singleton pregnancy in healthy women. *Healthy woman* is understood as: *not suffering from a disease or a complication during pregnancy, such as preterm labour, hypertensive disorders of pregnancy, intrauterine growth restriction, multiple pregnancy, induction of labour, etc., which might require specific care or measures*.

This guide provides evidence-based information for both professionals and pregnant women in order to assist them during decision-making about appropriate care in each specific circumstance. This guide complements the Clinical Practice Guideline on Normal Birth Care published by the Spanish National Health System in 2010 stating recommendations for clinical practice in the care of women with normal deliveries[a].

[a] Working Group for the Clinical Practice Guideline on care at childbirth. The Clinical Practice Guideline on care at normal childbirth. Quality Plan for the National System of Health from the Ministry of Health and Social Policy. Agency for Health Technology Assessment of the Basque Country (OSTEBA). Technology Assessment Agency of Galicia (Avalia-t); 2010. Clinical Practice Guidelines within the Spanish NHS. OSTEBA No. 2009/1

2. Scope and aims

This Clinical Practice Guideline (CPG) contains recommendations based on scientific evidence for the control, monitoring and basic care in pregnancy and the puerperium. The CPG aims to:

- Identify the best clinical practice in the management of pregnancy and the puerperium.
- Establish a set of recommendations based on scientific evidence about the care for pregnant women and during the puerperium.
- Provide evidence-based information on prenatal care processes without complications.

The target population of this guide are women in these stages of life. Care in childbirth is explicitly excluded, as it is addressed in the CPG on normal birth care.

In the section entitled "situations that require extra care," those women who besides the follow-up recommended in this guide require additional care are identified; however, these specific cares are not addressed in this guide.

2.1 Situations requiring additional care

This guide offers recommendations on the basic care that all women should receive during pregnancy and the puerperium period, but does not provide information on situations that require extra care such as:

Previous pathology

- Heart disease, including high blood pressure
- Kidney disease
- Diabetes mellitus and other endocrine disorders
- Chronic respiratory disease: severe asthma
- Hematologic diseases, including thalassemia, sickle cell anaemia and thrombophilia
- Autoimmune diseases with systemic involvement: antiphospholipid antibody syndrome
- Epilepsy and other neurological diseases
- Psychiatric disease requiring medication
- Liver disease with failure
- Thromboembolic disease
- Neoplastic disease
- HIV infection or hepatitis B virus infection
- Cystic Fibrosis
- Other serious medical and surgical conditions
- Family history of genetic diseases
- Physical or mental disability

Obstetrical pathology during pregnancy and the puerperium:

- Pregnancy-induced hypertension
- Severe anaemia
- Gestational Diabetes
- Recurrent urinary tract infection
- Perinatal transmission infection
- Rh isoimmunisation
- Multiple pregnancy
- Polyhydramnios / oligohydramnios
- Genital bleeding
- Placenta previa after week 32
- Intrauterine growth restriction
- Congenital foetal default
- Preterm childbirth
- Premature rupture of membranes
- Uterine and adnexal lump
- Female Genital Mutilation
- Women with a history in previous pregnancies with:
    - Repeated abortions
    - Severe preeclampsia, HELLP syndrome or eclampsia
    - Rh isoimmunisation or other blood antibody
    - Uterine surgery including caesarean section, myomectomy or cone biopsy
    - Prematurity
    - Neonatal death
    - Newborn with low weight for gestational age (lower than the 5th percentile)
    - Newborn larger than common for gestational age (above the 95th percentile)
- Newborn with congenital (structural or chromosomal) malformation.
- Women with a history of 2 or more episodes of uterine bleeding before or after childbirth
- Postpartum haemorrhage and childbirth pathology
- Severe perineal trauma
- Surgical and postsurgical complications due to caesarean section
- Postpartum psychosis
- Newborn with severe malformations, aneuploidy or sick
- Mastitis

Clinical conditions:

- Obesity (body mass index or BMI of 30 kg/m2 or higher) or underweight with a BMI less than 18 kg/m2
- Addiction to toxic substances
- Delivery of the newborn for adoption
- Vulnerable women (under 18 years) or at high risk of social exclusion
- Women at increased risk of developing complications (for example, women over 40 and heavy smokers)
- Sexual abuse
- Women who suffer from domestic violence

2.2 Aims

The aim of this Clinical Practice Guideline for Care in Pregnancy and Puerperium is a set of recommendations based on the highest quality scientific evidence available to improve the health of pregnant women and of those who have just given birth, as well as the health of the newborns. In situations where there is NOT sufficient evidence, recommendations based on the consensus of the members of the Working Group will be carried out.

This guide is aimed specifically at midwives, obstetricians, paediatricians, family medicine practitioners and nurses who work in both primary care and hospital care. It is also addressed to other health professionals involved in the field of sexual and reproductive care who are responsible and managers of health strategies. An adapted version of this guide will be offered to pregnant women and their families.

Pregnancy and the puerperium are generally physiological processes that are of a singular personal, family, and social importance. With appropriate care and support, most women will have a successful pregnancy and puerperium. However, efforts to prevent complications have led to the realization of a high number of prenatal visits during the pregnancy as well as additional tests and interventions that are sometimes not supported by scientific evidence. In contrast, the puerperium, despite being a particularly difficult period for women and their families, raised less attention and care measures than are possibly needed. Furthermore, not enough attention has been given to the adverse effects of unnecessary or inappropriate interventions or the need for a more comprehensive care that includes psychosocial aspects, respects the role of women and promotes informed decisions and the co-responsibility of their partner. This guide believes that the needs of pregnant women and those who have just given birth as well as their families should be at the centre of the care model and that during these physiological processes only interventions which have proven to provide some benefit should be proposed.

The Working Group aimed to address uncomplicated pregnancy and the puerperium in order to offer a series of recommendations to improve their basic care, avoid unnecessary procedures and reduce unjustified variability of clinical practice. Although the recommendations are addressed to a single foetus pregnant woman and whose pregnancy and puerperium run smoothly, most of them would apply to pregnancies and puerperiums which, as mentioned previously, require additional care.

Those relevant aspects of women's health history including lifestyle such as food, toxic habits, social and work environment or potential chronic diseases will be collected. Likewise, the documentation and information, which should be offered to pregnant women, those who have just

given birth and their partners is included. The number and content of each visit, as well as how to approach different symptoms is stated.

This guide will complement other documents and projects coordinated by the Ministry of Health, Social Services and Equality, for the development of healthcare activities related to pregnancy within the Spanish National Health System, with special emphasis on how such assistance is implemented and what professionals are involved in each intervention.

3. Methodology

The methodology used to create this Clinical Practice Guideline follows the guidelines described in greater detail in the *Methodological Manual for the creation of Clinical Practice Guidelines* of the Spanish National Health System, available at www.guiasalud.es/ (Aragon Institute for Health Sciences-I + CS, 2007).

The main stages in the elaboration process have been:

- Creation of the Guideline Working Group, of a multidisciplinary nature, so that it was composed of professionals from different hospitals and regions and represented by all the professional categories involved: obstetricians, midwives, paediatricians, family physicians, and methodologists belonging to the Agency for Health Technology Assessment of Andalusia (AETSA) and the Cochrane Iberoamerican Centre (CCIB). The Working Group also benefited from the participation in the whole process of representatives from "El Parto es Nuestro" (Childbirth is ours) and "Vía Láctea" (Milky Way) associations and the Observatory of Women's Health.
- Formulation of clinical questions using the PICO format: Population, Intervention, Comparison, and (*Outcome*).
- Literature search, prioritizing the identification of other clinical practice guidelines, systematic reviews (SR) and scientific literature critical synthesis, such as reports of health technology assessment. Therefore, in a first stage a search for other CPG was performed to check which SR had been considered to support its recommendations. Four CPGs were used as secondary sources, Demott (2006), Brocklehurst (2008), Bailon (2002), Akkerman (2010) and subsequently additional SRs were identified from the search date of the selected CPG. At this first stage, the following electronic databases were consulted:
  - *Trip database*
  - *NHS Evidence*
  - *Cochrane Database of Systematic Reviews (The Cochrane Library)*
  - *Database of Abstracts of Reviews of Effects* (DARE)
  - *Health Technology Assessment* (HTA) Database
  - *NHS Economic Evaluation Database* (NHS EED)
  - MEDLINE (Access through PubMed)

In a second phase, a specific search for individual studies was performed to update the relevant SRs and answer questions from the CPG for which literature had not been found in the initial stages. Mainly, randomised clinical trials (RCTs) and observational studies were identified respecting the original search strategies of the relevant SRs. These searches were carried out in specific searches in MEDLINE.

No linguistic limit was set on the searches carried out. Searches started in February 2012 although they were continuously updated until October 2012, to identify studies with greater impact throughout the CPG's creation process.

- The classification of the quality of evidence and grading of strength of the recommendations has been made following the guidelines of the GRADE (*Grading of Recommendations*

Assessment Development and Evaluation) International Working Group, Guyatt (2008a, 2008b, 2011a), and (see Appendix 2). In some sections of the clinical practice guideline, the recommendations stated in other high quality or useful practice guidelines for health professionals involved in the scope of the guidance were summarised. In these cases, the name "Other clinical practice guidelines" has been used. Those paragraphs that collect evidence summaries reflect the main results of the literature with a rating of the quality of the evidence, except for those for which no relevant studies or contextualization comments are made. In the latter case, these paragraphs do not include any quality of evidence.

- Expert partners have participated in the formulation of questions and the review of the first draft of the guide. External reviewers have taken part in the review of the second draft. Various scientific societies have been involved such as the Spanish Society of Gynaecology and Obstetrics (SEGO), the Spanish Federation of Midwives (FAME), the Spanish Society of Neonatology (SEN) and the Spanish Society of Family and Community Medicine (SEMFyC). Likewise, these companies are represented by members of the development group, expert collaborators and external reviewers.
- In www.guiasalud.es contains the material that provides detailed information of the methodological process of CPG (search strategies for each clinical question, critical reading records of the selected studies, tables summarising the evidence tables as well as the formal evaluation tables).
- It is planned to update the guide every three years, or within a shorter period, if new scientific evidence is found which modifies some of the recommendations offered in this guide. Updates will be done on the electronic version of the guide, available at URL: http://www.guiasalud.es.

4. Preconception visit

Key question:

- What is the aim and what should be the content of a preconception visit?

Since the health of women during pregnancy depends largely on their health before conception and since the period of greatest vulnerability to the embryo are the first 10 weeks of pregnancy, reproductive counselling during the preconception period is an important aspect of prenatal care.

4.1. Aims and content of the preconception visit

The results reported in this section have been obtained from the Preconception Care series published in the *American Journal of Obstetrics and Gynaecology* for its comprehensive scope and review of the literature (AJOG-Dunlop, 2008). This document was developed to update and develop implementation strategies on the recommendations for preconception care that the *Centres for Disease Control and Prevention* had published in 2005. A panel of authors got together to evaluate the evidence that supported the various proposed recommendations, support them with new studies, and review the recommendations.

The different documents evaluated reflect, for example, all interventions performed to all pregnant women, without considering whether to evaluate the relevance of studies, which assess whether there are aspects or factors that determine the indication of a preconception visit.

Chronic Diseases

Diabetes mellitus **Expert opinion**

The control of diabetes before conception reduces the risk of congenital malformations (AJOG-Dunlop, 2008).

High blood pressure **Expert opinion**

No well-designed studies that specifically address the effects of pre-pregnancy strategies for the management of high blood pressure with results on the pregnancy or the neonates have been carried out (AJOG-Dunlop, 2008).

Epilepsy **Expert opinion**

No well-designed studies that specifically address the effect of strategies, prior to pregnancy, for the management of seizures with results on pregnancy or infants have been carried out (AJOG -Dunlop, 2008).

Reproductive history

Preterm delivery **Expert opinion**

Some factors associated with recurrence of preterm delivery have been identified: Afro-American ethnicity, inflammatory changes in the placenta, low maternal weight before pregnancy (<50 kg) or body mass index below 19.8 kg / m2, large weight loss during pregnancy (> 5 kg / m 2), smoking, short interval between pregnancies (<12 months), a history of cervical insufficiency or short cervix by transvaginal ultrasound during pregnancy (Stirrat, 1990; AJOG¬Stubblefield, 2008; RCOG, 2011)

Repeated miscarriages **Expert opinion**

Repeated miscarriages (three or more spontaneous miscarriages <15 weeks of pregnancy) have been directly associated with maternal thrombophilic disorders, with chromosomal abnormalities of the parents or uterine structural abnormalities. Although, in most cases, the pathophysiology remains unknown (AJOG-Stubblefield, 2008).

Intrauterine foetal death **Expert opinion**

Table 1 lists maternal risk factors associated with foetal death from a recent systematic review (Fretts, 2005; AJOG-Stubblefield, 2008).

Previous caesarean section **Expert opinion**

A factor that influences in the future delivery is the time gone by from the last caesarean section. A short interval between births increases the risk of a caesarean section (AJOG-Stubblefield, 2008). One study found an increased risk for childbirth intervals of <24 months (Bujold, 2002); another study in calving intervals of <18 months (Shipp, 2001); and a third study in intervals between pregnancies (defined as from birth to the later conception) of <6 months (Stamillo, 2007).

Infectious diseases

Hepatitis B **Expert opinion**

There are no specific studies evaluating the impact of a vaccination program before pregnancy (AJOG-Coonrod, 2008).

Hepatitis C **Expert opinion**

There are no studies on the impact of HCV screening before pregnancy in low-risk women. However, screening based on risk factors appears to be adequate, although there is no long-term data showing improved outcomes (AJOG-Coonrod, 2008).

It is important to inform women of what the major risk factors for contracting HCV may be. Transmission occurs primarily when there is contact with blood from someone infected with the virus. Therefore, the main risk factor is derived from the exchange of syringes, needles or other equipment between users of intravenous drugs, or health professionals who are accidentally stuck. The virus can also be transmitted sexually, mainly in people who have sex with multiple partners or who have sex with someone infected with the virus (CDC, 2012).

Tuberculosis **Expert opinion**

Tuberculosis screening before pregnancy allows complete prophylaxis, reduce the risk of complications during pregnancy and avoid conversion to active disease (AJOG-Coonrod, 2008).

Chlamydia **Expert opinion**

Screening and treatment for Chlamydia trachomatis infection before pregnancy reduces infertility and ectopic pregnancy (AJOG-Coonrod, 2008).

Gonorrhoea **Expert opinion**

There are no studies related to greater effectiveness of screening for Neisseria gonorrhoea before pregnancy compared to screening during pregnancy to prevent complications during its development (AJOG-Coonrod, 2008).

Genital herpes **Expert opinion**

Most people infected with the herpes simplex virus are asymptomatic, so it is important to explain to couples the signs and symptoms of genital herpes (AJOG-Coonrod, 2008).

Listeriosis **Expert opinion**

Most cases of Listeria monocytogenes infection are caused by ingestion of contaminated food (pate, soft and fresh cheeses made from unpasteurized milk, ready to eat food such as sausages or cold meats, leftovers) (AJOG-Coonrod, 2008).

Parvovirus **Expert opinion**

No studies suggest that screening for parvovirus before pregnancy is beneficial (AJOG-Coonrod, 2008).

Malaria **Expert opinion**

Screening for malaria is not carried out in Spain because it is not endemic.

Cytomegalovirus **Expert opinion**

No studies suggest that screening and / or treatment programs of cytomegalovirus prevent its infection (AJOG-Coonrod, 2008).

Toxoplasmosis **Expert opinion**

Toxoplasmosis is an infection caused by the protozoan Toxoplasma gondii that can be transmitted to the foetus by a pregnant infected woman. During pregnancy, raw meat and faeces of newly infected cats are the other sources of transmission of the protozoan infection (AJOG-Coonrod, 2008).

Preconception screening of immunity to Toxoplasma gondii (by measuring IgG titles) may provide physicians with useful information for women. Although there are no studies suggesting that screening is cost-effective or efficient (AJOG-Coonrod, 2008).

Rubella **Expert opinion**

During the prenatal visit, a screening for rubella should be performed by reviewing the women's vaccination history or a serology, to vaccinate them before pregnancy.

Considering that the rubella vaccine is contraindicated during pregnancy, the administration of a dose of the MMR vaccine should be provided to those women with no evidence of immunisation against the virus, taking precautions to avoid pregnancy for 28 days after the vaccination (see section 3.2.1 page 178).

Chickenpox **Expert opinion**

During the pre-conception visit, varicella screening should be performed reviewing the vaccination history of women in order to vaccinate those who are not immunised.

Nutrition

Balanced nutrition **Expert opinion**

Several studies have shown a positive association between a healthy diet during the preconception period and during pregnancy and an improvement in pregnancy outcomes (AJOG-Gardiner, 2008).

Overweight **Expert opinion**

Weight loss is not recommended during pregnancy. Therefore, to minimize the risks of obesity during pregnancy, interventions to reduce weight should be performed before. (AJOG-Gardiner, 2008).

An SR, carried out among adult population, showed that simple advice, or with pharmacotherapy can foster modest but steady weight loss. Although the number of studies evaluating the long-term improvement is limited (AJOG-Gardiner, 2008).

Caffeine **Expert opinion**

No reference has been found in the *Preconception care* series from the *American Journal of Obstetrics and Gynaecology* in relation to caffeine.

Herbal treatments **Expert opinion**

No reference has been found in the *Preconception care* series from the *American Journal of Obstetrics and Gynaecology* in relation to herbal treatments.

Drug abuse

Smoking **Expert opinion**

The screening on smoking in the preconception visit usually consists of information provided by women about their smoking habits when asked by the health professional (AJOG-Floyd, 2008).

Although studies have been published on the effectiveness of interventions to increase cessation of smoking in adults, women in general and pregnant women, no specific studies for non-pregnant women of childbearing age have been carried out (AJOG-Floyd, 2008).

Alcohol **Expert opinion**

There is a series of validated questionnaires to assess alcohol consumption in pregnant and non-pregnant women, including TWEAK, T-ACE, AUDIT or AUDIT-C (AJOG-Floyd, 2008).

Randomised clinical trials have evaluated counselling interventions to reduce heavy drinking among women of childbearing age. A significant decrease in alcohol consumption among women who received the intervention (AJOG-Floyd, 2008) was observed.

Illegal drugs **Expert opinion**

There are fewer tools to assess illegal drug consumption in women of childbearing age. An SR on illicit drug detection instruments has found reasonable evidence for the use of CRAFFT in adolescents. For adults, the *Alcohol and Substance Involvement Screening Test and the Drug Abuse Screening Test* have acceptable accuracy and reliability (AJOG-Floyd, 2008).

Effective interventions for the treatment of use and illicit drug dependence are both behavioural and pharmacological (AJOG-Floyd, 2008).

Educational and health-promoting interventions

Exercise **Expert opinion**

No direct benefits have been proven regarding pregnancy outcomes in relation to doing exercise before conception. Indirect benefits may include weight control and mood stability.

Sexuality **Expert opinion**

No reference has been found in the *"Preconception care"* series from the *American Journal of Obstetrics and Gynaecology* in relation to sexuality.

Pharmacological supplements

Folic Acid **Expert opinion**

We have identified a Cochrane SR (De-Regil 2010) evaluating the effects of pre-conceptional supplementation with folic acid to reduce neural tube defects (NTDs).

The SR included five studies with 6105 women (1949 with a history of a pregnancy affected by an NTD and 4156 with no history of NTDs).

In all RCTs, folic acid was administered daily; in one of the trials it was supplemented with <0.4 mg / day of folic acid (Kirke, 1992), while the remaining women were supplemented with> 0.4 mg / day (0.8 mg / day (Czeizel, 1994), 2.0 mg / day (Laurence, 1981), 4.0 mg / day (ICMR, 2000, MRC, 1991)).

In all RCTs, women began supplementation before pregnancy (one to two months before) and discontinued after 12 weeks of pregnancy.

The following interventions were compared:

– Folic acid versus placebo (Laurence, 1981).

– Folic acid and multivitamin versus trace elements (Czeizel, 1994)

– Folic acid and multivitamin versus placebo (ICMR, 2000).

– Folic acid versus multivitamins versus both (Kirke, 1992).

– Folic acid versus multivitamins versus both and versus placebo (MRC, 1991).

Supplementation of folic acid (alone or in combination with other vitamins and minerals) significantly decreased the prevalence of neural tube defects (NTD) compared to placebo or multivitamin complexes without folic acid (5 studies; 12/3066 cases in the intervention group versus45/3039 cases in the control group, RR 0.28, 95% 0.15 to 0.52) (De-Regil, 2010). **Low quality**

Only one study evaluated the presence of NTDs in women with no history and the effect was not statistically significant (1 RCT; 0/2104 cases in the intervention group versus 6/2052 cases in the control group, RR 0.08, 95% CI 0.00 1.33), although no records were found in the group receiving folic acid (Czeizel, 1994). **Low quality**

Folic acid supplements were associated with a significant decrease in the recurrence of NTDs (4 RCTs, 12/962 cases in the intervention group versus 39/987 cases in the control group, RR 0.32, 95% CI 0.17 0.60) (ICMR, 2000; Kirke, 1992, Laurence, 1981; MRC 1991). **Low quality**

One RCT reported adverse events in women (nausea, vomiting, constipation, or diarrhoea). The number of reported cases before and during pregnancy was very low, both in the group of women who received folic acid and multivitamins and the control group treated with trace elements (Czeizel, 1994). **Low quality**

Iodine

No studies have been conducted on the impact of iodine supplementation before pregnancy (AJOG-Gardiner, 2008). **Expert opinion**

Multivitamins

An SR (Goh, 2006) evaluating the effect of folic acid supplemented with multivitamins in the prevention of congenital malformations has been identified.

The SR by Goh (2006) included four RCTs evaluating women with no history (Czeizel 1994) or with a history of babies with NTDs (ICMR, 2000; Kirke, 1992; MRC, 1991).

Table 2 shows the vitamins, minerals and trace elements contained in each multivitamin included in the trials.

In all RCTs women began supplementation before pregnancy (one to two months before) and discontinued after 12 weeks of pregnancy.

The following interventions were compared:

– Folic acid and multivitamin versus trace elements (Czeizel, 1994)

– Folic acid and multivitamin versus placebo (ICMR, 2000).

– Folic acid versus multivitamins versus both (Kirke, 1992).

– Folic acid versus multivitamins versus both and versus placebo (MRC, 1991).

The RCT by Czeizel (1994) found no significant differences in the presence of NTD in the newborn of women with no history between the group under treatment with multivitamin (folic acid) versus the group under treatment with trace elements (4862 women, 0% (0/2471) NTDs in the group treated with multivitamin versus 0.3% (6/2391) in the group treated with trace elements; RR 0.07; 95% 0 to 1.32) (Czeizel, 1994). **Moderate quality**

The RCT by ICMR (2000) found no significant differences in relation to the recurrence of NTD in newborns of women in the group under multivitamin treatment compared to women in the placebo group (279 women, 2.9% (4/137) NTD in the group treated with multivitamin versus 7% (10/142) in the placebo group, RR 0.4, CI 95% 0.12 to 1.30) (ICMR, 2000). **Moderate quality**

The RCT by Kirke (1992) also observed no significant differences in relation to the recurrence of NTD in newborns between women in the multivitamin treatment group compared to women in the other groups (1/89 cases of recurrent NTDs among newborns or foetuses with multivitamin tablet; 0/85 cases with folic acid; 0/87 with both cases) (Kirke, 1992).

The RCT by MRC (1991) also observed no significant differences in relation to the recurrence of NTD in newborns between women in the multivitamin treatment group compared to women in the other groups (7/257 cases with multivitamin tablet; 2/258 cases with folic acid, 3/256 with both cases, 11/260 cases with placebo) (MRC 1991).

The RCT by MRC (1991) reported on the adverse events of the treatments. The average number of women who reported an adverse event (often non-specific symptoms such as infertility, irregular menses, vomiting in pregnancy, diseases of the upper respiratory tract) was similar in the four intervention groups (19% with multivitamin tablet, 16% with folic acid, 15% with both cases, 11% with placebo) (MRC, 1991). **Moderate quality**

More congenital anomalies other than NTDs were observed in the groups with multivitamin treatment (8/294 cases with multivitamin tablet; 7/296 with folic acid; cases with both 12/291; 5/287 cases with placebo; non-reported significance degree) (MRC, 1991). **Moderate quality**

Summary of evidence

Intervention	
Low quality	***Folic acid*** Supplementation with folic acid before conception and during the first 12 weeks of pregnancy significantly reduces the prevalence and recurrence of NTDs compared with placebo or multivitamins without folic acid (De-Regil, 2010).
Low quality	No statistically significant differences were observed in the adverse events between folic acid supplementation with multivitamins and the control with trace elements (Czeizel, 1994).
Iodine There is no evidence on the efficacy and safety of the treatment with iodine before conception.	

Moderate quality	***Multivitamins*** Multivitamins (with or without folic acid) administered before conception and during the first 12 weeks of pregnancy significantly do not reduce the risk of NTDs in women with no history or experience of a recurrence of NTD in newborns compared with trace elements, folic acid, folic acid fortified with multivitamins or placebo (Czeizel, 1994; ICMR, 2000; Kirke, 1992; MRC, 1991).
Moderate quality	No statistically significant differences were observed in adverse events between multivitamins and other treatments (folic acid, folic acid fortified with multivitamins or placebo) (MRC, 1991).

Recommendations

	Chronic diseases
√	Women planning a pregnancy and who suffer some chronic disease should be informed on the possible impact on the course of their disease and prenatal outcomes. A detailed anamnesis should be carried out to identify all potential risks and plan the pregnancy properly. In some cases of women with diabetes, epilepsy, hypothyroidism or other chronic diseases, it may be necessary at early pregnancy to re-evaluate the usual treatment by the attending physician.
√	Women planning pregnancy, who are overweight or obese (IMC≥25 kg / m 2) and with more than one additional risk factor for diabetes (including a history of gestational diabetes) should to undergo screening to detect pre-diabetes and diabetes type 2
√	In women planning pregnancy and who are diabetic, glycaemic control should be optimized to achieve, before pregnancy, the best control possible.
√	Women planning pregnancy and suffering from high blood pressure (HBP) should have their chronic antihypertensive medication reviewed to check if it should be modified.
√	Women planning pregnancy and suffering from epilepsy should have their medication reviewed to check if it should be modified or suspended before pregnancy and start supplementation with folic acid (5 mg / day) at least one month before conception and keep up to 12 weeks after gestation.
	Reproductive history
√	Reproductive history should be evaluated in all women planning pregnancy
√	History of preterm labour and control the possible causes of recurrence before the next pregnancy should be evaluated in women planning pregnancy
√	Women planning pregnancy and with a history of repeated abortions (over three reproductive losses according to the British College of Obstetrics and Gynaecology) should undergo a study to identify possible causes and assess their treatment.
√	Women planning pregnancy and with a history of stillbirth should complete a study of the possible causes and change the possible associated risk factors.
√	Women planning pregnancy and with a history of caesarean section should be adviced about waiting at least 18 months until the next delivery.

Infectious diseases	
√	Women planning pregnancy and who are not immunised against hepatitis B should be vaccinated before pregnancy.
√	Women planning pregnancy and who are at high risk of hepatitis C virus (HCV) infection should undergo screening for hepatitis C to provide information about the possible risks of vertical transmission.
√	Women planning pregnancy and who are not immunised against rubella should be vaccinated before pregnancy with the measles-mumps-rubella (MMR) vaccine and take precautions to avoid pregnancy during the 28 days following vaccination.
√	Women planning pregnancy should be adviced about the appropriate measures to prevent infection with *Toxoplasma gondii* during pregnancy.
Nutrition	
√	Women planning pregnancy should be adviced about a nutrient-rich balanced diet.
√	Women planning pregnancy should be adviced about taking iodized salt.
√	Women planning pregnancy and having a body mass index ≥25 kg / m 2 or ≤18 kg/m 2 should be provided information and dietary advice as well recommendations on physical activity.
Drug abuse	
√	Women planning pregnancy should undergo a detailed anamnesis on the consumption of tobacco , alcohol, drugs and other psychoactive substances.
√	Women planning pregnancy and who smoke or consume alcohol, should be adviced about giving up these habits and be provided with cessation measures.
√	Women planning pregnancy and who are drug users, should be adviced about quitting this habit and be provided with dishabituation measures.
Educational and health promotion measures	
√	Women planning pregnancy should be adviced about doing exercise on a regular basis.
Pharmacological supplements	
√	Women planning pregnancy should take a daily supplementation with 0.4 mg of folic acid for at least one or two months prior to conception. In women with a history of neural tube defects, who have had a child with a neural tube defect previously, are diabetic or are taking anticonvulsants, should take a daily supplementation with 5 mg of folic acid.
√	Women planning pregnancy should not be systematically administered a daily iodine supplementation.
√	Women planning pregnancy should not be systematically administered a daily multivitamin supplementation in order to avoid neural tube defects.

5. Care during pregnancy

5.1. Visits and monitoring during pregnancy

Key question:

- What professionals should provide prenatal care?
- Does the number of monitoring visits during pregnancy influence the health outcomes of the mother and / or the newborn?
- What should be the content of the medical record?
- What is the purpose of the routine examination of the body mass index (BMI) and weight watching, measurement of blood pressure, breast and gynaecological exploration in early pregnancy? What is the purpose of universal screening for hypertensive disorders [measurement of blood pressure (BP) and test strips] and in on what stage of pregnancy should it be done? What is the purpose of universal screening for cervical cancer and on what stage of pregnancy should it be done?
- What is the purpose of determining the plasma urea level in a biochemical test?
- What is the purpose of determining the plasma creatinine level in a biochemical test?
- What is the purpose of determining the plasma uric acid level in a biochemical test?
- What is the purpose of universal screening for syphilis in pregnant women and at what stage of pregnancy should it be done?
- What is the purpose of universal screening for Chagas disease in pregnant women and at what stage of pregnancy should it be done?
- What is the purpose of universal screening for chlamydia in pregnant women and at what stage of pregnancy should it be done?
- What is the purpose of universal screening for bacterial vaginosis in asymptomatic pregnant women and at what stage of pregnancy should it be done?
- What is the purpose of universal screening for rubella in pregnant women and at what stage of pregnancy should it be done?
- What is the purpose of universal screening for toxoplasma infection in pregnant women and at what stage of pregnancy should it be done?
- What is the purpose of universal screening for varicella in pregnant women and at what stage of pregnancy should it be done?
- What is the purpose of universal screening for cytomegalovirus in pregnant women and at what stage of pregnancy should it be done?
- What is the purpose of universal screening for hepatitis Bvirus in pregnant women and at what stage of pregnancy should it be done?
- What is the purpose of universal screening for hepatitis C in pregnant women and at what stage of pregnancy should it be done?
- What is the purpose of universal screening for group B streptococcus in pregnant women and at what stage of pregnancy should it be done?

- What is the purpose of universal screening for human immunodeficiency virus (HIV) in pregnant women and at what stage of pregnancy should it be done?
- What is the purpose of universal screening for symptomatic bacteraemia in pregnant women and at what stage of pregnancy should it be done?
- What is the purpose of universal screening for anaemia and at what stage of pregnancy should it be done?
- What is the purpose of determining the level of ferritin in a biochemical test?
- What is the purpose of universal screening for Rh incompatibility and at what stage of pregnancy should it be done?
- Which is the most effective and appropriate guideline for the anti-D prophylaxis in the prevention against Rh sensitisation?
- What is the purpose of universal screening for thyroid disease and at what stage of pregnancy should it be done?
- What is the most suitable screening method for gestational diabetes testing? At what stage of pregnancy should gestational diabetes screening be done? What are the appropriate criteria to consider a pregnant woman gestational diabetic?
- What is the purpose of universal screening for risk of preterm delivery and at what stage of pregnancy should it be done?
- Is it beneficial to make a birth plan during pregnancy?
- In what week of pregnancy should the ultrasound scans be carried out? Is any complication during the performance of ultrasound scans referred?
- What information from the ultrasound scans should be provided? How and when should this information be provided?
- What is the performance of the combined test for chromosomal screening versus performing invasive tests?
- Is the symphysis-fundal height (SFH) measurement useful to predict foetal growth control?
- What is the benefit of the Doppler study of uterine artery and umbilical artery in low risk pregnancies?
- Are routine cardiotocography checks needed for the prenatal assessment of foetal wellbeing? If so, in what week of pregnancy?

Organisation of prenatal care

Professionals providing prenatal care

The NICE guide (NICE, 2008) based its recommendations on a Cochrane SR that evaluated the efficacy and perception of prenatal care depending on the health care professional who provided such prenatal care (Villar, 2001). The SR compared a model in which care was coordinated by midwives and family physicians to a model in which prenatal care was coordinated by obstetricians or gynaecologists. The scope of the SR has been recently changed and has focused on evaluating the effect of prenatal care programs with reduced visits (4-9 visits) compared with standard prenatal care (13-14 visits) (Doswell, 2010). The SR included three RCTs on pregnant women with no risk and no medical or obstetrical complications (3,041 women).

These same studies were included in a previous SR that had the same aims as those in the mentioned reviews (Khan-Neelofur, 1998).

High quality

The RCTs included in the SR by Villar (2001) showed no difference between the care models (midwives and family physicians versus obstetrician or gynaecologists) for the rate of preterm delivery, caesarean section delivery, anaemia, urinary tract infections, antepartum haemorrhage, or perinatal mortality.

Furthermore, those women who received coordinated care by midwives and family physicians showed a lower rate of pregnancy-induced hypertension (3,041 women: OR 0.56, 95% CI 0.45-0.70) and preeclampsia (2,952 women: OR 0.37, 95% CI 0.22 to 0.64) compared with women who received regular care from an obstetrician or gynaecologist.

No differences were found between satisfaction with the care received by either professional. However, in the discussion of this outcome in the SR by Khan-Neelofur (1998) it is stated that women were more satisfied with the model coordinated by midwives and family physicians when asked about the continuity of care measures.

The results of this SR led the authors to conclude that women with an uncomplicated pregnancy, a care model coordinated by midwives and family physicians does not increase the risk of adverse perinatal or maternal outcomes (Villar, 2001; NICE, 2008).

Summary of evidence

High quality	In women with an uncomplicated pregnancy a care model coordinated by midwives and family physicians does not increase the risk of maternal or perinatal complications (Khan-Neelofur, 1998; Villar, 2001; NICE, 2008).

From evidence to recommendation

The aspects that have determined the strength and direction of this recommendation are:

- High quality of the evidence: the RCTs available were free of bias in their design and execution and have shown very consistent results.
- The balance between benefits and risks: studies have shown that care coordinated by midwives and family physicians does not increase the risk of adverse maternal or perinatal outcomes.
- The costs and use of resources: so specific studies have been identified in this section. However, one of the SRs evaluated (Khan-Neelofur, 1998) highlights in its conclusions, from the results of two of the RCTs included, that prenatal care provided by different professional gynaecologists or obstetricians has shown a reduction in the cost of this care.
- The values and preferences of pregnant women: the guide on pregnancy care by NICE (NICE, 2008) highlights among its recommendations for research the lack of qualitative studies on the perception of pregnant women about who provides prenatal care. Moreover, the SR by Villar (2001) showed no difference regarding satisfaction between the care provided by either type of professionals.

The Working Group made the following recommendations considering that care coordinated by midwives and family physicians does not increase the risk of perinatal adverse outcomes or

during pregnancy. Although indirectly, the cost of this care model is reduced, and despite the fact that the results on the perception of pregnant women in this area are sparse, the results of the RCTs evaluated have shown no differences between satisfaction with the care provided by either type of professionals. The Working Group proposed including the recommendation of good clinical practice.

Recommendations

Strong	It is recommended that prenatal care in pregnancies without complications are provided by midwives and family physician , with the participation of other health professionals in primary care teams and the support of the corresponding obstetric unit.
√	Scheduled prenatal visits in pregnancies without complications should be coordinated by midwives.

Visits and monitoring during pregnancy

Number of visits and findings on maternal and foetal health

Number of visits during pregnancy

An SR (Dowswell, 2010) evaluating programs with reduced perinatal visits for women at low risk of complications during pregnancy or childbirthhas been identified.

The SR by Dowswell(2010) included seven RCTs comparing the effects of perinatal care programs with reduced visits (4-9 visits) with standard perinatal care (13-14 visits) in 60,000 women. Four trials were conducted in high-income countries (by gross domestic product) individually randomised (Binstock, 1995; McDuffie, 1996; Sikorski, 1996, Walker, 1997) and three in low and middle-income countries cluster randomised (clinics as the unit of randomisation) (Majoko, 2007; Munjanja, 1996; Villar, 2001). The number of visits in the studies varied depending on the country in which they were carried out: in the high-income countries, the number of visits was about eight, while in low-income countries the visits were less than five.

In three studies carried out in high-income countries, the number of perinatal visits decreased to an average of 2.65 visits (95% CI 3.18 to 2.12) when comparing the perinatal care programs with reduced visits to standard perinatal care (Sikorski, 1996; Binstock 1995; McDuffie, 1996). **Moderate quality**

No differences were observed in maternal mortality between the two interventions (RR 1.13; 95% CI 0.50 to 2.57) in low and middle-income countries, (Villar, 2001; Munjanja, 1996; Majoko; 2007). **Moderate quality**

No differences were observed in the incidence of hypertensive disorders either (eclampsia or gestational hypertension) between the two interventions (RR 0.95, 95% CI 0.80 to 1.12). (Sikorski, 1996; Binstock 1995; McDuffie, 1996; Villar, 2001; Munjanja 1996; Majoko, 2007). **Moderate quality**

However, in trials in high-income countries, the number of deaths was small (0.6%), without showing differences between reduced perinatal visits and standard care (15/2536 versus 17/2572, RR 0.89 CI 95% 0.45 to 1.79). **Moderate quality**

Although a non-significant decrease in admissions to intensive care units in the reduced visits group (6 RCTs, RR 0.89, 95% 0.79 to 1.02) was observed, this effect disappeared when analysing data studies in high-income countries (6 RCTs, RR 1.06, CI 95% 0.80 to 1.41).	**Low quality**
No differences were observed in the number of small newborns **for gestational age** (RR 0.99, 95% 0.91 to 1.09) (McDuffie, 1996; Munjanja, 1996, Sikorski, 1996; Villar, 2001). (RR 0.99, 95% 0.91 to 1.09) (McDuffie, 1996; Munjanja, 1996, Sikorski, 1996; Villar, 2001).	**Moderate quality**

Summary of evidence

Moderate quality	No significant differences were observed in relation to maternal mortality (Villar, 2001; Munjanja, 1996; Majoko, 2007) or in relation to hypertensive disorders (eclampsia or gestational hypertension) (Sikorski, 1996; Binstock, 1995; McDuffie, 1996; Villar, 2001; Munjanja, 1996; Majoko, 2007) among perinatal care programs with reduced visits (4-9 visits) versus standard perinatal care (13-14 visits).
Low moderate quality	An increase was observed in the limit of statistical significance in perinatal mortality in the reduced visits group compared with standard perinatal care (Majoko, 2007; McDuffie, 1996; Munjanja 1996; Sikorski, 1996; Villar, 2001). However, no significant differences were observed in the number of preterm newborns (Binstock, 1995; Majoko, 2007; McDuffie, 1996; Munjanja, 1996, Sikorski, 1996; Villar, 2001, Walker, 1997) or in the number of newborns small for gestational age (McDuffie, 1996; Munjanja, 1996, Sikorski, 1996; Villar, 2001).

From evidence to recommendation

The aspects that have determined the strength and direction of this recommendation were:

1. Moderate / low quality of evidence.
2. The balance between benefits and risks. There is uncertainty about the balance of benefits and risks of the intervention. The mean difference in the number of visits between the two groups in the studies was approximately two. In the context of routine perinatal care in developed countries (10-14 visits), a difference of two visits are unlikely to show a measurable impact on pregnancy outcomes (NICE, 2008).
3. Costs and use of resources: in the SR by Dowswell (2010) two studies assessed the costs of the intervention (Villar, 2001; Sikorski, 2001). The RCT by Sikorski (2001), carried out in England, observed a reduction in the cost to the NHS with perinatal care programs with reduced visits versus standard perinatal care (251 £ (about 310 euros) compared to 225 £ (about 278 euros, respectively). Although there was an increase in costs related to the duration of stay of the newborns in the intensive care unit (181 £ (about 223 euros) compared to 126 £ (about 155 euros), respectively). The RCT by Villar 2001 included an economic analysis on two of the four participating countries (Cuba and Thailand). The results showed that the costs per pregnancy for women and providers were lower in the reduced visits model than in the standard perinatal care one.
4. Values and preferences of pregnant women: the SR by Dowswell (2010) found that women in countries of low and high income were less satisfied with the reduced visits model; some of them realised that the time between visits was too long (Dowswell, 2010).

The direction of the recommendation has therefore been established on the basis that there were no statistically significant differences observed between perinatal care programs with reduced visits (4 to 9 visits) versus standard perinatal care (13 to 14 visits) for results related to women or neonates. Despite the increased risk associated with perinatal mortality, the results were not statistically significant. Moreover, the evidence identified comes from indirect identified as the SR by Dowswell (2010) includes studies in high and low-income countries. Women were less satisfied with the reduced scheme visits and the costs of the reduced visits program were lower, but there was an increase in costs in relation to the duration of hospital stay of newborns, which determined the strength of the recommendation. In the section on diagnostic and therapeutic strategies, the contents of each proposal are presented.

Recommendation

Weak	We suggest a monitoring program of between 6 and 9 visits for women at low risk of complications during pregnancy or childbirth.

Contents of the medical history

An RCT comparing three modes of medical records for data collection during the first perinatal visit of 2,424 British women (Lilford 1992) has been identified. The study evaluated the number and clinical significance of a series of actions derived from the recording of information in a history described as unstructured, structured, or a computerised third history.

Moderate quality

The results of this RCT showed that the two modalities of structured medical history contributed to better gathering of information and derived in a better performance to address the risk factors identified in the medical record, when compared to an unstructured modality (actions arising from the information in the history in unstructured modalities: 1,063 versus those structured: 2.268, $p < 0.05$).

The clinical relevance of the actions that were derived from the information in the medical records was less in the unstructured modality than in the structured form. The authors of the RCT claimed that the computerised medical history does not provide more benefit than a simple structured one, since it only contributed to the implementation of the most relevant actions in one (symptoms, 191 against 179 actions, $P = 0.05$) of the seven data categories evaluated (medical and surgical, obstetric, personal, actions related to maternal age, cervical cancer screening and dental hygiene).Ultimately, the authors concluded that the use of a structured medical history contributes to a better response to the risk factors identified during the anamnesis.

Other clinical practice guidelines

Following are the basics that a medical history should include. These have been taken from various sources where the relevance of these aspects for the evolution of the health of pregnant women and the pregnancy is emphasised (ACOG, 2006; CSGC, 2007; NICE, 2008, ACOG, 2010; ICSI, 2010).

Personal details

- Age.
- Place of origin.
- Marital status.
- Language.
- Address and phone (or other contact details).

Psychosocial history

Perinatal evaluation of this aspect facilitates identification to health professionals of the main psychosocial risk factors (Austin, 2008), which significantly affect the health of pregnant women and the outcome of the pregnancy (ACOG, 2006). Since some of these factors may change during pregnancy, it is preferable to repeat this evaluation each trimester (ACOG, 2006).

- Socioeconomic status.
- Academic background.
- Existence of difficulties or barriers in communication.
- Domestic work and family responsibilities (caring for children, elderly or dependent people).
- Work activity (type of employment and possible risks (work fatigue, poor posture, shift work, exposure to toxics, harassment)). Although the work activity itself poses no risk for pregnancy, some aspects related to the job and its characteristics have been associated with poorer pregnancy outcomes (ICSI, 2010): working more than 36 hours per week or 10 hours a day, lifting heavy objects, excessive noise, work standing more than four hours per shift, work stress, cold working environment, exposure to chemicals (anaesthetics, solvents or pesticides).
- Working on double-shift.
- Cohabitation and stability of residence.
- Women with a partner: contact details, age, work activity, responsibility for housework.
- Existence of personal or family problems:
    - Unwanted pregnancy and / or desire to interrupt pregnancy;
    - Evaluation of family support and possible existence of problems or conflicts with relatives;
    - Possible existence of violence following the protocols available. All women should be asked on possible genre violence at different times of the pregnancy (first perinatal visit, and postpartum quarterly visit) (NICE, 2008; ACOG, 2012).
- Acceptance of pregnancy and experience of the situation.
- Assessment of emotional factors, stress, and mental disorders. In disorders such as depression, prevalence during the first trimester of pregnancy may be as high as 19%, therefore the perinatal visit is an opportunity to identify women with an increased risk (Gavin, 2005; ACOG, 2010).
- Consumption of alcohol, tobacco or other addictive substances.

Family history

Collection of information relating to any diseases that can be transmitted or have an impact on the offspring (diabetes, birth defects, hereditary diseases, Down syndrome, twin, etc.).

Personal history

- Previous illnesses.
- Infectious diseases.
- Vaccinations.
- Endocrine and metabolic disorders.
- Thromboembolic disease.
- Transfusions.
- Surgical interventions.
- Autoimmune disorders.
- Antiphospholipid syndrome.
- Hypertension.
- Kidney disease.
- Mental health disorders.
- Drug allergies.
- Drug abuse.
- Habits and lifestyle (diet, exercise, rest, and sleep).

Gynaeco-obstetric background

- Type of menstrual cycle.
- Contraceptive methods used previously.
- Genital mutilation.
- Previous sterility of partner.
- Pregnancies and births:
    - Evolution of pregnancies
    - Previous abortions.
    - Features of delivery.
    - Satisfaction with the birth experience.
    - State and weight of newborns.
    - Current health status and parenting difficulties.
    - Experience with breastfeeding and duration

Current pregnancy

- Date of last menstruation.
- Calculation of gestational age and possible birth date.
- Planned pregnancy.
- Evolution of pregnancy:
    - Common problems.
    - Complications.

Exposure to toxic substances, drugs or radiation.

Summary of evidence

Moderate quality	Using a structured medical history at the first perinatal visit improves the collection of information and allows a better response to the risk factors identified during the anamnesis (Lilford 1992).

From evidence to recommendation

The Working Group made the following recommendations given the clear benefit of collecting information in a structured medical history, which in any event will exceed an unlikely injury to the mother, at minimal cost, and without identifying any type of reluctance or variability among women.

Recommendations

Strong	We recommend that at the first prenatal visit an anamnesis be made by recording the information in a structured medical history in order to assess the overall status of women and to identify possible risk factors.
√	The medical history should be updated during every follow-up pregnancy visit.
√	All information should be registered and shared in a computerised medical record to facilitate the integration of all levels of health care (primary and hospital).

Utility routine screening of Body Mass Index (BMI), weight monitoring, measurement of blood pressure, breast examination, and pelvic examination during pregnancy. Utility of universal screening for hypertensive disorders and cervical cancer.

Weight and body mass index (BMI)

There are no quality studies evaluating potential foetal outcomes arising from weight control, therefore, a number of observational studies that demonstrate the importance of the weight of the mother and its change during pregnancy to foetus results have been assessed. Some of these studies have been evaluated in other clinical practice guidelines (P. Brocklehurst et al., 2008) to assess the usefulness of measuring the weight and BMI at perinatal visits.

Low quality

A retrospective study carried out on 1,092 women showed that the only measures that had an association with the newborn's weight, having considered confounders such as parity, age, and smoking, were the weekly weight gain and the mean maternal size at each visit (Rode, 2007). The study showed that low maternal weight (<51 kg) was the best indicator to detect a small infant for gestational age. Similarly, a low weekly weight gain of the pregnant woman (<200 g) was also an indicator of a small infant for gestational age. These indicators had limited positive predictive value (20% and 13% respectively).

Weight gain during pregnancy varies between 7 and 18 kg in women with an uncomplicated pregnancy and giving birth to babies between 3 and 4 kg (P. Brocklehurst et al., 2008). A prospective study performed on nearly 7,500 women in their first pregnancy compared the outcomes of women who gave birth at term with those who had a pre-term delivery without showing any differences in weight gain during the first trimester between the two groups (Siega-Riz, 1996). The study showed that a BMI <19.8 kg / m2 before pregnancy and inadequate weight gain during the third trimester (<300 g and <350 g) increased the risk of preterm delivery (OR 1.98 for BMI, 95 1.33 to 2.98%, poor weight gain OR 1.91, 95% CI 1.40 to 2.61).

A prospective study carried out on 41,500 women attending their first perinatal visit between weeks 11 and 13 showed that BMI was the aspect which, combined with other characteristics of the mother, further contributed to an increased risk of abortion (OR 1.03, 95% 1.01 to 1.05), perinatal death (OR 1.05, CI 95% 1.03 to 1.08), preeclampsia or gestational hypertension (OR 1.07, 95% CI 1.06 to 1.08), gestational diabetes (OR 1.11, CI 95% 1.10 to 1.12), giving birth to a little baby (OR 0.97, CI 95% 0.96 to 0, 98) or a large baby for its gestational age (OR 1.08, CI 95% 1.07 to 1.09), or giving birth by both elective (OR 1.05, 95% CI 1.04 to 1.06) and emergency caesarean section (OR 1.06, CI 95% 1.06 to 1.07). Complications increased exponentially with an increasing BMI of the mothers (Syngelaki et al., 2011).

A study analysed the data of 5,377 pregnant women from a database of a population-based cohort to relate BMI before pregnancy to weight gain during pregnancy and a series of maternal events and the newborn (Crane, 2009). The study showed that women who had a weight gain during pregnancy within the recommended parameters had fewer complications than women who had excessive weight gain (OR 1.53, 95% CI 1.17 to 1.99). In women with a normal BMI or overweight before pregnancy, excessive weight gain during pregnancy increased the risk of gestational hypertension (normal BMI OR 1.27, 95% 1.08 to 1.49, overweight OR 1.31, 95% 1.10 to 1.55) and giving birth to a baby> 4 kg (normal BMI OR 1.21, 95% CI 1.10 to 1.34; overweight OR 1.30, CI 95 % 1.15 to 1.47). In women with obesity, excessive weight gain during pregnancy increased the risk of giving birth to a baby>4 kg (OR 1.20, CI 95% 1.07 to 1.34) and metabolic abnormalities in the newborn (OR 1.31, CI 95% 1.00 to 1.70).

The study noted that weight gain between 6.7 and 11.2 kg in women with overweight and less than 6.7 kg in women with obesity is associated with a reduced risk of complications.

Screening for preeclampsia

Low quality

The measurement of blood pressure is recommended in various clinical practice guidelines as a strategy for screening for preeclampsia at the first perinatal visit and then in the rest of visits as a way to control the appearance of hypertensive problems occurring during the pregnancy (USPTF, 1996, Brocklehurst P. et al, 2006).

The U.S. Preventive Task Force recommendations remain in effect since 1996, and the clinical practice guideline from NICE (2008) based its recommendations on the results of three observational studies (Reiss, 1987; Odegard, 2000; Stamilio, 2000) and one RCT (Sibai, 1995) in which different risk factors for preeclampsia were evaluated. The studies evaluated in the NICE document are the most relevant in this regard and other studies have not been considered for this clinical practice guideline. There are no studies comparing the results of performing or not a screening for preeclampsia, so this section is based on the results of studies that establish a relationship between blood pressure levels in early pregnancy and preeclampsia.

An American study of cases and controls compared the medical records of 30 pregnant women with preeclampsia with 30 normotensive controls (Reiss, 1987). Similarly, in a nested Norwegian case-control study, possible risk factors for preeclampsia in 323 women who were matched with 650 healthy controls (Odegard, 2000) were evaluated. In a retrospective cohort study, cases of women with preeclampsia were compared with a series of controls in terms of their clinical features and the results of biochemical markers. This comparison served to validate a clinical prediction in which a predictive value for each woman depending on the presence or absence of predictive factors (Stamilio, 2000) was assigned. Finally, in the course of an RCT on the benefit of low-dose aspirin in pregnant women with preeclampsia, the characteristics that could predict the occurrence of this hypertension problem were sought to be identified (Sibai, 1995).

The results of the Norwegian case-control study showed that a systolic blood pressure ≥130 mmHg compared to <110 mmHg values at a prenatal visit before 18 weeks of gestation was associated with the risk of preeclampsia in late pregnancy (OR 3.6, 95% CI 2.0 to 6.6). A similar relationship was observed, although not statistically significant in the diastolic pressure values ≥80 mmHg compared to <60 mmHg (OR 1.8, 95% CI 0.7 to 4.6) (Odegard, 2000). The only factors that had a predictive value in the validation study of a clinical prediction guide (with a sensitivity of 74% and a specificity of 46%) were the facts of not having given birth before, history of preeclampsia, a low concentration of estriol or high blood pressure in the prenatal controls (RR for the latter factor 3.5, 95% CI 1.7 to 7.2) (Stamilio, 2000).

Moreover, the American case-control study showed that both systolic and diastolic blood pressure were significantly higher in women with preeclampsia in the first trimester than their controls. This difference persisted throughout pregnancy and was repeated 6 weeks after childbirth (Reiss, 1987). The levels of systolic and diastolic blood pressure at the first prenatal visit of the participants treated with aspirin were also associated to an increased risk of preeclampsia (Sibai, 1995).

The clinical practice guideline from NICE (2008) also highlights the usefulness of a test protein in urine from the results of an American retrospective study. In this study, the foetal outcomes of 53 women who underwent testing for proteinuria were evaluated. The aim was to determine the relevance of detecting certain values during pregnancy, which in other situations could be considered as an asymptomatic proteinuria (Stettler, 1992).

Low quality

The results showed that the determination of the presence of protein in urine was related to the development of preeclampsia. 58% of women who presented proteinuria and renal failure developed preeclampsia, while all women with proteinuria and chronic hypertension, developed preeclampsia.

This same guide stated that there is no method to determine the risk of preeclampsia with sufficient diagnostic performance (Brocklehurst P. et al, 2008.), though it does emphasize a number of risk factors to be taken into account during the perinatal visit:

Other clinical practice guidelines

- Women ≥40 years old.
- Nulliparity.
- Interval between two pregnancies longer than 10 years.
- Family history of preeclampsia.
- ≥30 BMI kg / m2.
- History of vascular or kidney disease.
- Multiple pregnancy.

The guide recommends more frequent monitoring of blood pressure in women who have been identified with any of these risk factors, and warns that the determination of hypertension or proteinuria in any perinatal visit should alert the healthcare professional.

It also describes a number of preeclampsia symptoms, which should warn the pregnant woman in case she notices them and immediately contact a health professional:

- Severe headache
- Vision problems (blurred vision or flashes behind his eyes).
- Sharp pain under the ribs.
- Vomiting.
- Sudden swelling of the face, hands, or feet.

Breast examination

A Cochrane SR (Lee, 2008) and the clinical practice guideline on pregnancy care carried out by NICE (P. Brocklehurst *et al*., 2008) assess the need for a breast examination during the physical examination. This procedure has been proposed as a possible strategy to anticipate problems during breastfeeding by determination of flat or inverted nipples.

Low quality

On the other hand, self-examination or clinical breast examination has shown no benefit as screening method for early diagnosis of breast cancer. A Cochrane SR (Kösters, 2003) included two large clinical trials involving 388,535 women who

Moderate quality

performed self-examination, or were assigned to a control group in which no action was performed. An update of this systematic review identified a clinical trial evaluating the clinical examination combined with breast self-examination, but the study was stopped due to poor compliance with the follow-up procedure.

Breast self-examination did not contribute to decrease mortality from breast cancer when compared to not taking the exam (2 ACA, 587 deaths in total, RR 1.05, 95% 0.90 to 1.24). By contrast, self-examination was effective in double the women who underwent biopsy as they were identified a benign lesion (3406) compared to the women who did not perform any action (1.856) (RR 1.88, CI 95% 1.77, 1.99).

Gynaecological examination

Low quality

The clinical practice guideline from NICE (2008) (P. Brocklehurst et al., 2008) presents the results of an RCT in which the rate of premature rupture of membranes was compared among 174 women who had not undergone any exploration and 175 women who underwent digital exploration routinely (Lenihan, 1984). Women who underwent a gynaecological examination accounted for three times more cases of membrane premature rupture than those who had not undergone this control (p = 0.0001 6% versus 18%). Additionally, a further RCT has been identified (Jenniges, 1990) which compared the outcomes of 56 women in whom a weekly scan was performed after 37 weeks of gestation with 45 women who had not carried it out; it also showed a higher percentage of membrane premature rupture in women who underwent exploration (18% versus 13%), although the difference was not statistically significant. A final RCT performed on 604 patients which performed the same comparison as the RCT by Jenniges (1990) found no significant difference in cases of premature rupture of membranes between the groups compared (McDuffie, 1992).

The clinical practice guideline does not provide either a value to this method for the detection of ovarian cysts by their low incidence during pregnancy (1 in 15,000 to 32,000 women), as these can be detected by ultrasound examination (P. Brocklehurst et al., 2008).

Pelvimetry

Low quality

A Cochrane SR (Pattinson, 1997) reported the results of four RCTs in about 900 women, which showed that the X-ray pelvimetry increases the risk of caesarean section (OR 2.17, 95% CI 1.63 to 2.88) without providing any additional benefit to the mother, foetus, or newborn.

Membrane separation

Moderate quality

Membrane separation during the gynaecological examination aims to initiate labour by increasing local production of prostaglandins, thus trying to avoid formal induction of labour with other methods such as oxytocin, prostaglandins, or amniotomy.

A Cochrane systematic review (Boulvain, 2005) included 22 RCTs (with 2,797 women) evaluating the separation of membranes for the induction of labour in the third trimester. Studies performed this procedure only in women at term.

The Cochrane SR showed that the separation of the membranes performed on women with term pregnancies was associated with a reduction in the duration of the pregnancy and the frequency of pregnancies which continued beyond 41 weeks (6 RCTs, 937 women, RR 0.59, CI 95% 0.46 to 0.74) and 42 weeks (6 RCTs, 722 women, RR 0.28, 95% CI 0.15 to 0.50). On the other hand, a considerable number of women felt discomfort during vaginal examination (2 RCTs, 320 women, RR 2.83, 95% 2.03 to 3.96) and other adverse events as mild bleeding (3 RCTs, 391 women, RR 1.75, 95% 1.08 to 2.83) or irregular contractions. The authors of the SR concluded that, although the separation of the membranes has been proved to promote labour, it cannot be justified as a routine procedure in women with an uncomplicated pregnancy before term (between weeks 37 to 40).

The National Strategy for Sexual and Reproductive Health (ENSSR, 2011), in the section dealing with the procedures for visits and monitoring of pregnancy, explicitly dissuades routine pelvic examination for all women, as well as performing the Hamilton manoeuvre in healthy women with no indication of pregnancy completion.

Screening for cervical cancer

Low quality

Several reviews of the literature (Hunter et al, 2008; McIntyre-Seltman et al, 2008.; Yang, 2012) emphasize that cervical cancer is one of the most neoplasms diagnosed during pregnancy with an incidence in the USA estimated at 1.2 cases per 10,000 pregnancies (Yang, 2012), which means that up to 3% of new cases of cervical cancer are diagnosed in pregnant women. This fact can be attributed to the fact that this cancer screening is included in the tests included in perinatal visits (McIntyre-Seltman et al., 2008).

These data and the opportunity to make contact with women with an increased risk of infection by the human papilloma virus at the perinatal visit has led some authors to recommend that a Pap smear is performed to all women during the first perinatal visit (Hunter et al., 2008). However, no RCTs or controlled studies that have evaluated the usefulness of screening for cervical cancer in pregnant women have been identified. Nevertheless, four observational studies that have evaluated the results derived for screening for cervical cancer during pregnancy have been identified (Abe, 2004; Morimura, 2002; Sarkar, 2006; Nygård, 2007).

In a large Japanese cohort study the results of 28,616 women (half of them younger than 30) who had undergone a cervical cytology at the first perinatal visit with those of 108 289 participants were compared in a population screening program (Abe, 2004). The results showed a higher percentage of women with a cytology result requiring more intensive monitoring in pregnant women than among the participants i n the screening program (1.12% versus. 0.84%, P <0.001). Younger women showed more often results that required more intensive control. The authors concluded that implementing a cervical cancer screening at the perinatal visits is a good opportunity to identify women with this neoplasm, a fact that may lead to reduce the morbidity associated with this disease. A previous similar study carried out in 1,593 pregnant women who had undergone a cytology compared these results with those of 214.375 participants in a Japanese population-screening program (Morimura, 2002).

The cytology showed abnormal results in 1.63% of women that led to the diagnosis of cervical cancer in 0.82% of women. The incidence of abnormal cytology results was significantly higher than the one of participants in the screening program (1.63% versus. 0.9%, p <0.001), but there were no differences in those cases diagnosed with cancer (0.82% versus 0.46%).

A final retrospective study evaluated the results of 100 Irish women who had undergone screening for cervical cancer during one of their perinatal visits (Sarkar, 2006). The cytology results were abnormal in only 6% of women, being similar results to those of other non-pregnant women, which made the authors of the study conclude that the perinatal cervical cancer screening is an opportunity to identify those women at higher risk.

Notably, 36% of citologies showed a result that the authors defined as unsatisfactory

Furthermore, in a Norwegian population cohort the extent to which the performance of a cervical cytology during pregnancy had an impact on the coverage of a population-screening program for cervical cancer was assessed (Nygård, 2007). The study showed that the cytology was performed in 69% of pregnant women during the follow-up year from the beginning of their pregnancy. During the monitoring period, the possibility of performing a citology in a pregnant woman quadrupled that of non-pregnant women (OR: 4.3, 95% CI 4.2 to 4.4).

The results also indicated that it was much more common to carry out a cytology on a pregnant woman as a response to the letter of invitation to participate in a screening program, than on women who were not pregnant (63.2% versus 28 7 %, OR: 2.1, 95% CI 1.9 to 2.4).

Nevertheless, these studies do not take into account the impact a false positive result can have on women, or the determination a cytology with abnormal results can have on the morbidity and mortality of cervical cancer.

In the absence of RCTs on the usefulness of performing screening for cervical cancer in pregnant women, the modest results of observational studies (Morimura, 2002), the impact of false positive results and the fact that the quality of the sample cells in a cytology taken during pregnancy may become unreliable, the European recommendations for screening and diagnosis of cervical cancer discourage screening during this period (Arbyn, 2008). This clinical practice guideline recommends the delay of a cytology in pregnant women with a previous negative result up to 6 or 8 weeks after childbirth, except in those cases in which the results of the last cytology are 5 years old or there is a doubt about the participation of women in a screening program. The cytology should be performed only in the case of a woman with an abnormal result who gets pregnant in the interval between two control sessions (Arbyn, 2008).

Summary of evidence

Low quality	A pathological body mass index of women prior to pregnancy and little or excessive weight gain during pregnancy are associated with several complications like pre-term childbirth (Siega-Riz, 1996,) perinatal death, abortion, gestational diabetes, giving birth by caesarean section (Syngelaki, 2011), gestational hypertension, or giving birth to a small or large infant for its gestational age (Syngelaki, 2011; Crane, 2009).
Low quality	High values of systolic and diastolic blood pressure have been associated with an increased risk of occurrence of preeclampsia in pregnancy (Reiss, 1987; Sibai, 1995; Odegard, 2000). Similarly, high blood pressure values in perinatal controls have shown an adequate predictive value of risk of preeclampsia (Stamilio, 2000).
Low quality	Identification of proteinuria in the pregnant woman is associated with the development of preeclampsia (Stettler, 1992).
Moderate quality	There are no adequate studies to conclude that breast examination brings any benefit to promote breastfeeding, or as a method of screening for breast cancer (Kösters, 2003, Lee, 2008; NICE, 2008).
Low quality	Pelvic examination has proved to increase the risk of premature rupture of membranes and not to provide any additional benefit (Lenihan, 1984; Jenniges, 1990). The procedure has also shown to have no value in the detection of ovarian pathology (P. Brocklehurst et al., 2008).
Low quality	Pelvimetry X-rays increases the risk of caesarean section (OR 2.17, 95% CI 1.63 to 2.88) without providing any additional benefit to the mother, foetus, or newborn (Pattinson, 1997).
Moderate quality	The separation of the membranes showed to foster labour, but has no justification as a routine procedure in women with an uncomplicated pregnancy before term (between weeks 37 to 40) (Boulvain, 2005).
Low quality	Although it has been suggested that performing a cervical cytology at perinatal visits is an opportunity to identify women with an abnormal result (Hunter et al., 2008), there are no clinical trials on the usefulness of screening for cervical cancer among pregnant women. Likewise, observational studies have shown that the number of women who were diagnosed with cervical cancer derived from results of a cytology during pregnancy was low and very similar to that of women who were diagnosed with cancer after participating in a screening program (Morimura, 2002).
Other clinical practice guidelines	The recommendations at European level discourage conducting a cytology during pregnancy in women in whom the result of the last cytology is known, and suggest that the procedure should be delayed from 6 or 8 weeks after childbirth. Cytology in pregnancy should only be performed in women who have had one within more than 5 years, or in those cases where there is doubt about regular participation in a screening program (Arbyn, 2008).

From evidence to recommendation

The aspects, which have been measured to determine the direction and strength of the recommendations, were:

1. The low quality of evidence: The studies assessed in this section have been mostly observational, retrospective in some cases, and in no case has it been able to assess the possibility of increasing the quality of the evidence.
2. Balance between benefits and risks: The procedures assessed have shown an impact on the health of the pregnant woman. While weight changes by excess or defect during pregnancy and alterations in blood pressure are associated with major obstetric complications, breast and pelvic examination, pelvimetry, pelvic examination for membrane separation before term, as well as screening for cervical cancer have shown no benefit, and in the case of the second procedure, it may be associated with unwanted effects.
3. No studies examining the costs and use of resources or preferences of pregnant women on this question were identified.

The procedures in this section are evaluated depending on the impact of these interventions on the health of the pregnant woman and the value they have within prenatal care. While the initial measurement of height and weight of women, and controlling blood pressure have shown a clear impact on the health of pregnant women, the other procedures do not provide any value to prenatal screening. These arguments determined the direction of the recommendations. Moreover, the benefits of weight and height measuring of women at the first prenatal visit, and controlling blood pressure have a clear impact to avoid complications during pregnancy. The quality of evidence determined the strength of the recommendations.

Recommendations

Strong	It is recommended to calculate the BMI at the first prenatal visit, to identify those women who require weight gain monitoring during pregnancy.
Strong	Blood pressure should be measured at each prenatal visit to detect the risk of preeclampsia.
Weak	We suggest not carrying out a mammary exploration as a screening of breast cancer, or to promote breastfeeding or identify potential difficulties in breastfeeding.
Weak	We suggest not developing a gynaecological exploration during prenatal visits in order to predict the likelihood of a preterm delivery or detect any gynaecological pathology.
Weak	We suggest not developing a pelvimetry in order to assess the need for caesarean section in women with a baby with cephalic presentation at term.
Weak	We suggest not performing vaginal examinations or Hamilton's manoeuvre as a routine procedure in women with an uncomplicated pregnancy before term and who have no indication of completion of pregnancy.
Weak	We suggest not performing a cervical smear at the first prenatal visit to assess the risk of cervical cancer.
Weak	We suggest the determination of proteinuria at each prenatal visit to detect the risk of preeclampsia.

√	The smear should be delayed up to 6 or 8 weeks after childbirth in women with a history of negative smears and who should undergo a new screening test, except in cases where there is doubt about the monitoring of screening by woman or when more than 5 years have passed since the last smear.
√	Individualised assessment of weight during pregnancy should be performed avoiding routine weights in all prenatal visits.

Useful biochemical parameters during pregnancy

Determination of urea

No studies assessing the usefulness of determining blood urea levels in pregnant women with an uncomplicated pregnancy were identified. Only one study was identified in which the level of blood urea was measured as a predictor of pregnancy outcome in women with hypertension during pregnancy (Redman, 1973).

Study investigators determined the levels of urea in the blood of participants in an RCT on antihypertensives during pregnancy, in pregnant women up to 32 weeks of gestation with hypertension (two consecutive measurements with values ≥ 140/90 m Hg).

Other observational studies with design limitations, and which have been conducted among African population with significant differences from women of our environment have been identified. In one of them, the urea levels in blood were determined in a series of 109 Caucasian pregnant women and 117 African pregnant women residents in an urban area of Nigeria (Nduka, 1987). Both groups showed an increase in urea levels during pregnancy, which in the case of the Caucasian women was manifested from the 13th week of gestation and increased until the third trimester, a fact that the authors could attribute to a greater intake of foods rich in proteins. The study did not assess whether there was any relationship between this increase and the maternal or foetal outcomes. Another case-control study compared the levels of urea, creatinine, and uric acid of 34 Nigerian women with hypertension during pregnancy with 34 pregnant women without hypertension. In this study, urea levels showed no association with the risk of developing preeclampsia (Egwuatu, 1986). A recent similar study showed comparable results. Outcomes related to blood urea and uric acid of 27 pregnant women were compared to 17 Nigerian women who were not pregnant. The authors only discussed the role of the elevation of uric acid levels and its relation to proteinuria (Ahaneku, 2009).

Very low quality

The study by Redman (1973) collected 120 samples of women in weeks 28, 32 and 36 of gestation with a mean blood urea level of 15 mg / 100 ml and a maximum level of 45 mg / 100 mL. Although it did not provide values , which allow calculating incidence, the study authors stated that the weight of the newborn was lower in those mothers with higher urea levels. This was especially noticeable after 32 weeks of gestation in which urea levels above 20 mg / 100 mL increased the risk of giving birth to newborns with lower weight. At 36 weeks of gestation, this relationship was observed with blood urea values higher than25mg / 100 mL. Similarly, the study authors reported an increased risk of perinatal death above 15 mg / 100 mL after 28 weeks of gestation or 20 mg / 100 mL after 32 weeks ($p < 0.0001$), although once again the authors did not provide more information on this matter.

Summary of evidence

Very low quality	There are no studies, which have evaluated the usefulness of determining the levels of blood urea in pregnant women without risk of complications during pregnancy.

From evidence to recommendation

The very low quality of the evidence and the fact that the studies conducted in women with hypertension during pregnancy provide limited relevant data and present data, which do not apply to our environment, determined both the strength and the direction of the recommendation.

Recommendation

Weak	We suggest not determining the level of blood urea routinely in pregnant women.

Determination of creatinine

A retrospective study that evaluated whether the level of serum creatinine in the first 20 weeks of pregnancy could be a predictor marker of the development of preeclampsia during the second half of pregnancy (Wolak, 2011) has been identified. The study reviewed the medical records of all women who had given birth within a period of 7 years, excluding those cases that had not determined the level of creatinine, it was a multiple pregnancy, or had a diagnosis of hypertension or gestational diabetes. Plasma creatinine levels were obtained during the first 20 weeks of pregnancy of 8,890 women (9,341 births) from laboratory data and their possible relationship with the incidence of preeclampsia was evaluated.

Two other studies with similar objectives but with limited applicability of their results as they are studies exposed to considerable bias include a small sample and a population that may have features with large differences with respect to our environment (Salako et al. 2003). In a study carried out on 59 Nigerian women in their first singleton pregnancy without risk of complications, whether a measurement before the first 20 weeks of pregnancy of total serum protein, creatinine and uric acid could be a hypertensive predictor of other problems during pregnancy (Salako, 2003) was assessed. In a longitudinal study, the same markers were applied to 256 Sri Lankan pregnant women after 28 weeks of gestation and the determination of these levels was repeated every week until week 36 and thereafter at the time of delivery (Weerasekera, 2003).

The study by Wolak (2011) showed that high levels of creatinine in the first 20 weeks of pregnancy are associated with an increased risk of developing preeclampsia. When compared with women without hypertensive disorders during pregnancy, the study showed that women with mild preeclampsia had significantly higher mean levels of creatinine in the first 20 weeks of pregnancy (creatinine level in women without preeclampsia (n = 8,890): 51 mmol / L ± 13 versus creatinine levels in women with mild preeclampsia (n = 345): 53 mmol / L ± 11, P = 0.026). Women with severe preeclampsia (creatinine levels (n = 106): 54 mmol / L ± 15, P = 0.043) or who developed a hypertensive disorder (creatinine levels (n = 451): 53 mmol / L ± 13, P = 0.003) also showed higher levels than women without hypertension disorders. A ROC curve analysis confirmed a significant association between the level of serum creatinine in the first 20 weeks of pregnancy and the development of moderate preeclampsia (area under the curve 0.54, 95% CI 0.51 to 0.57; p = 0.02) or severe (area under the curve 0.56, 95% 0.50 to 0.62, p = 0,03)

Very low quality

Furthermore, the Salako (2003) study results showed no relationship between the average levels of creatinine (n = 59, 93.7 mmol / L ± 11) and the risk of hypertensive disorders during pregnancy. The study by Weerasekera (2003) also showed a difference between women with preeclampsia and hypertensive women without problems (59 women with preeclampsia compared to 197 women without hypertension, 0.74 mg / dL versus 0.69 ± 0.05 mg / dL ± 0.07).

Summary of evidence

Very low quality	Although the results are not consistent across studies, a study with a large sample has shown that the level of serum creatinine in the first 20 weeks of pregnancy may be a predictor of the development of moderate preeclampsia.

From evidence to recommendation

Although the results of the study by Wolak (2011) in favour of the intervention were based on a large sample study, this is a retrospective study of discrete outcomes. Moreover, the results are not consistent with other studies (on the other hand, studies with design limitations and study samples can provide results that are not applicable to our setting). This helped to determine the direction of the recommendation. Moreover, the lack of quality of the studies that evaluate the procedure and the lack of data to establish a better balance between the potential risks and costs resulted in a weak recommendation.

Recommendation

Weak	We suggest not determining the level of creatinine in blood on the initial biochemical assay to control the risk of hypertension during pregnancy in women with no risk of complications during pregnancy.

Determination of uric acid

Given that hyperuricemia is a factor observed in many women with preeclampsia, numerous studies have tried to relate the high levels of uric acid in women with hypertension during pregnancy with adverse maternal and foetal outcomes.

A systematic review (Meads, 2008) prepared by the Health Technology Assessment in 2008 with the aim of identifying possible combinations of diagnostic tests and treatments that help predict and prevent preeclampsia has been identified. One of the 27 diagnostic tests included in this review was the determination of serum uric acid. To determine the predictive diagnostic accuracy five prospective observational studies that evaluated 514 women without preeclampsia were included. The mean age of the women ranged from 23.8 to 28 years and the gestational age at which the test was carried out ranged between 20 and 24 weeks of gestation. The reference tests used were the systolic or diastolic blood pressure and / or proteinuria levels (≥100 to 300 mg / l).

In addition, two SRs evaluating the role of uric acid in pregnant women who already had a diagnosis of preeclampsia to predict health complications of the pregnant woman and foetus, with conflicting results (Thangaratinam, 2006; Koopmans 2009) have been identified. Thangaratinam (2006) conducted a search for studies (until 2004) which evaluated the performance of the blood levels of uric acid in women with preeclampsia as a predictor of complications. These included 18 studies with 41 evaluations in different degrees of severity of preeclampsia, with 3,913 women. The results from the positive and negative (LR + and LR-) likelihood ratios of the test for

eclampsia, severe hypertension, caesarean birth, infants small for gestational age, and neonatal death were presented.

Subsequently Koopmans (2009) developed an SR with the same aim of correcting a number of limitations of the SR by Thangaratinam (2006): using the likelihood ratio as the measure of effect, and the fact of presenting the results to a single cut-off point, ruling out the possibility that higher cut-off points could make the predictive value of uric acid higher. The authors of this SR updated the search until 2007 and evaluated the same studies as in the previous SR, restricting the analysis to maternal outcomes (eclampsia, severe hypertension, and caesarean section childbirth). A bivariate analysis combined the sensitivity and specificity data of the eight included studies (1,565 women) and developed a clinical decision analysis based on a decision tree with three scenarios. For a woman with mild preeclampsia (blood pressure of 160/95 mmHg, proteinuria 700 mg / 24 h and normal laboratory values) at 37 weeks of gestation with a foetus in good condition (growth at the 50th percentile, normal amniotic fluid and normal foetal movements), the following situations were identified: i) expectant management with monitoring until delivery (worst case scenario with the possibility of serious complications); ii) induction of labour (possibility to reduce complications but with risk of caesarean section); and iii) determination of uric acid to induce labour only if abnormal results are evident. From these epidemiological data, a number of incidences of various complications were evaluated and an indicator to express how much worse would it be to suffer a complication during pregnancy compared to having a caesarean section delivery was defined.

Estimates regarding cumulative sensitivity and specificity from the determination of serum uric acid to predict the occurrence of preeclampsia in non-hypertensive women were 36% (95% CI 22-53%) and 83% (95% CI 73 to 90%), respectively. **Very low quality**

Table 3 shows the results of the SR by Thangaratinam (2006) for eclampsia, severe hypertension, caesarean section, infants small for gestational age (PEO in the table) and neonatal death outcomes. **Low quality**

The authors of this review concluded that although uric acid may have a role to detect preeclampsia, it is not a good predictor of complications during pregnancy.

Although the results for some of the outcomes showed RV + suggesting, for example, twice as likely that a value of uric acid ≥350 mmol/L predicted a caesarean section delivery, the authors considered that a test had a clinically acceptable predictive value of LR + greater than 2 and 5. Furthermore the confidence intervals of some RV- cross the threshold of 1, indicating the possibility of detecting the same number of complications in women with normal uric acid values as in women with a ≥350 mmol / L value.

Although Koopmans (2009) sought to overcome the possible limitations of the SR by Thangaratinam (2006), the complexity of the analysis and the many assumptions made in the analysis of clinical decision greatly limit the applicability of the results of the SR. **Very low quality**

This SR included eight studies in which highly variable sensitivity (0.15 to 0.92) and specificity (0.32 to 0.95) values were shown in the estimation of the complications derived of preeclampsia. The authors simulated a scenario in which it is assumed that suffering a complication during labour would produce an experience 10 times worse than having a caesarean section delivery, and assumed a complications rate between 2.9% and 6.3%, based on epidemiological data in the Netherlands. Given the parameters of this assumption, the authors stated that the preferred strategy in clinical practice would be to perform a routine determination of uric acid and acting according to the results.

Summary of evidence

Very low quality	The identification of high levels of serum uric acid showed accumulated sensitivity and specificity levels for the prediction of preeclampsia between 36% and 83%, respectively.
Low quality	The determination of uric acid has shown mixed results and seems to have a very moderate value to predict pregnancy complications (eclampsia, severe hypertension or caesarean delivery) and foetal health (newborns small for gestational age or neonatal death) (Thangaratinam, 2006).

From evidence to recommendation

The aspects that have been measured to determine the direction and strength of recommendation were:

1. The quality of the studies that included normotensive pregnant women was considered very low since it was from observational studies that although these had a comparison group, in no case was there any justification found for increasing the level of quality. In the group of women diagnosed with preeclampsia, the quality of evidence was rated as low by serious limitations in the study design (most studies were retrospective (56%), did not perform a consecutive enrolment (85%) and were not blinded (100%)), and their heterogeneity (significant differences in the definition of preeclampsia among the studies, the determination threshold of uric acid, or the frequency of tests). Given that the studies were developed in women with preeclampsia, which is outside the scope of this guide, the results have a very limited applicability.
2. Costs and use of resources: an economic analysis that considered several scenarios with different combinations of diagnostic tests is included in the SR carried out by Meads (2008). However, it concluded that the most cost-effective technique to reduce the development of preeclampsia is probably the addition of an effective, feasible, and safe procedure that is applied to all pregnant women without a prior diagnostic test to assess the level of risk.
3. No studies examining the values and preferences of pregnant women in relation to this question were identified.

The direction of the recommendation was made taking into account the low sensitivity shown by the determination of serum uric acid as well as the mixed results it has shown in predicting pregnancy complications. The low quality of the studies reviewed, and the uncertainty about its effects on clinical outcomes determined that the recommendation be reformulated as good clinical practice.

Recommendation

√	The level of serum uric acid should be determined in the blood test carried out in the second trimester as a warning sign of preeclampsia in normotensive women.

Utility of universal screening for infections

Screening for syphilis

Syphilis is a sexually transmitted infection caused by Treponema pallidum. According to data in 2009, 2,506 cases of syphilis were reported in Spain, representing an incidence of 5.56 cases per 100,000 inhabitants. The annual incidence of syphilis experienced a significant growth between 2005 and 2008, followed by a levelling off in the last year (National Epidemiological Surveillance Network, 2009). Regarding congenital syphilis, in 2009 10 confirmed cases were reported, representing an incidence of 2.03 cases per 100,000 live births (National Epidemiological Surveillance Network, 2009).

An SR by the US Preventive Services Task Force (USPSTF) on screening for syphilis during pregnancy (Nelson, 2004) and a later update (Wolff, 2009) was identified.

In addition, another systematic review on interventions to reduce stillbirth and preterm birth (Barros, 2010) that assessed the utility of screening for syphilis was located, although it is a review focused on the applicability of these interventions in developing countries and most studies included participants with a high risk of syphilis, which do not correspond to the women in our context.

The SR by USPSTF included two cohort studies (Coles, 1998; Cheng, 2007). The study by Coles (1998) compared the reported cases of congenital syphilis in New York State during the previous year to the implementation of a mandatory program of universal screening for syphilis (n = 69) with those reported during the subsequent three years (n = 239).

The study by Cheng (2007) evaluated the impact of a universal screening program for syphilis in 418 871 pregnant women at 61 hospitals in a region in China. In this study, 94% of the participants were screened. 2019 cases of syphilis were diagnosed during the 3 years of study, the majority of which (92%) received treatment.

After the implementation of the program of mandatory screening from the Coles study (1998) a decrease of newborns with clinical manifestation of syphilis was observed as well as an increase in the proportion of infants with positive serologies but no symptoms (p = 0.002). The authors of the SR stated that these results were due to improved early detection, which allowed early treatment before the disease developed (Nelson, 2004). **Low quality**

The screening program from the study by Cheng (2007) allowed the diagnosis of syphilis in 2019 pregnant women within the three years of the study during which they were monitored until the end of their pregnancy in 79% of cases. Among these women, 92 cases of congenital syphilis were observed. Compared with a rate of 53.6 cases of congenital syphilis per 100,000 pregnant women, the implantation managed to reduce the rate of congenital syphilis to 22 cases per 100,000 pregnant women. A case of congenital syphilis was observed in 4.6% of pregnant women who had presented a positive serology outcome in the screening.

The SR by USPSTF discusses the unwanted effects resulted from the screening for syphilis in pregnant women in terms of false positives or false negatives that may be obtained from serological tests, specifically from the rapid plasma reagin (RPR) test and the VDRL (Venereal Disease Research Laboratory). **Low quality**

In this regard, a retrospective study analysed data from a database of about 300,000 women hospitalised in Vienna (Geusau, 2005). The incidence of syphilis

in this study was 1.8% and a false positive occurred in 0.26% of all study participants. However, the study results have limited validity because no disaggregated data for pregnant were offered, and the context of the study would have little applicability in primary care (Wolff, 2009). In another study, false positive results from the serological tests performed on 8,892 pregnant women at four urban hospitals in Bolivia (Tinajeros, 2006) were described. Of all samples collected, a false positive result was reported in 0.91% of the participants. Given these results, the authors of the SR by USPSTF consider that the unwanted effects resulted from the screening for syphilis in pregnant women do not in any case exceed their benefit (Wolff, 2009).

Summary of evidence

Low quality	Screening for syphilis in pregnant women has shown a reduction in the clinical manifestation of infection among newborns (Coles, 1998; Cheng, 2007).
Low quality	False-positive results from serology with RPR and VDRL tests are approximately 1%. (Coles, 1998; Cheng, 2007).

From evidence to recommendation

The aspects that were considered in determining the strength and direction of the recommendations were:

1. Quality of the evidence: all the results discussed come from observational studies, some of them retrospective, thus it is considered that the quality of evidence is low.
2. Balance between benefits and risks: the unwanted effects (in terms of false positive results from the serology) derived from the screening of syphilis in pregnant women do not in any case exceed their benefit.
3. No studies examining the costs and use of resources or values and preferences of pregnant women in relation to this question were identified.

Finally, a recommendation in favour, which considered the clinical benefit regarding the reduction of the clinical manifestation of infection among newborns derived from this screening, was formulated. The weak strength of the recommendation was determined by the quality of the evidence that supports it.

Recommendations

Weak	We suggest a routine syphilis screening to all pregnant women at the first prenatal visit.
√	Since syphilis-screening tests may produce false positive results, appropriate diagnostic protocols should be used.

Screening for Chagas Disease

A publication that summarizes the recommendations derived from the Resolution WHA 63.20 of the World Health Organisation (WHO) for the control and elimination of Chagas disease (Carlier et al., 2011) was identified.

Furthermore, the results of three studies that provide data on the experience of implementing a screening at a hospital in the province of Almería (Muñoz-Vilches et al., 2012) and two in Valencia (Barona-Vilar et al, 2011; Ramos-Rincon et al, 2012) are also discussed.

These studies are longitudinal studies examining the outcomes of case series. It is considered that the quality of the available evidence from these studies is low.

Carlier (2010) summarizes the main recommendations made by the WHO for the 'Prevention and Control of Congenital Transmission and Case Management of Congenital Transmission' (Carlier et al., 2011).

Other clinical practice guidelines

Carlier (2010) summarizes the main recommendations made by the WHO for the 'Prevention and Control of Congenital Transmission and Case Manageme nt of Congenital Transmission' (Carlier et al., 2011).

This Working Group determined that a screening for Chagas disease must be performed during pregnancy to identify women with *Trypanosoma cruzi* and therefore with risk of vertical transmission to their foetuses. The group recognized that there is no method to determine which female carriers will transmit the infection to their foetuses.

Based on these recommendations, in our context, a serological test should be performed to women: i) residents born in a non-endemic country or who have previously lived in endemic countries or whose mothers were born in an endemic country, and ii) residents in a non-endemic country who have received on any occasion a blood transfusion in an endemic country.

The recommended test for screening is the indirect immunofluorescence (IIF) test or the enzyme-linked immunosorbent assay (ELISA) (Otani et al, 2009; Remesar et al., 2009). Both tests are available at a low cost, with the drawback that the results are not immediate. The use of a rapid immunochromatographic test was also proposed for the first perinatal visit to perform a serological test for Chagas disease (Muñoz et al., 2009).

Today Catalonia (Chagas) and Valencia (Servici de Salut Infantil i de la Dona, 2009) have protocols for universal screening for Chagas disease in Latin American pregnant women.

Very low quality

In a number of cases the results of a screening for Chagas disease in a hospital in the province of Almería (Muñoz-Vilches, 2012) were tested. The study required the IFA and ELISA tests to all pregnant women from Latin America or who had resided more than a month in an endemic country on their first visit. The presence of the disease was confirmed with a positive outcome in the two tests. Of the 261 women screened in the period from 2007 to 2011, the disease was confirmed in four women (one from Argentina, one from Peru and two from Bolivia), yielding conflicting results in four women (two women from Peru with positive ELISA and negative IFA outcomes, a woman from Argentina and one from Colombia with negative ELISA and positive IFA outcomes). In all cases, the women were asymptomatic. This determination corresponded to a prevalence of 1.5%, extrapolated to 65 annual risk pregnancies in the hospital under study. No cases of vertical transmission were observed.

A similar study assessed the systematic screening for Chagas disease protocol compliance in Valencia and its results in a university hospital (Ramos-Rincon et al., 2012). In the period between 2008 and 2011, 295 LatinAmerican women attended a consultation and were required the IFA and ELISA tests. ELISA positive cases were confirmed by IFA and in those cases with both positive outcomes in the serological tests, a genomic amplification (real time PCR) was requested. Of the 295 women who attended the consultation, only 115 underwent screening (40% of protocol compliance); Chagas disease was diagnosed in only one case (0.3% prevalence).

Very low quality

Summary of evidence

Screening for Chagas Disease	
Very low quality	Carrying out a universal screening for Chagas disease in women from endemic areas may contribute to the detection of a prevalence of up to 11.4% (Barona-Vilar et al., 2011).
Expert opinion	It is convenient to perform a serological test to women: i) residents born in a non-endemic country or who have previously lived in endemic countries or whose mothers were born in an endemic country, and ii) resident in a non-endemic country who have received on any occasion a blood transfusion in an endemic country (Carlier et al., 2011).
Expert opinion	The recommended test for screening is the indirect immunofluorescence (IIF) test or the enzyme-linked immunosorbent assay (ELISA) (Carlier et al., 2011).

From evidence to recommendation

The following aspects were considered to determine the strength and direction of the recommendation:

1. Quality of evidence: the studies, which have provided data on the experience of implementing a screening for Chagas disease in pregnant women, are descriptions of case series, therefore their quality is considered low.
2. Balance between benefits and risks: the benefits of a screening for Chagas disease in all cases outweigh the risks or disadvantages of performing a serological test for pregnant women. It was considered that the benefit of early detection of this disease is important because chronic cases transmission may reach 6%, and in those cases of acute infection, a treatment cannot be established as effective treatments for the disease are contraindicated.
3. Costs and use of resources: a cost analysis study contrasted two models of decision against a hypothesis of no screening. In the model of the newborn, the cost effectiveness of screening was 96 euros per QALY gained compared to 125 euros per QALY gained for no screening. The results showed greater cost effectiveness in the model of the mother (96 euros per QALY gained for screening compared to 1,675 euros per QALY gained for no screening). Even when a fall in the prevalence of Chagas disease from 3.4% to 0.9% was calculated, the screening results were cost effective, with an increase of 37.5 euros per QALY gained.
4. No studies examining the values and preferences of pregnant women were identified.

Finally, when establishing the strength and direction of the recommendation, the benefit from the intervention, the absence of side effects for pregnant women and the cost benefit of this screening for the intervention were prioritized.

Recommendation

Strong	We recommend thatscreening for Chagas disease be offered at the first prenatal visit for all those women originating or having spent time in an endemic area.

Screening for chlamydia

It is estimated that the prevalence of chlamydia in Spain is around 4%, being the foreign origin, having a new sexual partner in the last 3 months and smoking for <12 months, the main risk factors associated (Evelin, 2010). The untreated chlamydia infection in women can lead to serious complications such as pelvic inflammatory disease, ectopic pregnancy, and chronic pelvic pain. During pregnancy, chlamydia infection can lead to neonatal conjunctivitis, pneumonia, and postpartum endometritis (www.cdc.gov/std/Chlamydia/ STDFact-Chlamydia.htm#Complications).

To know the utility of the universal screening for chlamydia in pregnant women, an SR by the *US Preventive Services Task Force* (USPSTF) was identified to formulate its recommendations on screening for chlamydia (Nelson, 2001) and its subsequent updates (Meyers, 2007a; Meyers 2007b).

The SR by the USPSTF identified two observational studies (Cohen, 1990; Ryan, 1990) that evaluated screening for chlamydia in pregnant women in their first version of the SR (Nelson, 2001). In the updates of this SR, no new studies to support its recommendations have been identified.

Cohen (1990) was a case-control study that compared the outcomes of 244 pregnant women treated with erythromycin with 79 women who had tested positive for chlamydia screening but had not responded to treatment, and with the 244 controls, which had no chlamydia and therefore had not been treated. It should be noted that the study was conducted in a university hospital serving mostly African-American women, with low-income and homeless. The high risk of such disease in the participants who took part in the study denotes that their results should be interpreted with caution.

The study by Ryan (1990) evaluated in a time series screening for chlamydia in pregnancy outcomes of 11,544 women at their first visit during pregnancy. The participants in this study had a high risk for chlamydia.

The case-control study by Cohen (1990) showed that screening for chlamydia and the subsequent treatment of the infection reduced the risk of preterm birth when the outcomes of pregnant women diagnosed with chlamydia and treated successfully were compared to those who did not respond to the treatment (7/244 versus. 11/79; OR: 0.16; 95% CI 0.06 to 0.47; p = 0.00002), as well as compared to pregnant women who had shown a negative result in the screening (7/244 versus 29/244; OR: 0.22; 95% CI 0.99 to 0.54; p = 0.0001). **Low quality**

The same study showed that women who had been diagnosed and successfully treated for chlamydia showed a lower frequency of premature rupture of membranes and preterm labour than women who had been diagnosed but had not responded to treatment. The results showed no significant differences when compared with women in the control group. **Low quality**

The time series of Ryan (1990) showed in a group of women who received no treatment despite obtaining a positive culture (n = 1,110), an increased risk of premature rupture of membranes and giving birth to a child with underweight, comparing their results with those of the treated women (n = 1,323) or who had a negative culture for chlamydia (n = 9,111).

Summary of evidence

Low quality	Chlamydia screening of pregnant women provides a clear benefit in obstetric outcomes in terms of reduced risk of preterm birth (Cohen, 1990), or premature rupture of membranes (Cohen, 1990; Ryan, 1990).

From evidence to recommendation

The aspects that were considered in determining the strength and direction of the recommendations were:

1. The low quality of evidence: the studies included in the SRs identified have not evaluated in a prospective and comparative manner the screening for chlamydia, and have been developed in women at high risk of infection, although they show consistent results. There is no evidence about the potential benefit of a screening in asymptomatic women.
2. The balance between benefit and risk: the benefit of a screening for chlamydia and a proper treatment of women with a positive result in all cases exceeds the potential unwanted side effects arising from this process, although this cannot be assessed for women at low risk for chlamydial infection.
3. Values and preferences of pregnant women: an Australian study (Bilardi, 2010) conducted in-depth interviews to 100 young pregnant women aged between 16 and 25 years who accepted undergoing screening for chlamydia. The results showed low awareness of the infection and its impact among the interviewees, and a good acceptance of screening and urine testing compared to other evidence.
4. No studies examining the costs and use of resources on screening for chlamydia were found.

Finally, the fact that no studies directly comparing the results of a screening for chlamydia versus those with regular care and that the available evidence is only applicable to women at high risk for chlamydia infection have been identified, determined both the direction and strength of the recommendations.

Recommendations

Weak	We suggest not performing a systematic chlamydia screening to all pregnant women.
Weak	We recommend offering a chlamydia screening for asymptomatic pregnant women who are at risk of sexually transmitted infections.

Screening for vaginosis

Screening for bacterial vaginosis in asymptomatic pregnant women

An SR by theUS Preventive Services Task Force (USPSTF) formulated its recommendations on screening for bacterial vaginosis during pregnancy (Guise et al., 2001) and a later update (Nygren et al., 2008) was identified.

A Cochrane SR (Us et al., 2009) was also identified but not assessed because it included only one study considered in the SR by the USPSTF.

The SR by the USPSTF has not identified studies comparing the results obtained from a screening for bacterial vaginosis in asymptomatic pregnant women with those of women who did not perform a screening (Nygren et al., 2008). The available studies evaluate the results derived from a diagnosis of bacterial vaginosis and institute the appropriate treatment to those women who have been identified with the infection.

The SR by the USPSTF identified in its initial version 7 placebo-controlled RCTs with a low risk of bias, but with a large variability in the method of diagnosis of bacterial vaginosis (Gram stain or Amsel criteria), the area of study, the risk of vaginosis in those participants taking part in the study, and an indication of the treatment for those women who had been identified with the presence of vaginosis (Guise et al., 2001): three RCTs used metronidazole, one RCT combined metronidazole and erythromycin and three RCTs used intravaginal clindamycin. The studies were performed during the second trimester of pregnancy. This review also evaluated the results of five RCTs carried out in women with permanent vaginosis and who had had a previous preterm delivery, but they have not been taken into considerations as they are outside the scope of this Clinical Practice Guideline.

The update of the new SR identified seven RCTs (Nygren et al., 2008). Three of these studies were conducted in pregnant women at low risk of vaginosis, two evaluated a treatment with clindamycin in women from 17 weeks of pregnancy, and another a treatment with metronidazole in South African women between 15 and 25 weeks of pregnancy.

The four RCTs included in the SR by Guise (2001) showed no benefit of a screening for bacterial vaginosis in asymptomatic women and treating them according to the screening results in any of the outcomes assessed. **Moderate quality**

No difference between the treatment of bacterial vaginosis was observed after the diagnosis resulting from screening and placebo in the absolute risk of preterm delivery at 37 weeks of gestation (3 RCTs, 2840 women; RAR 0.001; 90% CI -0.017 to 0.019). The update by Nygren 2008 (Nygren and Fu, 2008) included four new RCTs in this analysis showing very similar results (7 RCTs, 4477 women; RAR 0.006; 90% CI -0.009 to 0.022).

These results were also observed when the results were analysed in women at low risk of vaginosis (3 RCTs, 626 women; RAR -0.019; 90% CI -0.056 to 0.018).

Two of these studies showed that treatment for bacterial vaginosis after diagnosis resulting from screening increases, although not significantly, the risk of rupture of membranes (2 RCTs, 2095 women; RAR -0.014; 90% CI -0.027 to 0.000), while another showed no benefit. **Low quality**

Three RCTs showed that treatment of bacterial vaginosis after diagnosis resulting from screening influences the rate of newborns with underweight (3 RCTs, 3160 women; RAR -0.004; 90% CI -0.020 to 0.013). **Low quality**

Summary of evidence

Moderate quality	Screening for bacterial vaginosis in asymptomatic pregnant women and the treatment in accordance with the outcome of diagnosis offers no clinical benefit for major outcomes such as the risk of preterm labour or rupture of membranes (Guise, 2001; Nygren, 2008).

From evidence to recommendation

The lack of benefit of the intervention, and the fact that no studies directly comparing the results of a screening for vaginosis with regular care have been identified, determined both the direction and the strength of the recommendation.

Recommendation

Weak	We suggest not performing routine screening for bacterial vaginosis to all pregnant women.

Screening for rubella

Other clinical practice guidelines

Screening for rubella by reviewing the history of vaccination or by a serological test is recommended in the pre-conception visit to prevent the congenital rubella syndrome (ICSI, 2010), which during the first 12 weeks of pregnancy can lead to severe defects to the foetus (vision, hearing, or heart). In the event that the pregnant woman has no immunity and rubella is contracted during the first five months of gestation vertical transmission to the foetus may occur. After 12 weeks ofpregnancy, the consequences for the foetus are not so serious and there is practically no risk if the transmission of rubella during pregnancy (NICE, 2008).

As discussed in the section on vaccines, vaccination against rubella in seronegative women of childbearing age can prevent infection during pregnancy, so the pre-conception visit is the best time to determine whether women are immunised. It is common that this vaccine has been administered as part of the MMR vaccine in infancy (Dominguez, 2011; CDC, 2001).

Given that the vaccine is contraindicated during pregnancy, it is recommended that those women who during pregnancy are determined as not being immunised, the MMR vaccine should be administered immediately after childbirth (Dominguez, 2011; CDC, 1998; CDC, 2012).

During pregnancy, screening for rubella aims to identify those unimmunised women and therefore may benefit from the vaccine after childbirth to reduce the risk in future pregnancies (NICE, 2008).

Summary of evidence

Other clinical practice guidelines	Given that there is no treatment to prevent or treat the vertical transmission of rubella, it should be determined whether women of childbearing age are immunised during the pre-conception visit (ICSI, 2010). During pregnancy, screening for rubella aims to identify those unimmunised women and therefore may benefit from the vaccine immediately after childbirth to reduce the risk in future pregnancies (NICE, 2008).

From evidence to recommendation

Since the quality of the evidence for this section is not evaluated because its development has been based on other clinical practice guidelines and recommendations, the strength and direction of the recommendation were determined by the fact that the screening for rubella is aimed at preventing the congenital rubella syndrome when it is performed in a pre-conceptional way or to immediately immunize after childbirth those women identified as seronegative during pregnancy.

Recommendation

Strong	We recommend that a screening of rubella is offered to pregnant women at the first prenatal visit to assess immunity to rubella and provide vaccination as soon as possible in the postpartum of unimmunised women.

Screening for toxoplasmosis

Universal Screening for Toxoplasma Infections in Pregnancy

There are no systematic reviews (SR) or randomised clinical trials (RCTs) on the subject.

A narrative review, which describes most of the studies (mostly case series) on the diagnosis and treatment of congenital toxoplasmosis from 1953 until 2009 has been identified. (McLeod, 2009).

Universal Screening for Toxoplasma Infections

Very low quality

Congenital toxoplasmosis (CT) is one of the main problems of Toxoplasma infection during pregnancy. It can only be avoided through mechanisms such as preconception counselling (and / or early pregnancy) on possible sources of infection, and once acquired, preventing transmission from mother to foetus through the treatment of the acute infection. In the case of confirmed transplacental transmission, the manifestation of foetal infection could actually decrease by treating the infection in utero (Stillwaggon, 2011).

Some supporters of universal screening programs advocate for newborn screening, while others emphasize treating only children with symptoms of acute infection or even not try at all in the absence of data derived from randomised controlled clinical trials versus placebo, which show its effectiveness (Stillwaggon, 2011). However, in most cases, congenital birth subclinical infection and sequelae may develop over time and cause further damage.

Neonatal screening can be achieved at relatively low cost. The clear disadvantage is that damage before birth cannot be avoided and this can become permanent (Stillwaggon, 2011).

There are two main reasons for maternal screening and foetal diagnosis of Toxoplasma infection: (1) provide clinicians and pregnant women information that could assist them in making treatment decisions and (2) give pregnant women the opportunity to make informed decisions regarding their pregnancy (Khoshnood, 2007). Some studies suggest that T. gondii may be present in the placenta for weeks before being transmitted to the foetus (4 to 16 weeks). However, not all mothers transmit the infection to the foetus, increasing the frequency of vertical transmission with gestational age (McLeod, 2009; Stillwaggon, 2011).

Regarding treatment, McLeod (2009) argues that there is evidence proving that the active toxoplasma infection can be treated and its consequences reduced or avoided. This argument is based on (1) the fact that the treatment used for T. gondii in cell cultures and animal models actively eliminates the parasite replication and leads to the prevention or resolution of signs of disease in these models; (2) in the treatment of ocular toxoplasmosis, toxoplasmosis in immuno-compromised people and congenital toxoplasmosis, the treatment in humans improves symptoms and signs of active infection as well as the results; (3) the faster human congenital toxoplasmosis is diagnosed and treated, the shorter the time available for the parasite to destroy the tissue, and therefore the better the results; (4) detection of foetal infection acquired during pregnancy and its rapid treatment is often associated with favourable outcomes.

Thus, there is now a wide variety of screening programs for toxoplasmosis in pregnancy ranging from countries that incorporate it on a mandatory basis (such as France, Austria, Belgium), and others where it is not done routinely or in a less standardized way (US) (McLeod, 2009; Montoya, 2008). The mandatory prenatal screening would limit pregnant women regarding the opportunity to make decisions about the options for perinatal screening for toxoplasma. However, in cases such as France, there is freedom of choice on whether or not to perform the diagnostic amniocentesis after carrying out the screening. In the case of confirmed infection in the foetus and / or significant abnormalities, it may also be considered whether to terminate the pregnancy (Khoshnood, 2007).

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In France, since the introduction of a screening protocol in 1992 (systematic serological screening before conception and intra-partum) diagnosis (amniocentesis)

and treatment (spiramycin / sulfazocin / pyrimethamine as a result) it is uncommon to see children suffering clinically significant secuelae as a result of a congenital infection (McLeod, 2009).

In 2007, according to the results of the national laboratory surveillance system, the overall prevalence of congenital toxoplasmosis in France was 2.9 to 3.2 per 10,000 live births, and the incidence of symptomatic congenital infection of 0.34 per 10,000 live births (Stillwaggon, 2011). According to these results, there has been an 87% decrease in the rate of congenital infection in France since the 1970s; however, it is difficult to distinguish between the impact the reduction in seroprevalence by almost 50% has had on these results, and the impact due to the effectiveness of education versus the CT treatment. This effect of elective abortions, which were common in the early years of the screening program in France, is added, but now they are very rare. Despite these facts, the screening program in France has tended to eliminate or reduce the severity of significant adverse consequences due to CT (McLeod, 2009; Stillwaggon, 2011).

However, in countries like the United States (USA), where screening is not done routinely, CT is not a notifiable disease; its CT prevalence is estimated by seroprevalence studies in the population, which range between 1-10 per 10,000 live births according to different studies. Having extrapolated these results to the population, there would be from 400 to 4000 cases of CT per year in the USA (Stillwaggon, 2011).

Home screening for Toxoplasma infection and frequency of performance during pregnancy

Very low quality

The detection (and quantification) of T. gondii in serum is used to establish if a pregnant woman is infected, and if so, to determine the time when the infection was contracted. If the results of the serological tests suggest a newly acquired infection, an effort to determine whether the infection was probably contracted during pregnancy or shortly before conception is done. If so, the foetus is at risk (Montoya J, 2008). Thus, the faster the test is performed, the more useful the results will be. It has been suggested that routine serological screening for T. gondii (IgG and IgM) to all pregnant women should be done as early as possible (ideally during the first trimester) (Montoya J, 2008). Later, in seronegative women, every month or three months. This scheme would allow the detection of seroconversion and early initiation of a treatment. Moreover, Stillwaggon (2011) suggests that screening should initially include serological tests to determine the presence of IgG and, in the case of obtaining positive results, determining the presence of IgM antibodies. Pregnant women who obtained negative results (at risk for infection) would need to undergo the tests on a monthly basis throughout the pregnancy.

McLeod (2012), through a test run by enzyme-linked immunosorbent assay (ELISA) developed recently, detected two different types of T. gondii (serotypes II and not solely II [NE-II]) responsible for congenital toxoplasmosis in the USA.

The NE-II would be the most prevalent type; it would be more related to prematurity and with greater severity at the presentation of the disease. This opens a new window on the possibility of a more specific screening of T. gondii and with it, an approach regarding the risk of transplacental transmission, the development of CT and its possible sequelae in the newborn.

On the other hand, women can learn a number of dietary and hygienic measures aimed at the primary prevention of Toxoplasma infection (CDC, 2011):

Other clinical practice guidelines

- Wash vegetables and fruits thoroughly
- Peel fruits properly
- After handling raw meat, poultry, seafood, unwashed fruits or vegetables, wash hands and kitchenware thoroughly with soap and water
- Freeze meat for a few days and cook well to reduce the risk of infection as much as possible
- Avoid direct hand contact with cat faeces or dirt soil
- Wear gloves and wash hands properly after gardening or working with soil

From evidence to recommendation

The aspects assessed to determine the direction and strength of recommendation were:

1. The low quality of the evidence: the studies that have provided data on the utility and initiation of Toxoplasma infection screening in pregnant women are narrative reviews (MacLeod, 2009; Stillwaggon, E2011; Montoya, Khoshnood, 2007), with descriptions of case series and experimental programs carried out in different countries, so the quality is considered to be very low. There has not been any time when the quality of the evidence was thought to be increased.
2. Balance between benefits and risks: conducting screening for toxoplasma infection in pregnancy helps early detection of infection. Although early detection would allow early assessment of the situation and of the treatment options available, the poor results of the treatments available and the iatrogeny that could result from the positive cases are also important factors to consider.
3. Costs and resources: an economic study that constructed a model of cost-minimization screening for congenital toxoplasmosis in the United States (Stillwaggon et al, 2011) has been identified. The aim was to compare the monthly maternal serologic screening for toxoplasmosis, according to the French protocol (prenatal treatment, postnatal follow-up and treatment), compared to the non-performance of a routine screening or perinatal treatment. Among other outcome variables the probability of not presenting illness or loss due to amniocentesis and in case of not carrying out the screening, the non-recognition of the disease, being misdiagnosed, delayed diagnosis and treatment with its sequelae were included. The costs were based on published estimates of life social costs by the development of disabilities and the costs of diagnosis and treatment. The results showed that the monthly universal screening for CT infections in the mother, as well as monitoring and treatment according to the French protocol, is a strategy which reduced costs, to produce a saving of $620 (USD) per child examined (390 USD screening versus $1,010 (USD) for no screening). Taking the parameters of the proposed model and cost per test of maternal screening of $12 (USD), this decrease in costs would be possible for congenital infection rate of 1 in 10,000 live births. With the implementation of universal screening for CT in the US and considering the 4 million births per year, universal screening would save about $2.5 billion USD per year, compared to the non-performance of the screening.
4. Values and preferences of pregnant women: In one of the narrative reviews identified (Khoshnood, 2007), the psychological aspects in those parents who could undergo

screening for toxoplasmosis, which could be associated with the development of considerable parental anxiety due to the possibility of a false positive result and / or uncertainty related to the prognosis of apositive diagnosis of congenital toxoplasmosis were addressed. An initial positive test leads to a series of confirmatory tests, including a diagnostic amniocentesis. Should congenital toxoplasmosis be confirmed, the author mentions that there is no evidence that the duration of prenatal treatment produces a positive effect on the reduction of the anxiety of parents. However, it highlights that any psychological evaluation of the effects of screening on the parents should also consider its potential benefits. In particular, the sense ofcalm in case of obtaining negative results and / or the ability to make informed decisions regarding their pregnancy.

Finally, the direction of the recommendations was established considering aspects such as the low prevalence of toxoplasmosis in pregnant women, the poor efficacy of available treatments for this disease and the iatrogeny (amniocentesis) that may arise in those cases where the screening provided a positive outcome. The very low quality of the evidence determined the weak strength of the recommendations.

Recommendations

Weak	We suggest not offering screening for toxoplasma infection to all pregnant women.
√	Women should be informed about dietary and hygienic measures aimed at reducing the risk of toxoplasma infection.

Screening for varicella

Other clinical practice guidelines

Some institutions recommend that screening for varicella should be performed by reviewing the women's medical history as well as her vaccination history during the pre-conception visit (ICSI, 2010).

It is considered that the fact of having had varicella can predict immunisation between 97% and 99% of cases (RCOG, 13; ICSI, 2010; CDC, 1996). Therefore, during the first prenatal visit any possible medical history of the mother should be known. Having had varicella may have less prognostic value for those women born or who grew up in sub-Saharan Africa, Southeast Asia, and Latin America and the Caribbean (RCOG, 13; MacMahon, 2004).

Women who are seronegative to varicella zoster should avoid contact with people who have varicella during their pregnancy, and warn them to immediately contact a health professional if this contact occurs (RCOG, 2007). Although the incidence of varicella during pregnancy is low if the disease is acquired during pregnancy, especially during the first half of the pregnancy, there is a risk that the foetus suffers from congenital varicella syndrome or from other complications (ICSI, 2010; Dominguez, 2011).

The varicella vaccine is contraindicated during pregnancy, so the best time for vaccination would be in seronegative women of childbearing age who wish to become pregnant, or shortly after childbirth (RCOG, 2007; CDC, 2012).

Summary of evidence

Other clinical practice guidelines	If women of childbearing age are immunised or have suffered from varicella should be determined during the pre-conception visit. Seronegative women to the varicella zoster virus should be advised to avoid contact with people who have varicella during their pregnancy, and to consult with their health professionalas soon as possible if the contact occurs (RCOG, 2007; ICSI 2010).

From evidence to recommendation

The aspects considered to determine the strength and direction of this recommendation were as follows:

1. Quality of the evidence: the quality of the evidence for this section has not been evaluated since its development was based on other clinical guidelines and recommendations.
2. Balance between benefits and risks: Adverse effects of this vaccine are minor (fever, rash, or pain at the injection site), although there have been exceptionally severe reactions such as pneumonia or convulsions (the latter in less than 1 in 1,000 vaccines). The varicella screening targets to identify women who are not immunised and prevent congenital varicella syndrome.
3. Costs and use of resources: a British study on cost effectiveness (Pinot Moira, 2006) evaluated two strategies for perinatal screening for varicella, which derived in postpartum vaccination of unimmunised pregnant, in British and Bangladeshi women. One strategy was based on the history followed by a serological screening in women with no history or who had doubts, while the other strategy was a universal serologic screening. Both strategies prevented cases of varicella in pregnant women and the economic model showed that verbal strategy could be cost-effective compared to the current strategy used in the National Health Service at the time of the study. The strategy of universal serological screening, although more expensive, was more effective and the study authors said it could be cost-effective for the screening of young immigrant women. These results are similar to those of other previous US cost-effectiveness study (Smith, 1998) in which a screening program and subsequent immunisation in women of reproductive age was assessed in a hypothetical cohort of women aged between 15 and 49 who attended a health centre for perinatal care over a period of one year. The study showed that selective serological screening and postpartum vaccination could reduce almost half of the varicella infections, being therefore a cost effective strategy. However an earlier US study (Glantz, 1998) suggested that routine screening of pregnant women with a negative or unclear history of varicella was not cost effective (assuming an increase of $ 4,000 per year of life), and it would only be so in the context of a vaccination program and in women with an increased risk of exposure.

This recommendation was made in favour of the intervention given that the clinical benefit derived from this screening was much higher than the possible consequences of vertical transmission.

Recommendations

√	During pregnancy, in the anamnesis, a varicella screening should be carried out by reviewing the personal medical history of varicella of women, in order to avoid contact with anyone who has chickenpox in the case of not being immunised, and to consult with a health professional in case of contact.
√	Pregnant women who are seronegative to the varicella zoster virus should be warned to avoid contact with anyone who has chickenpox, and to consult with a health professional in case of contact.

Screening for cytomegalovirus

Other clinical practice guidelines

Cytomegalovirus (CMV) is the most common cause of congenital viral infection. Primary infection during pregnancy occurs between 1 and 4% of seronegative pregnant women (Baquero-Artigao, 2010) and carries the risk of between 30% and 50% of vertical transmission (Carlson, 2010; García-Bermejo, 2003) being far less in viral reactivations (between 0.3% and 0.5%). In our context, seroprevalence has increased in recent years and may reach 90% in women between 31 and 40 years old (Ory, 2004).

Despite some promising results, vaccines to prevent congenital CMV infection are still experimental (Pass, 2009) and on the other hand, the infection is usually asymptomatic, so screening of pregnant women at risk does not provide a value to the practice (Garcia-Bermejo, 2003), making it difficult to identify all risk factors for pregnant women. Detection of HIV-positive pregnant women in early pregnancy does not add any value because in their state it would not be possible to administer any antiviral treatment (Garcia-Bermejo, 2003). Finally, there is a difficulty in diagnosing viral reactivation and the possibility of symptomatic congenital infections in children of immune women (Baquero-Artigao, 2010). Despite significant diagnostic and therapeutic advances in recent years, there is not enough evidence about its usefulness, and the prevalence of CMV in pregnant women and newborns is unknown as well as their long-term real impact(Baquero-Artigao, 2010).

The National Health Service does not support this screening since it is not possible to determine accurately how many infections during pregnancy have an impact on the pregnancy and the newborn (NICE, 2008; Peckham, 1983). It is difficult to determine the number of children who will have long-term sequelae and there is no adequate prophylaxis for vertical transmission of infection or a way to determine adequately when there has been an intrauterine transmission (Boylard, 1998).

The CDC does not recommend routine screening for CMV in pregnant women, although it does state that for women who are planning pregnancy, it may be useful to comment how the infection by this herpesvirus can be prevented (Carlson, 2010; CDC, 2010). The reasons for not recommending this practice are based on i) the difficulty of making an accurate diagnosis because of the high rate of false positive results in the serological test, ii) the lack of effective treatment for infection during pregnancy, and iii) the possibility of reinfection or reactivation of the virus that exists in HIV-positive women. In an Italian study performed on 1,857 pregnant women who had shown positive results in a CMV serological test (Guerra, 2007), only 27% of the serological test results could subsequently con-

firm a primary CMV infection, while in 54% of cases the result corresponded to an old infection without an active disease. These facts make preventive measures, mainly hygienic ones, very important (ACOG, 2002; Carlson, 2010).

Some measures have been proposed to reduce the risk of exposure to CMV and lessen the risk of infection, mainly aimed at preventing exposure to saliva and urine that may contain the CMV (CDC, 2010):

- Wash hands with soap and water after performing certain activities such as diapering, feeding toddlers, or touch children's toys or pacifiers.
- Do not share food for toddlers or use utensils or containers for food or drink which are normally used by toddlers.
- Avoid brushing one's teeth with the same brush from a toddler.

Summary of evidence

Other clinical practice guidelines	At present, routine screening for cytomegalovirus is not recommended in the absence of an effective vaccine. The inability to establish effective measures to prevent vertical transmission of the virus and the possibility of symptomatic congenital infections in children of immune women is discouraged(NICE, 2008; Baquero- Artigao, 2010; Carlson, 2010; CDC, 2010).

From summary to recommendation

Since no studies on costs and the use of resources or values as well as the preferences of patients were found, the guideline development group considered making this recommendation against this intervention based on the low efficiency associated with this procedure and the inability to establish effective measures in preventing vertical transmission.

Recommendations

Strong	Screening for cytomegalovirus should not be carried out during pregnancy.
Weak	We suggest that women are informed of hygienic measures aimed at avoiding exposure to saliva and urine, which may contain cytomegalovirus.

Screening for Hepatitis B

An SR by the US Preventive Services Task Force (USPSTF) was identified to make its recommendations on screening for the hepatitis B virus (HBV) during pregnancy (Lin, 2009). The purpose of this SR was to update the search of the literature on previous recommendations (Krishnaraj, 2004; USPSTF, 1996).

A Cochrane review (Lee, 2006) includes all RCTs identified in the SR bythe USPSTF to make its recommendations. This SR aimed to determine the benefits and risks of the hepatitis B vaccine alone or in combination with hepatitis B immune globulin in the vertical transmission of HBV.

The SR by Lee (2006) identified 29 RCTs published until 2004, which in general had methodological limitations due to problems with the information related to the lack of randomisation or blinding (only three double-blind RCTs were included). In these tests; five compared the hepatitis B vaccine with placebo; other five compared the plasma-derived vaccine against the recombinant, other five compared high and low doses of the vaccine; 10 compared the vaccine against a combination of the vaccine with hepatitis B immunoglobulin, and the remainder

compared different administration strategies (number of doses, early versus late strategies, etc.). In most RCTs (18) only pregnant women, carrying antigen and hepatitis B (HBeAg) were included, and in three of them, HBeAg negative pregnant women were included. None of the RCTs was conducted in European countries and most of them were carried out in countries with a high prevalence of hepatitis B.

The search conducted in the SR by Lin(2009) in 2008, did not identify any new relevant RCTs.

Moderate quality

A combined analysis of the results of 5 RCTs showed that hepatitis B vaccine compared against placebo, significantly reduced the risk of vertical transmission of HBV (5 RCTs, 403 participants, RR 0.28, 95% CI 0.20 to 0.40). This benefit does not depend on the type of vaccine used (plasma-derived or recombinant, 5 RCTs, 382 participants, RR 1.00 CI 95% 0.70 to 1.42).

The combination of the vaccine with hepatitis B immunoglobulin showed a greater benefit than the vaccine alone in reducing the risk of vertical transmission of HBV (10 RCTs; RR 0.54, 95% CI 0.41 to 0.73).

Low quality

The available information on adverse effects is scarce. The SR by Lee (2006) was unable to obtain information from studies on adverse effects, and only highlights one death of a newborn in one of the RCTs of the combined vaccine with hepatitis B immunoglobulin, although it was not related to the vaccine.

On the other hand, the SR from the USPSTF (Lin, 2009; Krishnaraj, 2004; USPSTF, 1996), analyses the damage from hepatitis B screening in terms of false positives as these can lead to psychological harm to pregnant women, increased costs and unnecessary treatment in the newborn. Neither version of the SR identifies studies evaluating screening-related harm in these terms.

Other clinical practice guidelines

Taking these results into account, the USPSTF, recommends screening for hepatitis B for all pregnant women during the first perinatal visit whether the woman has been vaccinated previously or negative results of previous tests (USPSTF, 2010) are known, by serological determination of HBsAg, as a sensitivity and specificity of 98% has been proved (USPSTF, 1996; McCready, 1991; Hwang, 2008).

A new determination should be carried out on all those pregnant women in which their status is unknown with respect to HBsAg and those suspected of exposure to risk factors (USPSTF, 2010).

Summary of evidence

Moderate quality	The universal prenatal screening for hepatitis B substantially reduces the transmission of the virus and the subsequent development of infection (Lin, 2009; Lee, 2006).
Low quality	There is not enough information on the damage (in terms of false positives) that can be derived from the implementation of a universal screening for hepatitis B during pregnancy (Lin, 2009; Krishnaraj, 2004; USPSTF, 1996).

From evidence to recommendation

The aspects considered by the guideline development group to determine the direction and strength of the recommendations were:

1. Quality of the evidence: despite the methodological limitations of the studies (related to randomisation and lack of blinding), a sensitivity analysis with those studies containing a lower risk of bias were consistent, implying that the quality of evidence was not lowered for this reason. However, the quality of the evidence was reduced because the question has been answered from studies that did not answer directly, or which may have limited external validity. The aim of the studies included in the SR by Lee (2006) was to determine the benefits and risks of the hepatitis B vaccine alone or in combination with hepatitis B immune globulin in the vertical transmission of HBV in children of HBeAg positive mothers and not to compare the performance of universal screening versus not doing so. On the other hand, none of the RCTs was conducted in European countries and most of them were carried out in countries with a high prevalence of hepatitis B.
2. Balance between benefits and risks: the HBV screening substantially reduces perinatal transmission of HBV and the subsequent development of chronic HBV infection. Although the studies included in Krishnaraj (2004) and the Lin update (2009) did not include studies that assess the benefits and adverse effects of screening, the non-empirical evidence of 40 years of screening in the United States does permit the recommendation of universal screening for HBV (Lin, 2009).

Considering these aspects and the lack of studies on costs and the use of resources as well as values and preferences of pregnant women, the development group made this favourable recommendation considering that the clinical benefit derived from this screening is much higher than the possible consequences of vertical transmission.

Recommendations

Strong	Hepatitis B screening should be provided to all pregnant women at their first visit.
√	In those cases where the pregnant woman presents antigen HBsAg (+),she should be referred to the corresponding healthcare service in order to study whether she is an asymptomatic carrier or has a chronic liver disease, and thus establish a treatment if is appropriate and program a monitoring schedule.

Screening for Hepatitis C

Other clinical practice guidelines

Although the possibility of vertical transmission of the hepatitis C virus (HCV) does exist, it is not very common. The prevalence of the HCV antibody in pregnant women ranges from 0.1% to 2.4% and the rate of vertical transmission is between 4% and 7%, but can fivefold if there is HIV coinfection (Roberts, 2002). For the UK, the prevalence of vertical transmission has been estimated to occur in 70 deliveries per year, representing a prevalence of 0.16% (Ades, 2000). Although the risk of vertical transmission increases with the viral load of the mother, it is unknown whether there is a threshold to determine the increased risk of transmission (NICE, 2008). In Spain, 90% of paediatric HCV infections are acquired in this way (García-Bermejo, 2003).

The seroprevalence of HCV infection in the general adult Spanish population is close to 2%, and about 1.4% in pregnant women (Muñoz-Almagro, 2002; Solís Sánchez, 2003) and from 0.1 to 0 3% in the paediatric population (García-Bermejo, 2003). The time of greatest risk for vertical transmission is delivery by contact with the blood of the mother, while the risk during breastfeeding has not been so highly detected.

Identifying pregnant women likely to be carriers of specific antibodies against HCV (anti-HCV) does not add much value to the process due to the unavailability of any effective vaccine. The identification of HIV-positive pregnant women is not recommended because the antiviral treatment is contraindicated and there are no effective measures to prevent the infection (García-Bermejo, 2003; ICSI, 2010). Besides, the long-term implications of newborns who have acquired HCV through maternal transmission (NICE, 2008) are unknown. Considering these aspects, due to the complexity of the diagnosis to confirm HCV infection, some bodies advise against this screening because of the lack of efficacy and for not being cost effective (NICE, 2008). However, others suggest that serological screening should be performed for women who are considered to have a risk of HCV infection: history of drug injecting, or receiving blood transfusions or transplanted before the 90s (ICSI, 2010). The importance of informing women of the major risk factors for contracting HCV, related to times when there is contact with the blood of a person infected with the virus, has been highlighted. In addition to the risk factors discussed, HIV-positive women as well as those HBV carriers, with a history of endoscopic interventions or haemodialysis, or having a partner with HCV infection should be considered.

Summary of evidence

Other clinical practice guidelines	Screening for hepatitis C among women of childbearing age does not add value to the monitoring of pregnancy in the absence of an effective vaccine. In pregnant women, there are no effective measures to prevent vertical infection and antiviral therapy is contraindicated (García-Bermejo, 2003; ICSI, 2010). Further long-term implications on newborns who have acquired HCV maternal transmission are unknown (NICE, 2008).

From evidence to recommendation

The development group made the recommendations considering the fact that the prevalence of vertical transmission of HCV is low and that the long-term implications of newborns who have acquired HCV through maternal transmission are unknown.

Recommendations

Strong	A universal screening for hepatitis C virus (HCV) should not be carried out in pregnant women.
√	Evaluating the performance of screening for hepatitis C in women considered at risk for HCV infection should be carried out: history of intravenous drug using, receiving blood transfusions, having undergone a transplant before the 90s, Human Immunodeficiency Virus (HIV) positive women, HBV carriers with a history of endoscopic interventions or haemodialysis, or having a partner with HCV infection.

Screening for Streptococcus B

Universal screening versus screening based on risk factors or not performing any intervention

An SR (Taminato, 2011) which determined the best strategy for screening for group B streptococcus was identified. The interventions compared were screening based on maternal risk factors (preterm birth less than 37 weeks of gestation, previous bacteriuria attributed to group B streptococcus, fever, rupture of membranes for more than 18 hours, and neonatal infection in previous births), universal screening and not performing any type of intervention.

The risk of neonatal sepsis was significantly lower in the children of the group of women who underwent universal screening compared to those who were made based on maternal risk factors (5 cohort studies, 167,484 pregnant women; OR 0.25, CI 95% from 0.16 to 0.37). **Low quality**

Disaggregating the results according to the type of study showed the same results for both prospective studies (4 cohort, 65 962 pregnant women; OR 0.16, 95% CI .08-.32) and for the retrospective study (1 cohort, 101,522 pregnant women; OR 0.33, 95% CI 0.20 to 0.55).

The risk of neonatal sepsis was also significantly lower in the group of women who underwent universal screening compared with those who did not undergo any intervention (4 cohorts, 101,422 pregnant women; OR 0.43, 95% CI 0, 25 to 0.73). Similarly the same results were observed when they came from prospective studies (1 cohort, 42 074 pregnant women; OR 0.16, 95% CI .06-.42), or retrospective (3 cohorts 59,348 pregnant women; OR 0.56, 95% CI 0.30 to 1.02). **Low quality**

Time of the pregnancy when the screening for group B streptococcus should be done

A systematic review of the literature (Valkenburg-van den Berg AW, 2010) that determined the time of pregnancy when the screening for group B streptococcus should be done, was identified

This SR has some limitations related to the fact that:

- It does not include technology studies with an appropriate diagnostic accuracy as the microbiological highly sensitive rapid study for B streptococcus.
- The studies had a high heterogeneity in terms of the design and scope in which they were carried out. Besides, tracking of cohorts was not performed systematically.
- Prevalence rates were different between studies so the accuracy of the estimate of the positive predictive value was affected.

Risk profiles for B streptococcal colonization differed among the populations studied.

The systematic review of the literature by Valkenburg-van den Berg AW (2010) included nine cohort studies (7 prospective and 2 retrospective) involving 25,664 women, which in 8898 underwent crops for group B streptococcus in both neonatal period and during labour.

Compared to the performance of screening for group B streptococcus in various stages of the pregnancy, the completion of screening between weeks 35 and 37 of the pregnancy are more likely to detect group B streptococcus colonization. **Low quality**

The SR showed that the probability of obtaining a positive value in a group B streptococcus test is 19%. Among these pregnant women with a positive result, the positive predictive value of the test (to identify those women who actually experience a colonization during labour) is 70%. On the other hand, 6% of women with group B streptococcus are not detected by prenatal screening (9 cohorts, 25 664 pregnant women).

These results are reflected in some international guidelines, which recommend screening for rectal and vaginal colonization of group B streptococcus between weeks 35 and 37 of gestation (Verani, 2010). Similarly, a recent consensus document produced by multiple Spanish scientific societies, also recommends obtaining a sample of all pregnant women between weeks 35 and 37 of gestation for the detection of those streptococcus carriers (Marcos Melchor, 2012). This decision should be made in the outer third of the vagina and the rectum with one or two swabs.

The studies included in the SR performed culture tests variably, but in general, these were carried out between weeks 28 and 37 of gestation. The positive predictive value of prenatal B streptococcus cultures ranges from 43% to 100% (average 69%) while the negative predictive value ranges from 80% to 100% (average 94%). The culture tests performed in the last trimester had higher positive predictive values to detect B streptococcal colonization at childbirth (9 cohorts, 25,664 pregnant women). **Low quality**

Summary of evidence

Universal screening	
Low quality	The risk of secondary neonatal sepsis to B streptococcus is significantly lower in the group of women who undergo universal screening compared to those who undergo screening based on maternal risk factors (Taminato, 2011).
Low quality	The risk of secondary neonatal sepsis to B streptococcus is significantly lower in the group of women who undergo universal screening compared to those who do not undergo any type of intervention (Taminato, 2011).
Time of the pregnancy when screening should be performed	
Low quality	The performance of screening between weeks 35 and 37 of gestation are more likely to detect colonization by group B streptococcus (Valkenburg-van den Berg AW, 2010; Verani, 2010; Melchor Mark, 2012).

From evidence to recommendation

The aspects considered in determining the strength and direction of the recommendation were:

1. Quality of the evidence: the studies reviewed in this section have all been observational, retrospective in some cases. In no case was it considered appropriate to assess the possibility of increasing the quality of the evidence (mainly because of the limitations of the available studies, related, for example, to the lack of a control group in the studies) as well as the considerable heterogeneity between studies for the outcomes evaluated for universal screening. Similarly, the risk factors in the group

of women who underwent the screening are not explicitly described. Regarding the systematic review evaluating the appropriate timing for B streptococcus screening to be performed, it contained extensive limitations regarding the population under study, the field and the tracking of cohorts.

2. Balance between benefits and risks: regarding universal screening, a clinical benefit has been identified when compared to performing it based on risk factors or on women who have undergone no intervention. Due to the methodological limitations of the studies involved, further studies, which can confirm these results, are required. Up to 6% of B streptococcus carrier women are undetectable to prenatal screening. In relation to the time of pregnancy for screening to be done, although the best time for prenatal screening for group B streptococcus was determined, the limitations of the study are so broad that the results are of low accuracy. Further studies are needed to confirm these results.
3. A report on health technology assessment (Colbourn, 2007) calculated the expected net profit regarding non-intervention in each risk group with or without vaccination. Fourteen intervention strategies were assessed, including screening for B streptococcus in preterm or term pregnancies according to 12 types of clinical characteristics (for example, rupture of membranes, pyrexia, bacteriuria, B streptococcus positive vaginal smear). The net benefit of an intervention was one that passed the threshold of £ 25,000 per QALY gained. B streptococcus screening resulted cost-effective for term pregnancy, the bacteriuria, or positive vaginal smear to B streptococcus, and pregnant women with pyrexia. The authors of this report state that screening for B streptococcus in pregnant women at high risk may not be cost-effective because even those women in whom the screening result is negative, it might be better to have a pharmacological therapy to decrease the risk of early-onset infection.

Given these factors and the lack of studies, analysing the values, and preferences of pregnant women in this respect, the development group considered the available scientific literature shows consistent results from observational studies performed for universal screening, and has data on the most appropriate time to perform it. Nevertheless, a percentage of women who are carriers (6%) would not be detectable with the screening. Moreover, the availability of observational studies, sometimes retrospective and uncontrolled, determined the strength of the recommendation as low.

Recommendation

Weak	We suggest a universal screening for group B streptococcal colonization between weeks 35 and 37 of gestation to reduce the risk of neonatal sepsis.

Screening for HIV

An SR by the *US Preventive Services Task Force* (USPSTF) was identified to make recommendations on screening for HIV during pregnancy (Chou, 2005).

The SR by the USPSTF showed that there are no clinical studies comparing the performance of screening for HIV in pregnant women versus not doing it, or studies evaluating the potential benefit of increasing prenatal screening as a factor to increase the effectiveness of HIV treatments. Thereby, the SR indirectly evaluated the early and opportunistic use of antiretroviral treatments in women with an HIV infection as a means to decrease transmission from mother to baby, according to the Cochrane SR results (Siegfried, 2011). Moreover, the effect of these interventions on mortality and maternal and infant morbidity was evaluated. This SR included the same RCTs evaluated in another SR (Suksomboon, 2007).

On the other hand, a clinical practice guideline on screening for HIV during pregnancy carried out by the Society of Obstetricians and Gynaecologists of Canada was identified (Keenan-Lindsay, 2006).

The SR by Siegfried in 2011 included 25 RCTs with 18,901 participants. The results of the SR were stratified by regimen and breastfeeding status since the therapeutic schemas have changed since the first RCT was conducted in 1991. For the purpose of this guide only the results of the eight RCTs conducted in unexposed populations to breastfeeding were evaluated, assuming the risk of vertical transmission increases with breastfeeding and that studies should reflect the situation referred to in the question (implementation of the intervention during pregnancy). Most studies were conducted in Thailand (5 RCTs; Bhoopat, 2005; Limpongsanurak, 2001; PHPT-1, PHPT-2, Thai-CDC); two RCTs were multicentre multinational studies (PACTG 076, PACTG 316) and one study was conducted in South Africa (Gray, 2006).

Siegfried (2011) assessed three RCTs to compare antiretroviral versus placebo and long regimes versus short regimens using the same antiretrovirals, respectively. Another five RCTs evaluated antiretroviral regimens using different drugs and different treatment durations. Finally, an RCT compared triple regimens versus other treatment regimens.

Due to the heterogeneity of the population under study and the schemes administered, no meta-analysis was carried out; hindering the conclusions about what may be the optimal combination of antiretrovirals and its start time. None of the studies included in Siegfried 2011 performed a follow-up on newborns beyond 24 months of life, or determined the adverse events to the exposure of antiretrovirals in utero or immediate after childbirth.

Additionally, the SR from the USPSTF included four cohort studies evaluating the effect of different combinations of regimes in the risk of transmission from mother to child. This SR evaluated the effects of screening for HIV through Montecarlo simulations before the third trimester from three hypothetical cohorts of pregnant women (HIV prevalence of 0.15%, 0.30%, and 5%).

The authors used the following parameters to build the model:

- Prevalence of HIV infection.
- Accuracy of standard screening test.
- Proportion of women receiving screening results.
- Proportion of women receiving antiretroviral prophylaxis.
- Proportion of women having elective caesarean section.
- Rate of transmission from mother to child in the absence of interventions.
- Relative risk of mother to child transmission comparing mothers receiving active antiretroviral therapy versus those who do not.
- Rate of postpartum complications in women infected with HIV vaginal postpartum.
- Relative risk of elective caesarean section postpartum complications

Compared with placebo, zidovudine (ZDV) administered at 36 weeks of pregnancy and during labour (without any treatment for the newborn; Thai CDC regimen) did not reduce HIV transmission from mother to child (1 RCT, 1,140 participants; Relative Risk Reduction (RRR) 66.22%; 95% CI 33.94 to 98.50) (Connor, 1995; Siegfried, 2011).

Moderate quality

No significant differences in the rates of vertical HIV infection were observed in an extended regimen of ZDV (300 mg administered between 92 and 62 days before delivery (median 76 days), followed by 300 mg at onset of labour and every 3 hours from the onset of labour until delivery) versus a short regimen (300 mg administered between 14 and 35 days before delivery (median 28 days), followed by 300 mg at onset of labour and every 3 hours from the onset of labour to delivery) (1 RCT, 50 participants; RRR 100%, 95% CI 16.50 to 216.50) (Bhoopat, 2005; Siegfried, 2011). **Low quality**

No difference was observed in the rate of vertical transmission of HIV when comparing a regimen of a single dose of nevirapine and ZDV administered to mothers from a program in which nevirapine is also given to their babies (1 RCT, 1844 participants RRR 37.50%; 95% CI -40.94 to 115.94) (Lallemant, 2004; Siegfried, 2011).

No significant differences were observed in rates of perinatal HIV infection at birth when comparing placebo versus a standard antiretroviral regimen plus a dose of NVP administered during labour and a dose given to the newborn immediately after birth compared with placebo (1 RCT, 1506 participants, RRR 2.22%; 95% CI -140.39 to 144.83). **Moderate quality**

ZDV showed no significant differences in the incidence of vertical HIV infection when compared with stavudine (one RCT, 183 participants, 26.65% RRR; 95% CI -122.44 to 175.44), didanosine (one RCT, 186 participants, 52.66% RRR; 95% CI -88.01 to 193.33), or stavudine together with didanosine (one RCT, 180 participants, 49.43% RRR; 95% CI -94.88 to 193.74) (Gray, 2006). In these studies, antiretrovirals were administered between weeks 34 and 36 of pregnancy, during labour, completing the regimen with an administration of the same drugs to newborns 6 weeks after birth. **Low quality**

No significant differences were found in rates of HIV cross-infection among a triple regimen based on protease inhibitors (lopinavir / ritonavir, ZDV and lamivudine) from week 24 to 36 of gestation up to 6 months postpartum compared with ZDV and a dose of nevirapine (1 RCT, 855 participants, 18.18% RRR, 95% CI -83.48 to 119.84). **Low quality**

The SR from the USPSTF (Chou, 2005) further identified a number of epidemiological studies to justify the relevance of identifying women with HIV during pregnancy. A number of observational studies in the US showed that between 8% and 57% of pregnant women with HIV present identifiable risk factors during pregnancy. The variation between these estimates can be explained, however, by the criteria used to define high-risk behaviour and variation in the rigour of the evaluation (Chou, 2005). Furthermore, in a surveillance study carried out in seven US states, the proportion of women infected with HIV, diagnosed before pregnancy, increased 70-80% after the implementation of universal counselling recommendations (Wortley, 2001; Chou, 2005). **Low quality**

The SR from the USPSTF (Chou 2005) described the potential damage from HIV screening from false positives resulting from screening. The SR identified a rapid HIV test during labour, whichshowed that four women out of 4,849 presented false positives resulting in the initiation of antiretroviral prophylaxis before confirmatory results. Although there is no evidence of the frequency and damage of false positive results, some such as the elective termination of pregnancy, anxiety, discrimination, effects in the relationship have been described (Chou, 2005). **Low quality**

The incidence of adverse events was not significantly different in the RCTs included in the SR by Siegfried (2011).

Low quality

Finally, the SR by Chou (2005) conducted a simulation with a Monte Carlo model to calculate the number of women who would need to be screened to prevent vertical transmission of HIV in different situations. According to these results in a field with an HIV prevalence of 0.15%, it would be necessary to screen between 3,500 and 12,170 pregnant women to prevent one case of HIV transmission from mother to child, while in a context with a higher prevalence of 5%, the number would drop to the range of 105 and 305 women.

Other clinical practice guidelines

A clinical practice guideline on screening for HIV during pregnancy by the *Society of Obstetricians and Gynaecologists of Canada* (Keenan-Lindsay, 2006), offers a number of concrete suggestions regarding this situation.

This guide suggests that HIV screening be offered to pregnant women at their first perinatal visit, preferably between weeks 15 and 19 of gestation, being an ideal time to initiate antiretroviral therapy. It is also advisable to repeat the screening each trimester in women with a negative screening result but with persistent risk factors.

Those pregnant women admitted for labour and delivery, who did not undergo perinatal care and whose HIV status is unknown, should be offered screening at the time of admission. Furthermore, prophylaxis should be initiated for HIV infection at childbirth, both to the mother and the newborn.

Summary of evidence

Moderate quality	Different antiretroviral regimens tested have shown no significant difference in preventing the transmission of HIV from mother to child (Siegfried, 2011).
Low quality	The implementation of universal recommendations for HIV has shown that they can help identify a high rate of infected women (Wortley, 2001; Chou, 2005).
Low quality	There are not enough results to adequately assess the damage (in terms of false positive or false negative results) that may derive from the determination of a screening test for HIV during pregnancy, but in no case exceed the benefits derived from its performance (Chou, 2005).

From evidence to recommendation

The aspects considered by the guideline development group to determine both the direction and the strength of recommendation were:

1. Quality of the evidence: because there are no studies that compare directly the carrying out of a screening versus not doing so, the evidence supporting the recommendation of screening for HIV in pregnant women is based on a Cochrane SR (Siegfried, 2011) that analyses the RCTs of antiretrovirals to reduce the risk of HIV transmission from mother to child. The strong consistency in reducing transmission rates using antiretrovirals during pregnancy provides good evidence to give antiretroviral regimens in infected women. Therefore, it is necessary to perform a screening during pregnancy to detect cases early.
2. Balance between benefits and risks: Unwanted effects (in terms of false positive results) derived from HIV screening in pregnant women do not in any case exceed their benefit.

Finally, in the absence of studies on the use of resources and costs, as well as the values and preferences of pregnant women on this topic, the guideline development group made this favourable recommendation considering the clinical benefit derived from this screening. The main limitation to formulate a recommendation for this clinical question lays in the fact that there are no studies that compare HIV screening with not doing so. However, the benefit from being able to identify women with HIV infection and treat it early seems obvious. The RCTs evaluated in the SR by Siegfried (2011) and Suksomboon (2007) show in a very consistent manner the significant reduction in transmission rates when antiretrovirals are used early on infected women during pregnancy; thus, the recommendation was formulated as strong.

Recommendations

Strong	Universal HIV screening should be provided in the first prenatal visit.
√	We suggest repeating the determination of the last blood test during pregnancy in women at risk of HIV infection.

Screening for asymptomatic bacteriuria

For the detection of pathogen agents in urine, conducting a culture is considered the gold standard. There are other tests, mainly aimed at obtaining a faster diagnosis or one with less resources, whose diagnostic performance was evaluated versus the culture for the detection of uropathogens in urine in pregnant women.

Test strips

Test strips versus urine culture

A systematic review of studies that evaluated the diagnostic performance of the test strips (detection of nitrite and / or leukocyte esterase) compared to urine culture in different areas has been identified. The review includes a meta-analysis of the results including a subset of studies performed in pregnant women. However, this review gives only results of the diagnostic performance for urine infection (symptomatic) and asymptomatic bacteriuria together (Devillé, 2004).

Three subsequent studies that have evaluated the diagnostic performance of test strips for the detection of asymptomatic bacteriuria in pregnant women (Kacmaz, 2006; McNair, 2000; Mignini, 2009) have been identified.

Determination of nitrites

Low quality

In the SR by Devillé (2004), a total of 10 studies evaluated the performance of the detection of nitrite in pregnant women for the diagnosis of urinary tract infection or asymptomatic bacteriuria showing a sensitivity and specificity of 0.46 (95% CI 0.38 to 0.56) and 0.98 (CI 95% 0.79 to 1.00), respectively (Devillé , 2004).

A subsequent study carried out in 250 pregnant women showed that the sensitivity and specificity (compared to crop) determining nitrite in the test strips to detect asymptomatic bacteriuria were 0.6 and 0.992, respectively (Kacmaz, 2006).

Determination of leukocyte esterase **Very low quality**

The SR by Devillé (2004) shows the results for the detection of leukocyte esterase in the test strip in pregnant women, although a pooled analysis of eight studies (at different locations) shows a sensitivity and specificity of 0.56 (95 % 0.38 to 0.82) and 0.61 (95% CI 0.41 to 0.90), respectively for the detection of asymptomatic bacteriuria (Devillé, 2004).

A subsequent study in 250 pregnant women showed that the sensitivity and specificity (compared to crop) of the estaerasa leukocyte determination were 0.7 and 0.925, respectively (Kacmaz, 2006).

Determination of both tests: positive leukocyte esterase or nitrites **Low quality**

In the SR by Devillé (2004), five studies evaluated the detection performance of both tests (positivity of some of them) showing a sensitivity and specificity of 0.68 (95% CI 0.58 to 0 78) and 0.87 (CI 95% 0.81 to 0.92), respectively for the diagnosis of urinary tract infection or asymptomatic bacteriuria (Devillé, 2004).

A subsequent study carried out in 528 pregnant women (before delivery) showed that the sensitivity and specificity were 0.472 and 0.803, respectively for the detection of asymptomatic bacteriuria (McNair, 2000).

A later study in 3,032 pregnant women (between 12 and 35 weeks of gestation) and after excluding contaminated samples (22.4%) showed that the sensitivity and specificity were 0.53 (95% CI 0.48 to 0 58) and 0.92 (CI 95% 0.91 to 0.93), respectively for the detection of asymptomatic bacteriuria (Mignini, 2009).

Determination of both tests: positive leukocyte esterase or nitrites **Low quality**

In the SR by Devillé (2004), a study evaluated the detection performance of both tests showing a sensitivity and specificity of 0.68 (CI 95% 0.58 to 0.78) and 0.87 (95 % 0.81 to 0.92), respectively for the diagnosis of urinary tract infection or asymptomatic bacteriuria (Devillé, 2004).

Rapid culture methods (Dipslide)

Rapid culture methods against urine culture **Moderate quality**

A study evaluated the diagnostic performance for asymptomatic bacteriuria of a rapid culture method (dipslide culture) versus conventional culture in pregnant women between weeks 12 and 35. The publication shows the results in 17 Argentinean centres involving 3,048 participants in the context of an international clinical trial of antibiotic treatment in pregnant women with bacteriuria.

After excluding contaminated samples (28.6%), the sensitivity and specificity values for rapid culture technique were 0.98 (CI 95% 0.96 to 0.99) and 0.996 (95% CI 0.993 to 0.998), respectively (Mignini, 2009).

Completion of screening for bacteriuria in pregnancy

An SR from the US Preventive Services Task Force (Lin, 2008) that bases its recommendations on a Cochrane SR (Smail, 2007) comparing antibiotic treatment to placebo of bacteriuria in pregnant women has been identified. This SR included 14 randomised clinical trials (RCTs) or quasi-randomised in 2,302 women.

The Cochrane SR (Smail, 2007) showed a significant decrease in the incidence of upper urinary tract infections (11 studies, 1955 women; RR 0.23, 95% CI 0.13 to 0.41). **Low quality**

The Cochrane SR (Smail, 2007) also showed a significant decrease in the risk of low birth weight (7 studies, 1502 women; RR 0.66; CI 95% 0.49 to 0.89). **Moderate quality**

The SR showed that antibiotic treatment had no effect on the rate of preterm births (less than 38 weeks) when the results of the studies which restricted their inclusion criteria at a given gestational age (3 studies, 412 women; RR 0.37, 95% CI 0.10 to 1.36) were analysed. **Very low quality**

Time to perform screening for bacteriuria in pregnancy

No studies evaluating which is the optimal time for performing screening for asymptomatic bacteriuria in pregnant women were found. The consensus of experts now suggests performing a urine culture between weeks 12 and 16, which may be repeated between weeks 24 and 28(PAPPS, 2009). **Low quality**

Summary of evidence

Moderate quality	Antibiotic treatment after verifying the presence of bacteriuria in pregnant women reduces the risk of upper urinary tract infection and low birth weight.
Low quality	In pregnant women, urine test strips (for nitrites and / or leukocyte esterase) seem to have a low sensitivity and moderate specificity for detecting asymptomatic bacteriuria or urinary tract infection.
Moderate quality	In pregnant women, rapid culture methods (Dipslide) have a high diagnostic accuracy for the detection of asymptomatic bacteriuria.

From evidence to recommendation

The aspects considered by the development group to determine the strength and direction of the recommendation were:

- Quality of the evidence: the available literature on the need for universal screening for bacteriuria in pregnancy is moderate due to the availability of indirect data that have evaluated the efficacy of antibiotics in the treatment of bacteriuria in pregnant women after determining this health problem with a test strip. Furthermore, the results show a high inconsistency (I2 = 64%). The main limitation of the quality of the evidence in studies that evaluated the diagnostic performance of the test strips was indirect evidence; results estimators of the different studies showed results for the detection of bacteriuria or urinary tract infection. There were also limitations in the design and performance of the many of the studies considered. The main limitation of the quality of the evidence in those studies that evaluated the diagnostic performance of rapid culture methods was a high percentage of contaminated results (28%) that could profoundly alter the effect estimator. The evidence regarding the timing of screening comes from expert consensus.
- Balance between benefits and risks: the diagnosis of asymptomatic bacteriuria involves treatment with antibiotics in order to reduce the risk of pyelonephritis; urine culture is the gold standard. There is no apparent risk associated with the carrying out of a (conventional or fast) culture or test strip. The benefit which earlier treatment may involve based on the determination of a urine test strip has not been assessed, but these potential benefits may

not outweigh the risk of false results, which may lead to not treating women who could benefit from a treatment, or being administered a treatment, which is unnecessary. There is not enough information to assess this aspect regarding the timing of screening.

- Costs and use of resources: no specific studies have been located that assess the costs of the tests evaluated. Medical staff keeps track of the pregnancies of the vast majority of women in our environment, therefore, screening for bacteriuria should not be considered an isolated intervention but within the common pregnancy follow-up measure, whose cost would not increase significantly. The test strips are usually cheaper than the culture and do not require specialised personnel or material for their determination. There are doubts about the accessibility of the centres to rapid culture methods. There is not enough information to assess this aspect regarding the timing of screening.

Following the assessment of these aspects, the Working Group considered that the test strips showed no optimal diagnostic performance for the detection of bacteriuria in pregnant women, although the confidence in the results of the available studies is low or very low. The potential benefits of these tests versus culture do not seem to outweigh the risk of false results. Moreover, rapid culture methods (Dipslide) have an adequate diagnostic performance for the detection of asymptomatic bacteriuria in pregnant women. The balance between the benefits of obtaining a proper diagnosis (as reference test), and the risks seems optimal for performing a urine culture. Although the unit cost of the culture is higher in comparison to other tests, the impact of the culture in the routine monitoring of the pregnancy is probably lower. Therefore, a favourable recommendation was made. The virtual absence of reasoned judgments to propose screening for bacteriuria in a given period of the gestation, determined the weak recommendation; moreover, the time when the test should be performed is that stated in the USPSTF recommendations.

Recommendation

Strong	We recommend performing a urine culture for all pregnant women at the first prenatal visit to detect the presence of asymptomatic bacteraemia and prevent the risk of upper urinary tract infection and low birth weight.

Universal screening for anaemia

Several institutions recommend offering screening for anaemia to all pregnant women at the first prenatal visit (NICE, 2008; ICSI, 2010; AHRQ, 2010).

The most common cause of anaemia during pregnancy is caused by an iron deficiency. The iron requirement increases during pregnancy due to the requirements of both the foetus and the placenta as well as the increase of the total mass of red blood cells of the mother, so the absorption of iron increases to meet the increased demand (NICE, 2008; Lee, 2011). Generally, the plasma volume of the pregnant woman rises to 50% and the total mass of red blood cells to 20%, thereby decreasing the concentration of haemoglobin (Hb). This normal physiologic process has similarities with iron deficiency anaemia (Hytten, 1985; NICE, 2008).

The average concentration of haemoglobin (Hb) during pregnancy varies between 11g/dly and 12g/dL although the data are inconsistent with the available studies (NICE, 2008). It is important to note that haemoglobin levels vary with gestational age, being able to locate the threshold which would determine anaemia during the first and third trimester in values of Hb <11g/dL and Hb <10.5 g / dL during the second trimester (Breymann, 2010).

Low quality

A retrospective study performed on 153,602 British pregnant women from various ethnicities showed how the magnitude of decrease in haemoglobin levels during pregnancy was associated with the weight of the newborn (Steer, 1995). The fall in Hb levels from values below 10.5 g / dL was associated with risk of preterm birth and low birth weight (Steer, 1995; Steer, 2000). A review of observational studies has suggested a U-shaped correlation between haemoglobin levels and pregnancy outcomes so that the proportion of children with low birth weight increases when maternal haemoglobin values are at the lowest and highest range studied. (Rasmussen, 2001)

Other clinical practice guidelines

Given that anaemia can have many causes (iron deficiency, thalassemia, sickle cell anaemia), measuring haemoglobin by itself is a low yield test to determine iron deficiency, and it is necessary to perform further assessment to identify its aetiology (NICE, 2008; ICSI, 2010). Serum ferritin appears to be the parameter with the best sensitivity and specificity for the diagnosis of deficiency in women with anaemia (Guyatt, 1992; AHRQ, 2010) and can use a threshold of 30 mcg / L with a sensitivity of 90% (Breymann , 2002).

Summary of evidence

Low quality	Extreme haemoglobin levels during pregnancy are associated with an increased risk of preterm delivery and low birth weight (Steer, 1995; Rasmussen, 2001). Hb values between 9.5 and 10.5 g / dL are associated with improved foetal growth (Steer, 1995; Steer, 2000).

From evidence to recommendation

Since no studies on the use of resources, costs, and values as well as the preferences of pregnant women have been identified, the Working Group considered making this recommendation given the association of Hb levels with adverse pregnancy outcomes (low birth weight and preterm delivery). This recommendation was considered weak because, despite the results of the mentioned studies, a causal association between haemoglobin levels and birth outcomes (Rasmussen, 2001) has not yet been established.

Recommendations

Weak	We suggest a universal screening for anaemia in pregnant women during the first prenatal visit.
√	The universal screening for anaemia should be repeated in pregnant women after 28 weeks of gestation.
√	The diagnosis of anaemia in pregnancy should be set when the haemoglobin is below 11 g / dl in the first trimester, less than 10.5 g / dl in the second and less than 11 g / dl in the third trimester.

Determination of ferritin

Taking into account that anaemia can have many causes (iron deficiency, thalassemia, sickle cell anaemia), measuring haemoglobin by itself is a low yield test to determine iron deficiency, and may need some additional evaluation to identify its aetiology (NICE, 2008; ICSI, 2010). The blood haemoglobin levels can be considered outside the normal and, therefore, may require other confirmation tests to diagnose anaemia, these values being 11g/100 ml at the first visit and 10.5 g/100 ml on week 28 (NICE, 2008).

An SR (Guyatt, 1992) that assessed the value of five laboratory tests (serum ferritin level, free erythrocyte protoporphyrin, mean corpuscular volume, transferrin saturation index, and red blood cells distribution index) to diagnose iron deficiency anaemia has been identified. The authors evaluated the results of 55 studies of diagnostic performance in individuals over 18 with a low haemoglobin level who underwent at least one of the five tests and would at least allow the calculation of test sensitivity. These data were used to calculate the area under the ROC curve for each of the tests and the positive likelihood ratio (LR +).

Moderate quality

The results of the SR by Guyatt (1992) showed how the determination of the ferritin level is by far the best predictive value test for iron deficiency anaemia over the other parameters evaluated. The ferritin level showed an area under the ROC curve of 95% (95% CI 94-96), much higher than the rest of the parameters (free erythrocyte protoporphyrin: 77%, mean corpuscular volume: 76% transferrin saturation index: 74%, rate of red cell distribution: 62%; significant difference $p<0.001$).

On the other hand, the range of values of LR + was significantly different between the highest and lowest values of ferritin, adding value to this parameter:

Ferritin value	Number of women	LR + (IC 95 %)
≥100 µg/L	1,368	0.08 (0.07 to 0.09)
45<100 µg/L	474	0.54 (0.48 to 0.60)
35<45 µg/L	79	1.83 (1.47 to 2.19)
25<35 µg/L	108	2.54 (2.11 to 2.97)
15<25 µg/L	146	8.83 (7.22 to 10.44)
≤15 µg/L	494	51.85 (41.53 to 62.27)

Summary of evidence

Moderate quality	The determination of the levels of ferritin is the best parameter for the diagnosis of iron deficiency anaemia, with a positive predictive value of 95% (Guyatt, 1992)

From evidence to recommendation

Both the direction recommended and its strength were determined by the consistent results shown by the systematic review assessed in this section which states that ferritin is the best parameter to confirm the diagnosis of iron deficiency anaemia.

Recommendation

Strong	We recommend determining the level of serum ferritin to confirm a questionable diagnosis of iron deficiency anaemia.

Screening of Rh isoimmunisation

Other clinical practice guidelines

The application of the ABO blood group, Rh factor, and Coombs test at the first prenatal visit is a general recommendation in all clinical practice guidelines. Similarly, it is recommended to repeat antibody testing ANTI D in Rh-negative women between weeks 24 and 28 of gestation. (SEMFyC, 2002; USPSTF, 2004; BSH, 2008; NICE, 2008; AHRQ, 2010; ICSI, 2010).

Rh incompatibility (Rh-negative women with an Rh-positive foetus) occurs in 10% of all pregnancies. If preventive measures are not taken, an isoimmunisation occurs in up to 2% of women in the prenatal period, between 8% and 17% during delivery, up to 6% after an abortion, or up to 5 % after amniocentesis (Mollison, 1987; ICSI, 2010). In such cases, the maternal ANTI D antibody would cross the placenta in future pregnancies causing foetal erythroblastosis, and without treatment, up to a third of these foetuses will develop perinatal haemolytic disease or die during pregnancy or childbirth (Bowman, 1985; ICSI, 2010).

It is important to determine the Rh factor for Rh-negative women, so that they can receive immunoprophylaxis properly to prevent isoimmunisation in future pregnancies (NICE, 2008).

Summary of evidence

Other clinical practice guidelines	Rh incompatibility occurs in 10% of pregnancies; it can cause isoimmunisation in up to 2% of women in the prenatal period. If inappropriate prophylaxis is provided, perinatal haemolytic disease is developed (Bowman, 1985; NICE, 2008; ICSI, 2010).

From evidence to recommendation

To set the strength and direction of the recommendation, the Working Group felt that it was essential to carry out a proper identification of Rh incompatibility in order to establish the necessary prophylactic measures to help prevent Rh isoimmunisation and any severe complications for the foetus. The complications that can arise from an Rh isoimmunisation justify the recommendation to perform universal screening for Rh compatibility. The recommendation was set as strong by the impact of this procedure on the health of the mother and the foetus.

Recommendation

Strong	A screening for Rh compatibility, ABO blood group and irregular antibodies should be performed to all pregnant women at the first prenatal visit.
Strong	The determination of anti-Rh antibodies should be determined to Rh negative pregnant women with Rh incompatibility between weeks 24 and 28 of gestation..

Anti-D prophylaxis

Routine prenatal prophylaxis with anti-D immunoglobulin for Rh-negative women

A report on health technology assessment (Pilgrim, 2009) and a meta-analysis (Turner, 2011) evaluating the effectiveness, the most appropriate patterns of anti-D prophylaxis in the prevention of Rh sensitisation in pregnant women were identified.

Turner's meta-analysis (2011) was included as it considered all the studies of the evaluation report, and it performed a rigorous analysis of the results with a sensitivity analysis of the influence of bias on the results of the studies.

The meta-analysis included 10 RCTs, two of which (Bowman, 1978; Bowman, 1987) took the same group of women as control and were not strictly comparative studies, but provided useful data on the effectiveness of a single dose of anti-D immunoglobulin. The authors of this meta-analysis conducted adjusted analysis to internal bias (methodological limitations) and external bias (applicability of results) of included RCTs included, due to the heterogeneity regarding the anti-D immunoglobulin, obstetric characteristics of women and follow-up timemanagement guidelines.

The effectiveness of three anti-D immunoglobulin patterns for the prevention of Rh sensitisation was evaluated.

- For the 500 IU scheme (100 mcg), (two doses between weeks 28 and 34 of gestation) in four studies (Huchet, 1987; Mackenzie, 1999; Mayne, 1997; Tovey, 1983).
- For the 1,500 IU scheme (300 mcg), (two doses between weeks 28 and 30) and 1,250 IU (250 mcg), (two doses between weeks 28 and 34) The Expert opinion was consulted, which considered the effectiveness taking into account the half-life of anti-D immunoglobulin, the minimum current level to generate the adhesion and protection of pregnant women.

Compared with the administration of anti-D immunoglobulin postpartum or after sensitisation events during pregnancy, antepartum routine anti-D prophylaxis showed a reduction in the risk of sensitisation of Rh negative women (10 RCTs, 47,409 pregnant women; OR 0 31, 95% CI 0.17 to 0.56) (Bowman, 1978; Bowman, 1987; Hermann, 1984; Huchet, 1987; Lee, 1995; Machenzie, 1997; Mayne, 1997; Tovey, 1983; Trolle, 1989). **Moderate quality**

Another analysis that excluded two studies using as a control the same group of women (Bowman, 1978; Bowman, 1987) showed similar results (8 RCTs, 29,236 pregnant women; OR 0.31, 95% CI 0.16 to 0.61) (Bowman, 1978; Hermann, 1984; Huchet, 1987; Lee, 1995; Machenzie, 1997; Mayne, 1997; Tovey, 1983; Trolle, 1989).

Routine perinatal prophylaxis with different doses of anti-D immunoglobulin for Rh-negative women

Compared with the administration of anti-D postpartum or after sensitisation events during pregnancy, two doses of either anti-D immunoglobulin 500 IU (100 mcg) (Turner, 2012) (4 RCTs, 20,877 pregnant women; OR 0 31, 95% CI 0.09 to 0.65), 1,500 IU (OR 0.42, 95% CI 0.17 to 0.73) or 1,250 IU (OR 0.18, 95% CI 0.03 to 0.53), are effective in the prevention of Rh sensitisation. **Moderate quality**

Compared with the administration of anti-D postpartum or after sensitisation events during pregnancy, the probability that a dose of anti-D immunoglobulin of 1250 IU (250 mg) (Turner, 2012) (OR 0.18; 95% CI 0.03 to 0.53) is effective is 83%, while it is 76% and 15% for the 1,500 IU (300 mcg) and 500 IU schemes (100 mcg), respectively (4 RCTs, 20,877 women pregnant). **Moderate quality**

Summary of evidence

Moderate quality	Prophylaxis with anti-D immunoglobulin during pregnancy significantly reduces the risk of Rh sensitisation (Turner, 2012).
Moderate quality	The patterns of anti-D immunoglobulin 500 IU (100 mcg), 1,250 IU (250 mcg), 1,500 IU (300 mcg) decrease the risk of Rh sensitisation (Turner, 2012), being the dose of 1,500 IU (300 mcg) the most likely to be effective.

From evidence to recommendation

The issues considered by the development group to determine the strength and direction of the recommendation were:

1. Quality of the evidence: the quality of the evidence in most variables of the results assessed for anti-D prophylaxis in the prevention of Rh sensitisation has decreased, because the studies included have limitations such as lack of blinding, losses during follow up and a wide heterogeneity in the intervention and the population groups studied. Despite the above limitations, the results of the unadjusted data are consistent with those adjusted and with the sensitivity analysis.
2. Balance between benefits and risks: regarding the systematic perinatal prophylaxis with anti-D immunoglobulin for Rh-negative women, has been identified a clinical benefit, both in the adjusted and unadjusted analysis of the anti-D immunoglobulin in the prevention of Rh sensitisation. Regarding the systematic perinatal prophylaxis with different doses of anti-D immunoglobulin for Rh-negative women, there has been a unique benefit with the administration of the 500 IU, 1250 IU, and 1500 IU schemes in the prevention of Rh sensitisation. As the studies are scarce and with low precision, the analysis of prophylaxis with different doses of immunoglobulin are based on statistical models, making it necessary to carry out studies evaluating direct comparisons.
3. Use of resources and costs: the evaluation report on health technologies by Pilgrim (2009) showed that the cost per QALY gained by routine perinatal prophylaxis with anti-D immunoglobulin for Rh-negative primiparous women compared to non-treated, ranged from 9,000 and 15,000 £, and all women ranged between 20,000 and 35,000 £, thus being a cost-effective intervention. The authors considered that the cost resulting from the intervention in England and Wales would be between 1.8 and 3.1 million £ per year if applied to primiparous women, and between 2 and 3.5 million if applied to all women. A previous cost effectiveness analysis (Chilcott, 2004) had shown very similar results, providing similar conclusions to those by Pilgrim (2009).

Finally, considering the aspects described, the development group made a recommendation in favour of the intervention, as there is a strong statistical and clinical consistency between the adjusted and unadjusted results as well as in the sensitivity analysis. Furthermore, the recommendation is strong because the routine prenatal prophylaxis with anti-D immunoglobulin reduces the risk of immunisation and consequently of haemolytic disease of the newborn. For recommendations on the administration of anti-D immunoglobulin information from the data sheet and clinical practice guidelines (NICE, 2008; Servei de Salut de les Illes Balears, 2012) has been obtained.

Recommendations

Strong	Routine prenatal prophylaxis with an administration of 300 µg (1,500 IU) of anti-D immunoglobulin should be offered to unsensitised Rh-negative pregnant women to reduce the risk of sensitisation.
Strong	The prenatal prophylaxis should be administered as a single dose between weeks 28 to 30 of gestation to unsensitised Rh-negative women.
Strong	A single dose of anti-D immunoglobulin should be administered within 72 hours of any episode of potential sensitisation (abortion, ectopic pregnancy, partial molar pregnancy, chorial biopsy, amniocentesis, cordocentesis, External Cephalic Version –ECV-.)
Strong	Additional doses of anti-D immunoglobulin should be administered if a feto-maternalhaemorrhage of 10 to 15 mL occurs.
Strong	Prophylaxis with 300 micrograms (1,500 IU) of anti-D immunoglobulin should be administered to Rh-negative unsensitised women whose newborn (NB) is Rh positive during the first 72 hours of postpartum.

Screening for hypothyroidism

Two RCTs (Negro et al., 2010; Lazarus et al., 2012) evaluating the results of thyroid function screening in the first trimester were identified.

Negro (2010) (Negro et al, 2010) compared the impact of performing a universal screening of the thyroid function against an opportunistic identification on obstetric and neonatal complications on the 11th week of pregnancy. The trial randomised 4,562 pregnant women with no history of thyroid disease in two Italian health care centres; in one group samples were taken of all participants to determine the levels of TSH and T4 and those in which thyroid dysfunction was identified (n = 2,280) were treated or a group in which only the levels of TSH and T4 were analysed in women considered at high risk (family history or symptoms of autoimmune thyroid disease, personal history of type I diabetes or autoimmune disease, history of abortion or preterm delivery) (n = 2,282).

In this study the impact of participating in one group or another on the composite endpoint for a wide range of obstetric and neonatal complications was evaluated: abortion, hypertension, preeclampsia, gestational diabetes, placental abruption, gestational thyrotoxicosis, caesareansection delivery, congestive heart failure, preterm delivery, respiratory distress, admission to a neonatal intensive care unit (ICU), low or high birth weight, birth prematurity, Apgar ≤3 after 5 minutes, perinatal death.

A multi-centred RCT (Lazarus, 2012) comparing the intelligence quotient (IQ) of children at three years of age of women who had undergone screening for thyroid function in the first trimester (and who were treated depending on the results of the screening) against the IQ of the children of women who did not receive screening at any time during pregnancy or treatment has been identified.

The RCT took blood samples to determine the levels of thyrotropin and free T4 to 21,846 pregnant women (aged 18, with a single foetus, and a mean gestational age of 12 weeks) in their first hospital visit. These women had no known thyroid disease. The screening group included 10,924 women who underwent screening before week 16 of gestation and 390 who were diagnosed with underactive thyroid, thus being recommended a replacement therapy. In the control group (10,922 women) in 404 women thyroid function was not determined until after delivery. Three years after birth, a group of blinded psychologists determined the IQ of the children of women

who had altered their hormonal study by the Wechsler scale, as well as other outcomes related to the children's behaviour and the psychological status of the mothers.

The results of the study by Negro (2010) (Negro et al, 2010) showed a similar risk of obstetric or neonatal complications between the two groups compared (universal screening group: 1,559 events against opportunistic screening group: 1.545; OR 1.01, 95% CI 0.91 to 1.10). **Moderate quality**

Although a lower percentage of complications among women with low risk of thyroid disease universal group of opportunistic screening (OR: 0.43; 95% CI 0.26 to 0.70) was observed, this result was not observed between women at high risk (OR 0.60, 95% CI 0.26 to 1.39).

The results of the study by Lazarus (2012) (Lazarus et al., 2012) showed that screening for hypothyroidism between weeks 12 and 13 of gestation, and the treatment in case of alterations, poses no benefit for the prevention of cognitive impairment in children at the age of three compared to a study group who did not undergo that screening at any stage of the pregnancy. The result of the Wechsler scale showed no difference in the IQ of children of mothers in both groups (screeniing at any stage of the pregnancy. The result of the Wechsler scale showed no difference in the IQ of children of mothers in both groups (screening group: IQ 100 versus control group: IQ 99.2; mean difference 0.8 points; 95% IQ - 1.1 to 2.6; p = 0.40). **Moderate quality**

The percentage of children with an IQ below 85 points also showed no significant differences between the two groups (screening group: 12.1% versus control group: 14.1; difference 2.1%, 95% IQ -2.6 to 6, 7; p = 0.39). **Moderate quality**

The results of this study should be confirmed over a longer period (5 or 10 years of life) to confirm the lack of benefit of this intervention, and should examine whether the results would be the same if the screening is done at an earlier gestational age (Galdeano and Rodrigo, 2012). **Other clinical practice guidelines**

Recently, a Working Group of the Spanish Society of Endocrinology and Nutrition, jointly with the Spanish Society of Gynaecology and Obstetrics (SEGO), has developed a consensus document on the detection of thyroid dysfunction in pregnant women (Vila, 2012).

This consensus conference insisted on the benefit of universal screening for thyroid function rather than of selective screening in women with risk factors, mainly due to the importance of proper treatment of hypothyroidism during pregnancy. While recognising that the prevalence of clinical hypothyroidism does not exceed 1.6% in our environment, it is important to avoid major obstetric complications associated with thyroid dysfunction (such as infertility, abortion and intrauterine foetal death, restricted intrauterine growth, hypertension, placental abruption or prematurity), in some cases contradicting the results of the clinical trial by Black (2010).

The consensus document also highlights the limited applicability of the results of the clinical trial by Lazarus (2012) mainly due to a late start of the screening and the treatment during the second trimester as well as the lack of control of the women treated and the women untreated compared to euthyroid mothers (with a normal thyroid function).

The Working Group consensus conference mentioned justifies that considering that thyroid dysfunction is a disease easily diagnosed, with effective treatment and without risk, universal screening for thyroid function should be recommended before week 10 of gestation.

Moreover, the US Preventive Services Task Force (USPSTF, 2012) does not make any recommendation on the need for a screening for hypothyroidism in adults. This position takes into account that the determination of TSH can result in damage in the case of false positives, and that there is no data on the clinical outcome improvements deriving from the treatment of asymptomatic adults detected by screening. This paper intends to conduct a screening for hypothyroidism in the first visit to women at increased risk of thyroid disease. Screening for thyroid disease should be performed in the following situations:

- Women over 30.
- Women with a family history of autoimmune thyroid disease or hypothyroidism.
- Women with goiter.
- Women with antithyroid antibodies, mainly with peroxidase antibodies.
- Women with symptoms implying suggestive clinical signs of thyroid hypofunction.
- Women with type 1 DM or other thyroid disorders.
- Women with infertility problems.
- Women with a history of abortion or preterm labour.
- Women with a history of head or neck irradiation or previous thyroid surgery.
- Women on replacement therapy with levothyroxine.
- Women who live in areas presumably deficient in iodine.

Summary of evidence

Moderate quality	Screening for hypothyroidism in the first trimester of pregnancy has not been shown to be effective for the prevention of cognitive disorders in children at the age of three (Lazarus et al., 2012). On the other hand, it has not shown to increase the risk of obstetric or perinatal complications (Black et al., 2010).
Expert opinion	Some Working Groups have reported that the results of clinical trials may have limited applicability, and considered that the benefits of screening of the thyroid function to facilitate proper treatment of hypothyroidism during pregnancy should be taken into account, thus, warranted universal is screening considered justified for pregnant women (Vila, 2012).

From evidence to recommendation

The aspects that were considered to establish the strength and direction of the recommendation were:

1. Quality of the evidence: the quality of the evidence is considered moderate due to certain limitations in the design of the RCT by Lazarus (2012) (Lazarus et al, 2012), related to the monitoring of the participants (21.8% in the screening group and 26.7% in the control group). In the follow-up, many women in the control group also refused

to allow their children to undergo the IQ test (19 in the screened group versus 41 in the control group). A sensitivity analysis showed that this had no impact on the study results. On the other hand, women in the control group did not receive a placebo treatment, but it cannot be assessed whether this put the blindness of the study at risk.

2. Costs and use of resources: A US economic evaluation study (Dosiou, 2008) compared the cost effectiveness of making a universal screening for thyroid disease or not do it throug h a cost-utility analysis with a Markov model, but that obtained the efficacy and usefulness data indirectly from a review of the literature or expert consultation. The three models compared (no screening, screening by TSH or screening by anti-thyroperoxidase (anti-TPO) antibody) showed a very similar mean QALY gained of about 26.8. The screening by TSH showed the best cost-utility ratio for an additional cost per QALY gained of $15 when compared to the screening with anti-TPO antibodies. The authors concluded that screening during the first trimester was a cost-effective intervention. A subsequent study (Thung, 2009) evaluated whether routine screening of the thyroid function was cost effective for cases of subclinical hypothyroidism. The study adopted a decision tree from a social perspective to calculate QALY related to the IQ of children and the efficacy data derived from a review of the literature. The model showed that universal screening of 100,000 women would provide a gain of 589.3 QALY, and screening would result in savings of $8,356. The authors concluded that universal screening would be a more cost-effective intervention than not performing the screening, but the lack of reliable data from RCTs on the efficacy of this intervention does not allow the implementation of the strategy for the moment.

When formulating the recommendation, the Working Group assessed in detail the joint recommendation of the Spanish Society of Endocrinology and Nutrition and the SEGO (Vila, 2012). The recommendations of this consensus conference, highlights the need for a universal screening of the thyroid function, given the limited applicability of the results of the clinical trials included in this clinical question, and the benefit derived from the aforementioned screening aimed at a correct diagnosis and treatment of hypothyroidism during pregnancy, to prevent major obstetric complications associated with the thyroid dysfunction. However, the Working Group considered that the document by Vila (2012) does not pay enough attention to the results of the available clinical trials, though with some limitations, which show that universal screening for hypothyroidism has no effect on clinical impact outcomes with obstetric or perinatal complications or cognitive impairment. On the other hand, the routine determination of THS in all pregnant would pose a difficulty in clinical practice derived from the complexity of the proper interpretation of the test results and the possibility of false positive results, so it was agreed to focus the recommendation on the risk groups. The strength of the recommendation shows the uncertainty and potential controversy surrounding this issue.

Recommendation

√	A screening of thyroid function should be carried out at the first visit in pregnant women with risk factors for thyroid dysfunction: women over 30, women with a family history of thyroid disease, women with a history of thyroid disease, women with DM type 1 or other autoimmune disorders, women with a history of repeated abortions, irradiation of head or neck, on levothyroxine replacement therapy or who live in areas that are presumably deficient in iodine.

Screening for gestational diabetes

Four SRs (Syed, 2011; USPSTF, 2008; Farrar, 201; Tieu, 2010) have been identified. The SR by Syed (2011) evaluated the effect of screening for gestational diabetes (GD) and the management of diabetes during pregnancy on perinatal mortality. The SR included 70 studies, of which only three evaluated issues related to GD screening: one compared the impact of early detection strategies against late detection strategies (Dong, 1993); other compared two types of diagnostic criteria for GD, one proposed by the American Diabetes Association (ADA) and the other by the WHO (Schmidt, 2001); and a third study compared the effect of universal screening versus selective screening of women at high risk (Ezimokhai, 2006).

An SR conducted by the US Preventive Services Task Force (USPSTF, 2008) which provided additional information on the adverse effects associated with screening for gestational diabetes was also located.

Two SRs (Farrar, 2011; Tieu, 2010), evaluating different screening strategies for GD and its association with maternal and newborn outcomes were included.

Additionally, it has also included the HAPO study (HAPO Study Cooperative Research Group, 2008), an observational study carried out in 24,505 pregnant women from four continents whose results have prompted a review of the diagnostic criteria of GD.

Screening efficacy and safety for gestational diabetes

Other clinical practice guidelines

A high quality systematic review made by the USPSTF in 2008 (USPSTF, 2008) did not identify any clinical trial on the efficacy of using a screening for GD to reduce the morbidity and mortality for the mother or the newborn. From these results, the USPSTF did not make any recommendations on conducting screening for GD because the available evidence was insufficient to establish the balance between the benefits and risks of the intervention.

Early screening strategies compared to late screening strategies

Low quality

In the SR by Syed (2011) a retrospective cohort study conducted in Australia (Dong, 1993) that included 1,027 women with a history of GD in the previous pregnancy were included. In a group of 180 women, a glucose tolerance test (OGTT) was performed before 24 weeks of gestation, in another group of 685 women the test was performed between weeks 26 and 30 and in a group of 162 women, no screening for GD was performed. There were no differences in the rates of perinatal mortality in the three groups: 2.2% versus 0.6% versus 3.1%

Universal screening versus screening risk groups

Very low quality

In the SR by Syed (2011) a study (Ezimokhai, 2006) comparing universal screening versus selective screening of high-risk women (n = 11,738) was included. This retrospective study compared the neonatal outcomes of pregnant women attending the same hospital during two different periods in which different types of screening for GD were performed. The first group consisted of women seen between the months of June 1996 to December 1997, a period in which selective screening was done on the basis of risk factors (diabetes in a first degree relative, history of GDM, background of a newborn dead without apparent cause, previous newborn with macrosomia, maternal weight> 100 kg). A 1-h with 50 g glucose test was performed and if the result was ≥7, 8 mg / dl a second test was

conducted with 100 g. The second group consisted of women seen between June 2001 and December 2002, a period in which screening was performed to all pregnant women with a 1 h with 50 g OGTT.

In this study there was a higher percentage of caesareansection delivery, macrosomia and birth defects in the selective screening group (30.3% versus 19.8% p = 0.002; 22.2% versus 10.6%, p <0.001; 22.2% versus 10.6 p = 0.03 respectively). There were no differences in intrauterine mortality (2.9% versus 1.4%) or frequency of preterm delivery (22.5 versus 17.5)

In the SR by Tieu (2010) a quasi-randomised study with important methodological limitations (Griffin, 2000) was incorporated. This study included 3,742 women who were randomised to receive a universal screening test with 1-h 50 g glucose (regardless of the time of the last meal) in weeks 26 and 28 of gestation (in case of positive a 100 g glucose test was performed) or selective screening of women at high risk with a 3-h OGTT with 100 g in week 32. It was considered that women were at risk of Gd if they had first-degree relatives whit diabetes, weight >100 kg in the current pregnancy, previous newborn weighing >4.5 kg, history of unexplained foetal death, malformations, previous GD, glycosuria, macrosomia and polyhydramnios in the current pregnancy. **Low quality**

In this study, more women were **diagnosed** with GD in the universal screening group (n = 35) than in the group of selective screening (n = 22) (RR 0.44, 95% CI 0.26 to 0.75).

Gestational age at birth was lower in the group of women who received selective screening compared to those receiving universal screening (39.7 weeks versus 39.85 weeks on average; DM -0.15 weeks, 95% CI - 0.27 to -0.03), although this difference did not appear clinically relevant.

Adverse effects of screening for gestational diabetes

In the SR by the USPSTF (2008) three observational studies were included with a suitable design (2 prospective cohorts and a cross-sectional study) evaluating the psychological effects of screening for GD. **Low quality**

One study (Rumbold, 2002) included 209 Australian women and assessed anxiety, depression and worry about the health of the foetus before and after the completion of screening. No association was found between these three variables and the screening results. Women with negative screening results were more likely to rate the screening experience as positive than those with positive results (p <0.010).

Another cohort study (Daniells, 2003) compared the results of the Mental Health Inventory 5and the anxiety score from the Spielberg Inventory State-Trait Anxiety among women diagnosed with GD (50 women) and women with normal glucose tolerance (50 women). It was observed, that women with GD had higher scores on both instruments at 30 weeks of gestation, although there were no statistically significant differences at week 36 and 6 weeks after childbirth.

The cross-sectional study (Spirito, 1989) included in the SR by Hillier (2008) evaluated the psychological state of 68 women with GD and 50 controls without GD in the 35th week of gestation without any differences in mood according to the *Profile of Mood States bipolar Form*. **Very low quality**

Glucose administration strategies for conducting an OGTT

Two quality SRs (Farrar, 2011; Tieu, 2010), evaluated and compared different management strategies for conducting glucose OGTT for GD screening. Tieu (2010) included three RCTs that evaluated this aspect (230 women). Farrar (2011) included five RCTs (578 women), three of which coincided with those of the previous SR.

The comparisons studied in these SRs were: 1) 75 g versus 100 g OGTT test; 2) 50 g glucose monomer drink versus 50 g glucose polymer drink; 3) chocolate versus 50 g glucose monomer drink; 4) chocolate versus 50 g glucose polymer drink.

5 g OGTT test compared to 100 g OGTT test **Low quality**

The SR by Farrar (2011) included an RCT (Olarinoye 2004, 248 women, 21 events) comparing a screening with 75 g OGTT test (138 women) with a 100 g OGTT (110 women) after 28 weeks of gestation, using the diagnostic criteria proposed by the WHO. No statistically significant differences in the rate of diagnosis of GD were found from one test to another (95% CI 0.96 to 6.75 RR 2.55).

Glucose monomer drink compared to glucose polymer drink **Low quality**

Two studies (Bergus, 1992; Murphy, 1994) assessed this comparison (161 women, 5 events) with no significant differences in the rate of diagnosis of GD (RR 1.61, 95% CI 0.28 to 9.15). There were no differences in terms of taste preference between these two forms of administering glucose (1 RCT, 85 women, 16 events, RR 0.86, 95% CI 0.34 to 2.04).

Monomer or polymer glucose drinks compared to chocolate **Low quality**

A study (Murphy, 1994) evaluated these two comparisons. It found no differences in the diagnosis rate of GD for the first comparison (1 RCT, 80 women, 3 events, RR 6.67, 95% CI 0.36 to 125.02) nor for the second one (1 RCT, 80 women, two events, RR 4.44; I 0.22 to 89.84% C95). However, the chocolate was better assessed in terms of taste than the monomer glucose drink (RR 0.35, 95% CI 0.17 to 3.72) and the polymer glucose drink (RR 0.42; 95 0.22 to 0.82%).

Diagnostic criteria for GD

The publication of the study results on Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) has led to the revision of the diagnostic criteria of GD by different organisations. Recently, the ADA has changed its recommendations and adopted the criteria proposed by the International Association of Diabetes and Pregnancy Study Group (IADPSG), which are based on this study (HAPO Study Cooperative Research Group, 2008).

The HAPO study is an observational study carried out on 24,505 women that analysed the risk of the occurrence of adverse outcomes in pregnancy in relation to different levels of maternal glucose intolerance, below diabetes diagnostic levels.

One oral glucose tolerance test (OGTT) with 75 g was performed and ongoing associations were identified between the levels of maternal glycaemia (baseline, after 1 hour and after 2 hours) with an increased risk of having a birth weight above the 90th percentile and C-peptide levels in cord blood above the 90th percentile.

Other clinical practice guidelines

Associations between higher levels of maternal glycaemia and increased risk of caesareansection delivery, neonatal hyperglycaemia, premature delivery, shoulder dystocia, neonatal intensive care, hyperbilirubinemia, and preeclampsia were also found. The results of this study indicated a linear association between maternal glucose levels and adverse perinatal outcomes but could not define a cut-off level at which the risk of adverse outcomes increased.

The IADPSG based itself on the HAPO study to establish diagnostic cut-offs for fasting glucose after 1 hour and after 2 hours (5.1, 10.0 and 8.5 mmol / l, i.e. 95.4 mg / dl, 180 mg / dl and 154.8 mg / dl, respectively) using glucose levels associated with an incrased riks of having a large baby (above the 90th percentile for gestational age).

The Canadian Diabetes Association guidelines also based themselves on the HAPO study to establish the cut-offs. In this case they were higher than those proposed by the IADPSG as blood glucose levels with an OR> 2 for the outcome of a newborn large for gestational age were taken into account.

Criteria proposed by the ADA versus criteria proposed by the WHO for the diagnosis of gestational diabetes

The SR by Syed (2011) included a cohort study conducted in Brazil in 2001 with 4,977 women aged 20 years or more, between 20 to 28 weeks of gestation with no history of diabetes outside the pregnancy. All women underwent a 2 h OGTT with 75 g of glucose between weeks 24 and 28 and the diagnostic criteria of GD (in 2001 values) proposed by the ADA were compared (at least two plasma glucose values 5.3 mmol / l (95.4 mg / dl), ≥10,0 mmol / l (180 mg / dl) after 1 hour, and ≥8,6 mmol / l (154.8 mg / dl) after 2 hours) with those proposed by the WHO (fasting glucose ≥7,0 mmol/l or 126 mg / dl or blood glucose after 2 hours ≥7,8 mmol / l or 140 mg / dl) after a 2 h OGTT with 75 g). Following the criteria of the ADA, 119 women (2.4%; 95% CI 2.0 to 2.9) were diagnosed and according to the WHO 357 (7.2%; 95% CI 6.5 to 7.9).

Very low quality

After adjustment by health centre, age, maternal weight, weight gain, and ethnicity, it was observed that the diagnosis of GD based on the ADA criteria was not associated with a statistically significant increased risk of macrosomia but with an increased risk of preeclampsia (RR 2.28) and perinatal mortality (RR 3.10). However, applying the WHO diagnostic criteria, the diagnosis of GD was associated with an increased risk of macrosomia (RR 1.45), of developing preeclampsia (RR 1.94) but was not associated with a statistically significant increase risk of perinatal mortality.

Criteria proposed by the WHO versus criteria proposed by the IADPS

The SR by Wendland (2012) evaluated the association between the diagnosis of GD following the criteria proposed by the WHO (the same criteria as in the previous study) and those proposed by the IADPSG (values from 2010) with adverse outcomes in untreated women. The authors possessed the database from the Brazilian Study of Gestational Diabetes (EBDG), which allowed the analysis for both criteria.

Women diagnosed with GD according to WHO criteria were at increased risk of macrosomia than healthy women (five trials, 11,588 women, 482 events, RR 1.81, 95% CI 1.47 to 2.22; p <0.001). **Low quality**

No study assessing macrosomia according to the IADSPG diagnostic criteria was identified. The authors conducted an analysis using the database by EBDG and the calculated RR was 1.38 (4,377 women, 482 events, 95% CI 1.14 to 1.68; p = 0.001). **Low quality**

Women diagnosed with GD according to the WHO criteria showed a higher risk of having a newborn large for gestational age compared to those not diagnosed with GD (4 studies, 28,755 women, 2,755 events, RR 1.53, 95% CI 1 , 39 to 1.69). **Low quality**

Three studies evaluated the risk of having a newborn large for gestational age in women diagnosed according to the IADPSG criteria (3 studies, 35,902 women, 2,392 events, RR 1.73, 95% CI 1.28 to 2.35). The existence of significant inconsistencies between the three studies (I2 = 93%) limits the validity of the combined RR. **Very low quality**

Two studies provided data to evaluate the perinatal mortality using the WHO diagnostic criteria, observed an association, which did not reach statistical significance (2 studies, 9072 women, RR 1.55, 95% CI 0.88 to 2.73). **Very low quality**

There were no studies that allowed evaluating the diagnostic criteria according to the IADSP, so an analysis of the EBDG database was performed and found statistically significant similar results (1 study, 4,431 women, RR 1.40, CI 95% from 0.91 to 2.14).

A statistically significant positive association between the diagnosis of GD was observed following the criteria proposed by the WHO and the incidence of preeclampsia (3 studies, 2.6677 women, RR 1.69, 95% CI 1.31 to 2.18). **Very low quality**

Following the criteria of the IADPSG, the overall RR was of similar magnitude (3 studies, 35,052 women, RR 1.71, 95% CI 1.38 to 2.13) but the results were very inconsistent across the studies.

The two diagnostic criteria detected women with increased risk of caesareansection delivery, being the combination a little higher when the WHO criteria (RR 1.37, 95% CI 1.24 to 1.51) were used than when those proposed by the IADSPG (RR 1.23, 95% CI 1.01 to 1.51) were used. For the IADSPG criteria, the results were inconsistent across the 3 studies included. **Very low quality**

In Spain, the Spanish Group of Diabetes and Pregnancy recommends universal screening of GD considering the high prevalence of this disease (Spanish Group of Diabetes and Pregnancy, 2006). **Other clinical practice guidelines**

Other clinical practice guidelines with the same scope as this guide (Servei de Salut de les Illes Balears, 2012), provide universal screening as recommended by the Spanish Group of Diabetes and Pregnancy, taking into account the following considerations:

- It is necessary to make a shared and informed decision on the performance of this screening to women, and respect the decision of those women without risk factors that decide not to undergo the test.
- In the information sharing process, women should be informed of:

- Pregnancy with gestational diabetes finishes in most cases satisfactorily, without complications and with the birth of a healthy baby.
- Gestational diabetes is a nutrition problem to the foetus due to an excess of glucose received that stimulates its insulin secretion and, therefore, its growth can be accelerated and produce macrosomia, which in turn is associated with the risk of dystocia.
- An adequate glycaemic control during pregnancy can reduce perinatal complications.
- Gestational diabetes usually responds to changes in the diet and encouragement of physical activity, and a small percentage of women require drug treatment.
- Gestational diabetes increases the risk of women to repeat an episode of gestational diabetes in future pregnancies, or having type 2 diabetes so it is necessary to control women at least six weeks after childbirth.
- Maternal glycaemic control and breastfeeding can help reduce the risk of the baby developing obesity or diabetes in the future.
- Performing the O'Sullivan test as a screening test (administration of 50 g of glucose orally without being fasting, with blood drawn after an hour to determine plasma glucose), following the directions below.
- Perform screening during the first trimester of the pregnancy for women at high risk for gestational diabetes: women with an BMI ≥30 Kg / m2;personal history of gestational diabetes or other problems with glucose metabolism; obstetric history with suspected undiagnosed gestational diabetes (macrosomia).
- Repeat screening between weeks 24 and 28 in women at high risk for gestational diabetes with a negative result in the first trimester screening, or with a positive result and a normal blood glucose curve.
- Perform universal screening between weeks 24 and 28.
- Perform screening during the third trimester of pregnancy in women when the outcome of universal screening is not available.

Summary of evidence

Universal screening versus not screening	
There are no studies comparing the results of performing a universal screening for gestational diabetes with not performing it.	
Early screening strategies versus late screening strategies	
Low quality	Conducting a screening for gestational diabetes before 24 weeks of gestation compared to performing a late screening (between weeks 26 and 30) or not performing screening has shown no difference in the rate of perinatal mortality (Dong, 1993).
Universal screening versus selective screening in risk groups	

Low quality	Universal screening, compared to selective screening performed to women at high risk of developing gestational diabetes, presents higher diagnosis rates of gestational diabetes. Selective screening, compared to universal screening detects more women with infants small for gestational age at birth, although the difference is not clinically relevant (1 day on average) (Tieu, 2010).
Low quality	Universal screening compared to selective screening presents no differences in intra-uterine or percentage mortality of preterm births. Selective screening, compared to universal screening, is associated with higher percentage of caesareansection delivery, macrosomia, and congenital malformations.
Adverse effects of screening for GD	
Low quality	During the first weeks after screening, women with positive results may show more anxiety and psychological stress than women with negative results, although these differences are not kept at the end of the third trimester or in the puerperium.
Glucose Management Strategies to perform an OGTT test	
Low quality	There is no difference between using a 75 g OGTT or a 100 g OGTT in the rate of diagnosis of GD using the diagnostic criteria proposed by the WHO. There is no difference between using a glucose monomer drink or a glucose polymer drink in the diagnosis rate of GD. There is no difference between using a chocolate bar or a glucose monomer or polymer drink in the diagnosis rate of GD. There is no difference regarding taste preference between a glucose monomer or polymer drink. The administration of a chocolate bar is better valued in terms of taste than a glucose monomer or polymer drink.
Diagnostic criteria for GD	
Very low quality	Applying the diagnostic criteria proposed by the ADA in 2012[2], a higher percentage of women were diagnosed with GD than by applying the WHO[3] criteria. The diagnosis of GD according to the criteria proposed by the ADA in 2001, compared to those by the WHO, is associated with an increased risk of preeclampsia and perinatal mortality, but not with an increased risk of macrosomia.

Very low quality	Applying the diagnostic criteria proposed by the WHO, the risk of macrosomia appears to be higher than when applying the diagnostic criteria proposed by the IADPSG[4], although the data comes from indirect comparisons. Applying the WHO criteria, the risk of having a newborn large for its gestational age seems to be somewhat smaller than applying the diagnostic criteria proposed by the IADPSG. The risk of preeclampsia is similar when applying the diagnostic criteria of the WHO and the IADPSG. The diagnosis of GD applying the diagnostic criteria proposed by the WHO or those proposed by the IADPSG is not associated with an increased risk of perinatal mortality.

From evidence to recommendation

The aspects considered in determining the strength and direction of the recommendations were:

1. Quality of the evidence: there is no direct evidence that assessed the efficacy of performing a universal screening for gestational diabetes. In the literature, studies that have compared different screening strategies, primarily aimed at making a universal screening or screening in women with risk factors have been identified. From the available studies it can be concluded that:The quality of the evidence is very low due to the serious limitations of the available observational and mostly retrospective studies. It should be noted that in addition to providing indirect evidence to answer this question, they are a source of inconsistency between their results. These reasons make the reliability of these studies very low. This fact determines that all the recommendations in this section have been considered good clinical practice recommendations.

   a. Performing early or late screening did not show differences in terms of perinatal outcomes.

   b. In a retrospective cohort study (Ezimokhai, 2006), selective screening of women with risk factors, compared with universal screening, showed a higher percentage of caesareansection delivery, macrosomia and birth defects, with no differences in intrauterine mortality or frequency of preterm delivery. Another quasi-randomised study (Griffin, 2000) has shown that selective screening resulted in a lower gestational age at birth, unimportant from a clinical point of view, while universal screening contributed to the diagnosis of more women with GD.

   c. In Spain, the Spanish Group of Diabetes and Pregnancy recommends universal screening for GD considering the high prevalence of this disease.

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[2] GD diagnostic criteria proposed by the ADA in 2001: at least two basal plasma glucose values ≥5,3 mmol / L (95.4 mg / dl) ≥10,0mmol / l (180 mg / dl) after 1 h and ≥8,6 mmol / L (154.8 mg / dl) (at 2h) after a 2-hour 75 g OGTT test.

[3] GD diagnostic criteria proposed by the WHO: fasting glucose ≥7, 0mmol, / 126mg / dl or blood glucose after 2 hours ≥7,8mmol / lo 140 mg / dl) after a 2-h 75g OGTT test.

[4] GD diagnostic criteria proposed by the IADPSG: fasting glucose ≥5,1 mmol / 92mg / dL; glucose after 1 h ≥10,0 mmol / 180 mg / dl; blood glucose after 2 hours ≥ 8.5 mmol / l or 153 mg / dL after a 2-h 75g OGTT test.

d. Studies that have compared glucose administration strategies for carrying out the oral glucose tolerance test have shown no difference between the 75 gr and the 100 gr OGTT, or between the monomer or polymer drinks. However, a clinical trial showed that performing the test with a chocolate bar was better accepted than the monomer or polymer drinks, although there was no difference between the number of women diagnosed with gestational diabetes.

e. The diagnostic criteria for gestational diabetes are continuously evolving and it seems that the results of the HAPO study will involve a further review of these values, as that which has led the ADA to adhere the IADPSG criteria.

2. Balance between benefits and risks. Presenting a positive screening result was associated with a transient increase in anxiety and psychological stress by the pregnant woman though these disappear within a few weeks. A potential benefit of conducting screening outweighs the psychological risks associated with a positive outcome. There are no studies assessing the occurrence of other adverse events as the treatment of false positives.

3. Costs and use of resources: A study (Werner, 2012) evaluated whether the adoption of the criteria proposed by the IADPSG for the diagnosis of GD were cost-effective compared to regular care. An analysis decision model comparing the cost-utility of three strategies to identify GD was created: 1) no screening, 2) routine screening (1-h 50 g OGTT test between weeks 24 and 28 followed by a3-h 100g OGTT test when indicated), 3) screening strategy proposed by the IADPSG (2-h 75 g glucose OGTT test). The results showed that the recommendations of the IADPSG are cost-effective only if puerperium care reduces the incidence of type 2 diabetes after pregnancy. When puerperium care is not met, this strategy is no longer cost effective. For every 100,000 women screened under these criteria, 6178 years of quality-adjusted life (QALYs) are gained at a cost of $125,633,826. The cost-effectiveness increase according to the IADPSG criteria compared to the standard criteria was of $20,336 per QALY gained.

After assessing these aspects and considering the failure to identify studies examining the values and preferences of pregnant women, the development group considered that there is not enough evidence to assess the balance between the benefits and risks of using a screening for gestational diabetes, so the Working Group decided to base its recommendations on the considerations made in documents from the NICE on gestational diabetes (NICE, 2008) and the recommendations of the Spanish Group of Diabetes and Pregnancy (Spanish Group of Diabetes and Pregnancy, 2006). All the recommendations in this section are graduated as good clinical practice.

Recommendations

√	In those cases of pregnant women without risk of complications, the following risk factors for gestational diabetes should be measured during the first visits of pregnancy: BMI ≥ 30 kg / m2, history of macrosomic children with ≥4,5 kg birth weight, history of gestational diabetes, or family history of diabetes in first grade.
√	Screening for gestational diabetes should be carried out in the first trimester in women with a history of gestational diabetes.
√	The screening should be repeated between weeks 24 and 28 of gestation in those women in whom any of the risk factors for gestational diabetes with a negative result in the first trimester screening, or a positive result and a normal glucose curve.

√	The O'Sullivan test should be carried out between weeks 24 to 28 as a screening test, after having informed women about the characteristics of the test.

Screening for risk of preterm delivery

Ultrasound assessment in asymptomatic women

A technologies assessment report (Honest et al., 2009) that conducted a systematic review of studies evaluating the diagnostic performance of ultrasound measurements to detect asymptomatic preterm pregnancy in pregnant women has been identified. The studies evaluated primarily different cervix lengths and the presence of funnelling (5 mm protrusion of the amniotic membrane in the cervical canal), at different times of the pregnancy and for the prediction of preterm delivery before weeks 34 or 37 of gestation. The report provides the joint estimator of the studies without methodological limitations (prospective cohort studies, with blinded evaluation and an adequate description of the test to be performed and the reference value -in all cases the reference test was the presence or absence of preterm childbirth).

Screening cervix length

Preterm delivery before week 37 **Low quality**

Screening before week 20

The review located two studies evaluating different cervix lengths (between 22 and 39 mm), all small and with varying results. No pooled analysis of the results was performed.

Screening between weeks 20 and 24 **Moderate quality**

The review located two studies evaluating different cervix lengths (32.5 and 33.15 mm). The results of the higher quality study showed a positive likelihood ratio (LR +) of 3.99 (95% CI 2.84 to 5.62) and a negative likelihood ratio (LR-) of 0.33 (CI 95 % from 0.17 to 0.66) for a cervix length of less than 32.5 mm.

Preterm delivery before week 34 **Moderate quality**

Screening before week 20

The review includes three quality studies that evaluated the performance of the ultrasound measurement of the cervix with a common cut of 25 mm. The combined results showed a positive likelihood ratio (LR+) of 13.38 (CI 95% 6.90 to 25.96) and a negative likelihood ratio (LR-) of 0.80 (CI 95% 0.71 to 0.90), with consistent results for LR-.

Screening between weeks 20 and 24 **High quality**

The review includes two quality studies that evaluated the performance of the ultrasound measurement of the cervix with a common cut of 25 mm. The combined results showed a positive likelihood ratio (LR +) of 4.68 (95% CI 3.64 to 6.03) and a negative likelihood ratio (LR-) of 0.68 (95% CI 0.60 to 0.78), with consistent results.

Tunnelling presence

The review by Honest (2009) (Honest et al., 2009) located five trials assessing the presence of tunnelling for the prediction of preterm delivery although the criteria used to establish the criterion were variable or not described in some studies. The review does not show a joint result due to the variability of the results. The best quality trial performed an ultrasound measurement after 28 weeks of gestation and defines the presence of tunnelling as a 5 mm protrusion of the amniotic membrane in the cervical canal. The study showed a positive likelihood ratio (LR +) of 4.63 (95% CI 3.31 to 6.48) and a negative likelihood ratio (LR-) of 0.79 (95% CI 0.71 to 0.87).

Moderate quality

Summary of evidence

Moderate quality	Ultrasound measurement of cervix length (less than 25 mm) performed before week 20 or up to week 24 of gestation has good diagnostic performance to detect women at risk of preterm birth before 34 weeks of gestation.

From evidence to recommendation

The aspects considered to determine the strength and direction of the recommendations were:

1. Quality of the evidence: the main limitation of the quality of the evidence in studies that evaluated the diagnostic performance of the measurement of cervical length in asymptomatic women stems from the variability (heterogeneity) and the accuracy of the results. The selected studies were conducted in women with singleton pregnancies and in most situations, it has not been possible to assess the sources of variability and include the presence of other risk factors besides multiple pregnancies.
2. Balance between benefits and risks: although the determination of the length of the cervix has shown diagnostic performance to detect any risk of preterm delivery (LR+), the results are of relative clinical relevance. Considering the risk of preterm birth <37 weeks at 11% and 3.6% after <34 weeks (Martin, 2009) the absolute benefit from this procedure is relatively low. Thus, if the determination of cervical length is between 20 and 24 weeks, the probability of birth after <34 weeks increases to 14% after the test. Only if the determination is performed before 20 weeks, the chance of birth <34 weeks increases to 33% after the test. This result is obtained similarly with the tunnelling, with which the delivery probability after <34 weeks increases to 14% after the test. The absolute benefit is higher when evaluated for the probability of preterm delivery after <37 weeks, but its relevance is less than the detection of childbirths after <34 weeks. The absolute benefit is very low when a negative result is obtained in this procedure.
3. Costs and use of resources: the need to adapt the ultrasound transducers to assess cervical length or tunnelling, the possible need to increase the number of scans required during pregnancy, the need for trained personnel to carry out these determinations and the lack of criteria agreed on the positivity or negativity of these determinations, imply, according to the development group's criterion, very high costs which will most likely do not outweigh the potential benefits.

Finally, the development group formulated the recommendations taking into account the results reported in the literature (Honest et al., 2009) and the increase of the resource required to implement the interest procedure as determining factors of a recommendation against its use. On

the other hand, the quality of the evidence is generally moderate although there are doubts about the extrapolation of these results to the entire population that will include women with other risk factors, which led to consider these recommendations as weak.

Recommendations

Weak	We suggest not performing an ultrasound determination of the length of the cervix routinely.
Weak	We suggest not determing routinely ultrasound cervical tunnelling to all pregnant women without previous signs or symptoms of preterm delivery.

Labour and childbirth plan

Although there is a large number of studies highlighting the usefulness of childbirth plans (Bailey, 2008; Lothian, 2006), there are not too many controlled studies evaluating the impact of this intervention on health outcomes. The only RCT that has been published comparing the application of a childbirth plan against routine prenatal care (Kuo, 2010) only assessed outcomes related to the perceptions and expectations of participants. For this reason, the results of two recent observational studies evaluating the impact of childbirth plans on obstetric outcomes have been assessed (Deering, 2007; Hadar, 2012).

The single-blind RCT by Kuo (2010) randomised 296 pregnant women after more than 32 weeks of gestation, cared for in seven Taiwanese hospitals (Kuo, 2010) and assessed the effectiveness of a childbirth plan in which a number of options about some procedures that could be used during labour and which allowed women to express any expectation or desire on the procedure, were raised. Women assigned to the control group received regular care. The relevant outcomes were the experiences of women with childbirth, the feeling of control over the process and meeting the expectations of delivery without any obstetric outcome assessed.

A case-control study collected data from 154 women who had completed a childbirth plan in an Israeli hospital over a period of three years and compared the pregnancy outcomes with those of 462 women who had not completed the plan, matched by age, parity and gestational age (Hadar, 2012). In a previous case-control study (Deering, 2007), the data of childbirths of the 64 women who had completed a childbirth plan were collected, excluding those which had required a caesarean section at a different hospital to that under study, and their data were compared with those of 128 women matched by age and parity.

The case-control study by Hadar (2012) showed that, compared with women who did not follow a childbirth plan, those women who completed it had a lower risk of undergoing an unscheduled caesarean section (11.7% versus 20.3%; $p = 0.016$). On the other hand, the study by Deering (2007) showed no difference in this outcome (17% versus 12%; $p = 0.3$). **Low quality**

Regarding other obstetric outcomes, the study by Hadar (2012) showed that women who had completed a childbirth plan suffered a higher percentage of perineal tears (72.1% versus25.5%; $p < 0.001$). These women also used more epidural anaesthesia (81.2% versus 68.8%; $p = 0.004$) and received a lower percentage of intravenous analgesics (1.3% versus 10.2%; $p < 0.001$). In the case-control study by Deering(2007) women who had completed a childbirth plan and had a vaginal delivery received epidural anaesthesia less often (57% versus 78%; $p = 0.005$). **Low quality**

On the other hand, the study by Deering (2007) showed no significant differences between women who completed a childbirth plan and those who did not, in terms of number of episiotomies carried out (25% versus 23%; p = 0.83).

Moderate quality

The RCT by Kuo (2010) found that women who had completed the childbirth plan showed a more positive birth experience than women who received regular care. When comparing scores from a validated questionnaire covering a range of issues related to the perception of women giving birth (Marut, 1979), women who had completed the childbirth plan showed higher scores (with a score between 29 and 145; intervention group: 93.8 (10.3) versus control group: 90.5 (12.5); t = 2.48; p = 0.01). Similarly, women who completed the childbirth plan showed a greater sense of control at childbirth after answering a validated questionnaire (Hodnett, 1987, with a maximum score of 70 points; intervention group: 51.1 (5.1)versus control group: 43.3 (8.4); t = 9.60; p <0.001).

Summary of evidence

Low quality	Conducting a childbirth plan has an uncertain impact on obstetric outcomes. While some studies have shown a decrease in unscheduled caesarean section (Hadar, 2012), another showed no differences (Deering, 2007). This procedure has shown an increased use of epidural analgesia and a lower requirement for intravenous analgesia (Hadar, 2012), while no differences have been shown in the episiotomy rate compared to women who had not completed a childbirth plan. The only RCT that evaluated this process so far has shown that it can contribute to a better experience and increase the sense of control at childbirth (Kuo, 2010).

From evidence to recommendation

The aspects assessed to determine the strength and direction of the recommendations were:

1. Quality of the evidence: the quality of the evidence has been rated as low since the most relevant outcomes for the decision-making have been assessed in case-control studies in which the possibility of increasing this rating has not been considered in any case. Although there is an RCT, which has only taken into account outcomes related to the experience and expectations of pregnant women during childbirth, thus its importance was considered lower than the obstetric outcomes. In this case, it was decided to lower the evidence because, as has been mentioned, outcomes that are not related to the health of the mother or the newborn, and the context in which it was made can be different in a sense to our environment (on issues such as access to health care or a difference among women).
2. Values and preferences of pregnant women: several studies have explored different aspects related to birth plans through a survey. In one of them, it was detected that health professionals have a different perception to that of pregnant women regarding birth plans, which in some ways becomes negative (Grant, 2010). In this study, it was found that 65% of the professionals versus 2% of women, who completed a childbirth plan, believed that women who completed a childbirth plan had poorer obstetric outcomes and had a higher percentage of caesareansection at delivery (65% versus 8%). In another study, women who completed the childbirth plan did not always perceive the procedure as safe and assessed the information received related to childbirth as positive, but not that related to the puerperium (Gulbrandsen, 2004). Other studies have highlighted the utility of childbirth plans for the process

and possible interventions involved in childbirth, giving the possibility to discuss the options available (Whitford, 1998) to improve communication with the health professionals, reliability at childbirth and understanding of the process (Moore, 1995). In this regard, a recent study has confirmed that although the childbirth plan does not improve the birth experience itself, it does contribute to improving the worry or fear of some women to this process (Lundgren, 2003).

Considering these aspects and taking into account that no studies on the costs and use of resources for the implementation of a birth plan were identified, the development group considered that although the results related to obstetric outcomes were unclear, it would be good to provide a recommendation supporting childbirth plans due to the possible benefits of undergoing this experience and having control over the labour of women who have the ability to complete this procedure. Moreover, and given the uncertainty of the benefits of this intervention, it was decided to formulate this recommendation as weak.

Recommendations

Weak	We suggest offering to pregnant women the chance to develop a delivery and birth plan from week 28, which allows to know their preferences.
√	The delivery and birth plan should be sent to the hospital and incorporated into the medical record so that those professionals attending childbirth know the desires of women and can plan childbirth together.

Ultrasound examination and prenatal diagnosis

Chronology of ultrasound scanning

There is no evidence that the systematic use of ultrasound scanning is associated with better pregnancy outcomes (Kirkham, 2005). During a normal and uncomplicated pregnancy it may be enough to perform three ultrasound scannings, informing women at all times about the type and objectives of the scanning carried out (Prosigo, 2010). The scannings should be performed at different times of gestational age, with the objectives listed in Table 5:

An ultrasound scanning between weeks 8 and 12 of gestation helps to date the pregnancy, locate the correct location of the pregnancy, state foetal vitality, and discard multiple pregnancy as well as some malformations (PAPPS, 2009). With ultrasound scanning before week 12, by measuring crown to rump length, the gestational week is more accurately specified (SEMFyC, 2002). Other documents delay the completion of the first ultrasound scanning even before 14 weeks of gestation (Kirkham, 2005; NICE, 2008).

In this scanning, a measurement of the nuchal translucency should be carried out as a screening for Down syndrome. A further exploration between weeks 18 and 20 should serve to rule out structural abnormalities (Kirkham, 2005; NICE, 2008; Bricker, 2008; PAPPS, 2009).

In more advanced stages of pregnancy, ultrasound scanning can assess foetal growth (PAPPS, 2009), being as it is still common in our environment to have an ultrasound scanning between weeks 32 and 34 to assess foetal growth (SEMFyC, 2002). However, similar pregnancy outcomes have been seen among low-risk pregnant women when two routine ultrasound scannings were performed at weeks 20 and 32, in comparison to when none were performed (SEMFyC, 2002; Ewigman, 1993). The US Preventive Services Task Force (USPSTF, 1996) recommends the systematic use of ultrasound screening in the third trimester, unless clinically indicated by specific processes.

Performing ultrasound scanning before 24 weeks of gestation

A Cochrane SR (Whitworth, 2010) assessing the performance of a routine ultrasound scanning before 24 weeks of gestation and its impact on the diagnosis of foetal malformations, multiple pregnancy, and foetal outcomes has been identified.

The SR included 11 RCTs, mostly conducted in European countries where carrying out a routine ultrasound was compared before 24 weeks versus performing the ultrasound at specific clinical situations. In the trials, the scanning was performed at different times, from weeks 10 or 11 in the RCTs in which there were held earlier (Crowther, 1999; Ewigman, 1990) to weeks 20 or 23 in which it was made more belatedly (Ewigman, 1993, Saari-Kemppainen, 199; van Dyk, 2007). In other studies, the test was performed between weeks 15 and 18 of gestation.

Moderate quality

Routinely performing ultrasound scannings before week 24 contributed to an increased detection of foetal anomalies compared to performing the ultrasound scanning according to specific indications (2 RCTs, 17,158 pregnancies, 387foetal abnormalities; RR 3.46, 95% CI 1 67 to 7.14).

Similarly performing routinely ultrasound scannings before week 24 contributed to better detection of multiple pregnancies (7 RCTs, 295 multiple pregnancies; RR 0.07, 95% CI 0.03 to 0.17).

Although the results showed that routine screening detected the risk of induction of labour in post-term pregnancy better (8 RCTs, 25,516 women; RR 0.59, 95% CI 0.42 to 0.83), the results showed considerable heterogeneity.

The routine performance of ultrasound scanning before week 24 showed no significant differences in relation to the scanning conducted before a specific clinical situation in the risk of perinatal mortality (10 RCTs, 35,735 women; RR 0.89, 95% CI 0 70 to 1:12).

Performing ultrasound scanning after 24 weeks of gestation

A Cochrane SR (Bricker, 2008) assessing the performance of a routine ultrasound scan after 24 weeks of gestation in women without risk factors conducted in order to check foetal growth, measure the volume of amniotic fluid, or determine foetal presentation, among others, has been identified.

The SR included eight RCTs with 27,024 participants offering different types of ultrasound scannings. In three RCTs regular ultrasound scans were performed in the second and third trimester of the pregnancy compared to a group in which ultrasound scans were performed at specific clinical situations Eik-Nes (2000), Ewigman (1993) to all women during the second trimester and only the intervention group received an ultrasound scan during the third trimester (Duff, 1993), similar to that of the RCT by Neilson (1984) and Proud (1987) which was performed to all pregnant women in the second and third trimesters, but only the results of the second ultrasound scan in the intervention group were provided. Another study performed an ultrasound scan in the first trimester and again between weeks 30 and 32, and weeks 36 and 37 of gestation among pregnant women within the intervention group (McKenna, 2003). Finally, in a last RCT, an ultrasound scan was conducted in the second trimester to all women and then they were randomised to receive a final ultrasound scan in the third trimester or not to receive it (Newman, 1993).

The results of the SR showed no differences in the main outcomes of interest between those groups of women who underwent ultrasound scanning during the third trimester and those who did not. Birth weight and the incidence of preterm delivery were similar between groups, with no differences between groups in terms of perinatal mortality.

Moderate quality

Among the women who underwent an ultrasound scan during the third trimester, an increased incidence of caesarean section delivery was observed, without reaching statistical significance (5 RCTs, 21,035 women; RR 1.06, 95% CI 1.00 to 1, 13). On the other hand, women with ultrasound scanning during the third trimester showed a lower risk of childbirth after 42 weeks (2 RCTs, 17,151 women; RR 0.69, 95% CI 0.59 to 0.81).

Newborns did not show different results depending on whether their mothers had undergone an ultrasound scan during the third trimester or not. The studies reviewed did not collect data on the impact on psychological factors of mothers or other long-term outcomes.

Safety of ultrasound scanning during pregnancy

A Working Group of the WHO has recently published an SR on the safety of ultrasound during pregnancy for both pregnant women and the foetus (Torloni, 2009). The SR included 41 studies of different designs: 16 RCTs, 13 cohort studies and 12 case-control studies. The maximum number of scans performed in these studies was nine.

Studies of the review should be based on pregnant women without risk factors and should be controlled studies, and showed no major limitations in their design. Anyway they provided little information on the characteristics of exposure to ultrasound (only 44% provided information on the equipment used, 27% on the transducer frequency, 14% on the length of exposure and 12% on the acoustic intensity), and most results showed significant levels of heterogeneity. The long term effects of this technique were not analysed either.

The results of the SR by Torloni (2009) showed that exposure to ultrasound scans does not increase the risk of **low birth weight** (10 RCTs, 24,271 women: OR 1.06, 95% CI 0.84 to 1.35), or the risk of giving birth to a baby weighing <1500 g (2 RCTs, 1509 women; OR 1.26, 95% CI 0.78 to 1.98). The results of cohort studies were very consistent with those of the RCT.

Moderate quality

Studies of this SR also showed an association of exposure to ultrasound scans with other pregnancy outcomes such as the weight of newborns, their size, and the measurement of head circumference.

When preterm delivery, low Apgar scores, need for resuscitation of the newborn, neonatal admission in ICU or foetal and perinatal mortality or the incidence of malignancies in childhood were assessed, the ultrasound scan did not have a significant impact on these outcomes.

Carrying out ultrasound scans did not increase the risk of hospital admissions of pregnant women during pregnancy (9 RCTs, 25,200 women: OR 1.02, 95% CI 0.90 to 1.16).

The SR also evaluated some outcomes related to the neurological development of newborns when exposed to ultrasound scanning during pregnancy, though these showed no impact on the incidence of dyslexia or the acquisition of language skills, the results of observational studies available were inconsistent.

Low quality

On the other hand, a slight association to the exposure to ultrasound scans during pregnancy and the incidence of left-handedness in children (2 RCTs, 2,422 children; OR 1.26, 95% CI 1.03 to 1.55) was observed although the results were no longer significant when analysed together for boys and girls. **Low quality**

Summary of evidence

Moderate quality	Performing an ultrasound scan before 24 weeks improves the detection of multiple pregnancies and foetal abnormalities, as well as dating of gestational age, which could result in a lower rate of induction of post-term delivery (Whitworth, 2010).
Moderate quality	Performing a regular ultrasound scan after 24 weeks has not shown a benefit in terms of outcome of pregnant women or newborns, and may be associated with a higher rate of caesarean section at childbirth (Whitworth, 2010).
Moderate quality	Performing ultrasound scans during pregnancy is not associated with maternal, perinatal or children development short-term adverse events (Torloni, 2009) and effects are unknown in the long term.

From evidence to recommendation

The aspects considered to establish the strength and direction of the recommendations were:

1. Quality of the evidence: the literature on routine ultrasound scanning before 24 weeks has shown limitations related to the imprecision in estimating the results of some outcomes, and the heterogeneity shown in the outcome of post-term induction of labour (I2 = 68%). In the case of routine ultrasound scanning after 24 weeks, the quality of the evidence for the inaccuracy observed in any of the outcomes assessed has decreased. In the case of caesarean section, results suggest both an increase of 30% and an absence of risk. The safety-related ultrasound scan results showed a high variability.
2. Balance between benefits and risks. An SR on the safety of ultrasound scanning during pregnancy has not shown that they are significantly associated with complications for the pregnant woman, the foetus or child development (Torloni, 2009).

Considering these aspects and since studies on the costs and use of resources, values and preferences of pregnant on ultrasound scanning were identified, the development group made two recommendations in favour since performing an ultrasound scan before 24 weeks improves the detection of multiple pregnancies as well as the dating of gestational age, which could result in a lower rate of induction of post-term delivery. Besides, exposure to ultrasound tests during pregnancy has not been associated with significant adverse events. Given that the quality of the evidence supporting these findings is moderate, recommendations were formulated as strong.

Recommendations

Strong	Two scans should be performed during pregnancy in women with no risk factors.
Strong	A first scan should be carried out at the end of the first trimester (11 -13 + 6) and the second one, around week 20.
Weak	We suggest not carring out a routine ultrasound during the third trimester of pregnancy.

Information derived from ultrasound scans

A Cochrane SR (Af and Ma, 2010) comparing detailed information (ability to see the monitor screen and receiving verbal and visual details on the results of the test) versus the basic information (without the possibility of seeing the monitor screen and receiving a brief summary of the test results) received during the ultrasound scan has been identified. The SR assessed the impact of these two modalities on the state of anxiety of the mother and other variables related to her habits during pregnancy.

The SR included four RCTs that evaluated the results of 365 women. The small number of studies and the limited sample of participants, in addition to certain limitations related to the design of the study (lack of blinding, omission of information on how to randomize participants and losses in follow-up) limit the interpretation of these results.

Low quality

The results of the SR showed that women did not present different levels of anxiety depending on whether they received more or less information during the carrying out of ultrasound scans (3 RCTs, 346 participants; DM 0.92, 95% CI -0.58 to 2, 43).

On the other hand, women who received information during the scans, showed greater satisfaction with the information received than women who received less information (2 RCTs, 148 participants, RR 3.30, 95% CI 0.73 to 14.85).

Instead, the results of an RCT showed that women who received more information quit smoking and avoided drinking to a larger extent than women who received less information (Af and Ma, 2010)).

Summary of evidence

Moderate quality	There is not enough data to know how much information should be given to pregnant women during ultrasound scans to reduce their level of anxiety (Af and Ma, 2010).

From evidence to recommendation

The aspects considered to establish the strength and direction of the recommendations were as follows:

1. Quality of the evidence: the literature in this area is scarce. The available studies suffer from some methodological limitations.
2. Balance between benefit and risks: the systematic review evaluated aimed to assess the impact of information on ultrasound scans regarding the level of anxiety of pregnant women, though it was unable to show any difference between the interventions being compared.
3. Values and preferences of pregnant women: although no relevant studies were located in this section, the development group considered that it could be assumed that there will be great variability in the way that mothers face up ultrasound tests, the information they wish to receive and the ability to understand the information from the healthcare professional.

After considering these issues, and due to the failure to identify studies examining the values and preferences of pregnant women about the performance of ultrasound scans during pregnancy, the development group considered that although the data available about the information that should be provided to women during the ultrasound scan is very limited, it must be taken into

account that a great variability is likely in the way that mothers face up ultrasound tests, the information they wish to receive, and the ability to understand the information provided by the professional health; thus, a recommendation in favour of the intervention was made.

Recommendations

√	Before each ultrasound examination women should be informed about the characteristics and objectives of the test as well as the limitations of ultrasound, checking that the woman has understood the information provided.
√	Women should be informed about the purpose and implications of the pathological findings of ultrasound to facilitate informed decision-making, as well as the limitations of routine ultrasound examinations.

Diagnostic yield of the combined test for the screening of chromosome disorders

Down syndrome is the most common chromosomal abnormality, and the risk of trisomy 21 increases with maternal age (Snijders, 1999). It is estimated that its prevalence varies between 1/600 and 1/800 live newborns, being lower in other chromosomal abnormalities such as trisomy 18 (between 1/5,000 and 1/10,000) or trisomy 13 (1/5,000) (Fabre, 2011). Currently the chromosomal screening strategy attempts to select women with a high risk to justify performing invasive diagnostic procedures for a study of foetal karyotype (Prosigo, 2010).

The screening test with better performance is considered to be one capable of presenting a lower rate of false positives (FP) with the maximum detection rate of aneuploidy (TD), minimizing the number and risk of invasive procedures (Chitayat, 2011; Fabre, 2011). Currently, it is considered that a chromosomal screening program for Down syndrome during the first trimester should provide at least one TD of 75% with no more than 3% of FP, and during the second trimester, a TD of 75% with no more than 5% of FP (Chitayat, 2011). The screening needs to combine clinical and biochemical data of pregnant women with ultrasound techniques (such as nuchal translucency) for best results (Prosigo, 2010). Depending on the outcome of this screening test, an invasive test should be offered according to the estimated risk (ACOG, 2007).

First trimester screening

Four large prospective observational studies evaluating combined chromosomal screening (measurement of nuchal translucency and biochemical markers PAPP-A and free fraction of β-hCG (TN + PAPP-A + β-hCG) together with the age of the mother, between weeks 10+0 and 13+6of pregnancy (Wapner, 2003; Wald, 2003; Nicolaides, 2005, Malone, 2005), whose results are collected in a review of recent literature (Fabre, 2011), have been identified.

The study by BUN (Wapner, 2003) carried out a combined test on 8,514 women pregnant with a single foetus between weeks 10+ 4 and 13+ 6 of pregnancy in which 61 foetuses were detected with Down syndrome.

The SURUSS study(Wald, 2003) evaluated the most effective combined screening strategy (in terms of the ratio between TD and FP) in a study involving 47,053 women pregnant with a single foetus (median age of 29 years; 16% of women over 35 years), including 101 registered newborns with Down syndrome. The study prospectively performed different screening strategies including the measurement of TN and several markers in maternal serum and urine between 9 and 13 weeks of gestation. The study checked the number of pregnancies with a foetus with Down syndrome in the screening in the second trimester or at childbirth.

The study of the Foetal Medicine Foundation (Nicolaides, 2005) conducted the combined test to 75,821 women with a single foetus pregnancy, including 325 cases of trisomy 21 recorded between weeks 11+0 and 13+6. This study also evaluated the performance of a sequential screening, consisting in carrying out the first trimester screening and act depending on its outcome in terms of three risk groups with Down syndrome: high (1/100 newborns with Down syndrome), low (1/1,000) and intermediate (between 1/1,000 and 1/100). It was suggested that women with high risk would be offered an invasive prenatal diagnostic test (a sample of chorionic villi), while women with an intermediate risk would be offered genetic ultrasound scan, and women with low risk would not conduct further tests.

The FASTER study (Malone, 2005) recruited a cohort of 38,167 pregnant women with a single foetus (117 foetuses with Down syndrome) who underwent a combined screening between weeks 10+3 and 13+6 and were compared with the results of a quadruple screening in the second trimester (15 to 18 weeks) with the following parameters: alpha-fetoprotein (AFP), hCG, estriol, and inhibin A concentration. The results to be carried out were compared i) an independent sequential screening (in which the results were given to the pregnant women after each screening calculated independently); ii) stepwise sequential screening (the results of each screening communicated by calculating the risk in the second trimester given the markers of the first trimester); iii) aserum integrated screening (in which the values of PAPP-A were calculated in the first trimester without providing the results to the pregnant women, and these values were used to integrate them into the calculation of risk markers collected in the second trimester); or iv) a fully integrated screening (same as the previous one but in which the results of nuchal translucency were evaluated).

Moderate quality

The studies that have evaluated the result of the combined first trimester screening (Wapner, 2003; Wald, 2003; Nicolaides, 2005; Malone, 2005) have shown an average TD of 87% (95% CI 84% to 89.4%) with a rate of 5% FP (Fabre, 2011). The BUN study (Wapner, 2003) showed the lowest TD (78.5%) which increased (up to 85.2%) if the FP rate stood at 9.4%. The SURUSS study showed that combined screening (TN + PAPP-A + β-hCG) showed better detection of Down syndrome than triple or quadruple test during the second trimester. The combined test showed a TD of 83% with a FP rate of 5% assuming a cut-off of 1/300 live births with Down syndrome, equivalent to a TD of 78% with a rate of 3% FP (Wald, 2003; Chitayat, 2011).

The study by Nicolaides (2005) showed that a combined screening contributed 90% TD at a rate of 5% FP. Its strategy of sequential screening the TD rate remained and the FP values were adjusted to 2 and 3% depending on the case. The study found that a woman had high risk of having a pregnancy whit trisomy

21,78% of carriers of trisomy 18 or 13, and 57% of foetuses with other aneuploidies. In our environment, the prevalence of women at high risk is estimated at 1/270 live births (Fabre, 2011). It is considered that a woman had low risk (1/1,000 newborn with Down syndrome) in 82% of foetuses with a normal chromosome and 3.1% of foetuses with trisomy 21, equivalent in our environment to 1 case for every 2,800 foetuses (Fabre, 2011).

Finally, an intermediate risk of Down syndrome was estimated in 16.1% of normal foetuses and 15.4% of foetuses with trisomy 21. The latter group would require further testing and could produce more foetal losses, so the possibility of a new assessment by ultrasound scan or genetic marker analysis in the second trimester should be offered.

The FASTER study showed that the first trimester combined screening achieved with a FP rate of 5% in all cases, a TD rate of 87%, 85%, and 82% depending on whether it was performed at weeks 11, 12, or 13 of gestation, respectively. The TD rate for the second trimester quadruple screening was 81%. The sequential and integrated screening showed similar results: stepwise sequential screening showed a 95% TD rate while a serum serological screening and an integrated screening TD rate showed 88% and 96% respectively. The authors of this study (Malone, 2005) concluded that at 11 weeks of gestation, the first trimester combined screening is better than the quadruple test in the second trimester, but at week 13, the results are similar. The authors similarly equated efficiency in the same way to the stepwise sequential and integrated screening.

Finally, it is clear from the FASTER and SURUSS studies that integrated screening (joint assessment of the results of the nuchal translucency and PAPP-A in the first trimester and the quadruple biochemical test in the second trimester) a TD rate of 94 or 95% is obtained with a rate of 4 or 5% FP (Nicolaides, 2005; Malone, 2005). In the absence of a nuchal translucency measurement, the serum integrated test carried out in the two trimesters shows very similar results to those of the first trimester combined test (TD rate between 86% and 90%, with a rate of 5% FP) (Fabre, 2011).

Second trimester screening

From the 14th week of gestation, chromosomal screening is based on the determination of a series of biochemical markers. The most common are the triple screening (alpha-fetoprotein (AFP), free β-hCG fraction and unconjugated estriol) or the latest quadruple combined test (which adds the determination of inhibin-A). Data from studies available rated in the previous section show that universal screening for chromosomal abnormalities should be performed during the first trimester, leaving the second trimester screening for women who were unable to perform screening in the first trimester (Fabre, 2011).

Efficacy screening data by triple and quadruple biochemical test are derived from the SURUSS and FASTER studies (Wald, 2003; Malone, 2005), without having comparisons available among them.

Moderate quality

With a TD rate of 85%, the triple test showed in the SURUSS study, and a FP rate of 14% and a 10.9% in the FASTER study, while the rate of FP rate in the quadruple test was 7.3% and 7.1% for the two studies respectively. When a D rate of 95% was considered, the triple test showed a rate of between 28% FP (FASTER study) and 32% (SURUSS study). qhile the quadruple test showed in both studies a FP rate of 22%.

If these data were extrapolated to a population of 100,000 pregnant women with an acceptance test of 80% and a percentage of foetal losses derived from performing invasive tests of 0.9%, it is believed that for a TD rate between 75 and 95% between 30 and 106 foetal losses would take place with the triple test, and between 18 and 76 losses with the quadruple test (Fabre, 2011).

Combined tests of the first and second trimester

In the section dealing with the first trimester screening, it has been reported that the SURUSS and FASTER studies (Wald, 2003; Malone, 2005) evaluated the results of using the test results for the first trimester integrated with those from the second trimester. The following summarizes the data on the effectiveness of these tests combined in its various forms (Fabre, 2011).

Moderate quality

In the integrated test, first trimester nuchal translucency, PAPP-A data and the AFP, β-hCG and unconjugated estriol data from the second trimester, communicating the test result in the second trimester are used. With an 85% TD rate, the integrated test has shown a rate of 1.4% (Wald, 2003) and 1.6% (Malone, 2005), which increases to 8.6% (Wald, 2003) or 5% (Malone, 2005) with a 95% TD rate. Taking the data from the SURUSS study (Wald, 2003), it could be estimated that a population of 100,000 pregnant women with a test acceptance rate of 80% and 0.9% of foetal loss, conducting an integrated test result in 9 foetal losses with reference to an 80% TD rate and 22 foetal losses with a 90% TD rate (Fabre, 2011).

The serum integrated test includes the value of PAPP-A in the first trimester and the AFP, β-hCG, unconjugated estriol, and inhibin A in the second trimester, communicating the test results in the second trimester. The SURUSS study showed that withan 85% TD rate,the test would result in a FP rate of 2.7% and a 95% TD ratewould result in a 12.5% FP rate. Referencing the above-mentioned population, it is estimated that the serum-integrated test would result in 32 foetal losses for an 85% TD rate and 59 for a 95% TD rate.

Low quality

The authors of the SURUSS study used a Monte Carlo simulation model to add a new marker to the two types of integrated test consisting in a ratio between the values of the first and second trimester of different serum markers (PAPP-A in the first trimester and AFP, β-hCG, unconjugated estriol, and inhibin A in the second trimester) (Wald, 2006). Therefore the use of markers showed an FP rate of 0.28% (with an 80% TD rate), of 0.65% (90% TD rate) and 2.21% (95% TD rate) when added to the integrated test. The FP rate was 1.8% (80% TD rate), 2.37% (90% TD rate) and 5.86% (95% TD rate) when the ratio of markers was added to the integrated serum test.

Low quality

Finally, the effectiveness of two types of sequential tests was evaluated. In the stepwise sequential test, the NT and PAPP-A values are determined in the first trimester. If the result is positive, a chorial biopsy or amniocentesis is offered, while if it is negative, a quadruple test is performed estimating again the risk by integrating the results of the first and second trimester. A simulation using the Monte Carlo method with data from the SURUSS study showed the following data for this sequential test (Wald, 2006b):

First trimester TD	66 %	79 %
First trimester TFP	0.5 %	2 %
Breakpoint in the test of the second trimester	1:30	1:114
Overall TD	90 %	90 %
Overall TFP	2.25 %	2.97 %

Adapted from Fabre (2011)

In the contingent sequential test on the results of the first trimester (TN + PAPP-A) a cut-off of low and high risk is established and women are classified into three groups: i) high-risk women who were provided a diagnostic test, ii) women with a medium risk who are offered the quadruple test that results in a new estimate of risk, and iii) low-risk women who do not undergo more screening tests. The simulation study by Wald (2006b) showed that this test had a FP rate of 0.5% with a 90% TD rate. If a high risk cut-offis set at a rate of 1 in 30 or higher and a low risk cut-offat a rate of 1 in 2,000 or less, the contingent sequential test would result in overall FP rate of 2.42% and a foetal loss rate of 22 per 100,000 pregnant women. This rate represents an increase in the rate foetal losses of 16% over the rate shown by the integrated test (Fabre, 2011).

Summary of evidence

Moderate quality	The combined first trimester screening test is effective in detecting Down syndrome, showing better results than the second trimester screening (Wapner, 2003; Wald, 2003; Malone, 2005; Nicolaides, 2005). The combination of maternal age, nuchal translucency measurement and the determination of PAPP-A and free β-hCG fraction between weeks 11+0 and 13+6 contributes to a detection rate of 87%, with a FP rate of 5% (Fabre, 2011).
Moderate quality	When it has been unable to perform the test in the first trimester, between weeks 13 and 17, the quadruple test has demonstrated a better relationship between the detection rate and the false positive rate (detection rate above 75% with a false positive rate lower than 3%) than the triple test (Wald, 2003; Malone, 2005; Fabre, 2011).
Moderate quality	The integrated test showed a detection rate of 90% with a false positive rate of 2.6%, associated with fewer unintended foetal losses (Wald, 2003; Fabre, 2011). The incorporation in testing of a ratio marker in the second trimester may result in a reduction of false positives within this test and therefore in the number of foetal losses (Fabre, 2011), though it should be noted that the markers were obtained from a simulation model and can present problems in terms of generalised results (Wald, 2006b).
Other clinical practice guidelines	A recommendation on integrated testing has not been done due to the absence of adequate studies directly comparing various modalities and the fact that sometimes models have been developed from statistical models and simulations.

From evidence to recommendation

The aspects that the development group considered when establishing the strength and direction of the recommendations were:

1. Quality of the evidence. In the case of screening in the first and second trimester, there were extended observational studies available with adequate design that have shown consistent and accurate results. For this reason, it was decided to increase the quality of the evidence.
2. Balance between benefits and risks. In most cases, the number of foetal losses resulting from various situations determined by the rate of false positives obtained from different tests was estimated (Wald, 2003; Wald, 2006; Fabre, 2011).
3. Costs and use of resources. A North-American cost-effectiveness study compared a screening carried out in the second trimester with three screening strategies performed in the first trimester (TN alone, serum screening alone or combined), showing that the three strategies screening from the first trimester is cost effective for the diagnosis of Down syndrome. Different screening strategies in the first trimester showed a favourable increase in costs per QALY gained when compared to the strategy of the second trimester (Caughey, 2002). A similar study compared the results of cost-effectiveness in a cohort of simulated women in which no screening was done, but on the contrary, a TN single test or jointly with the determination of biochemical markers, a screening in the second trimester, as well as an integrated and a stepwise screening were performed (Odibo, 2005). The study showed that the integrated screening test was the most cost-effective when the costs, the detection rate of cases of Down syndrome and foetal losses were considered jointly, showing consistent results. The authors emphasized the advantage that the integrated screening test would imply, as it would avoid the logistical and technical problems, which may arise from performing a TN test, but also stressed that delaying the reporting of results until the second trimester could not be accepted by some women. A health technologies report showed that the most cost effective strategy in our environment would be the contingent sequential test followed by the stepwise sequential test (Estrada, 2006). The calculation of the cost was made on the assumption that the determination of nuchal translucency would be integrated into the prenatal care ultrasound scan in the first trimester, that 100% of women would accept undergoing the screening, that 90% of women with high risk would accept undergoing an additional diagnostic test, and that a foetal loss rate of 0.9% would occur. The cost of these tests would be 12,432 euros and 16,000 euros per confirmed case of Down syndrome. The cost of the combined first trimester test would be 27,740 euros per confirmed case.

After assessing these aspects and the failure to identify studies on values and preferences of pregnant women, the development group decided to make recommendations for interventions given the balance between detection rates and false positive rates of the combined test shown by different studies. Moreover, despite the evaluated studies being observational in their entirety, they are well designed and contain large trials, yielding consistent results between them. For this reason, the recommendations are considered strong.

Recommendations

Strong	A combined test (maternal age, nuchal translucency measurement, PAPP-A and free β-hCG fraction) should be recommended between weeks 11 and 13 + 6 to determine the risk of Down syndrome.
Strong	A quadruple test between weeks 13+0 and 17+0 should be offered only to those pregnant women who could not be screened during the first trimester.

Monitoring foetal growth and welfare

SFH measurement

SFH measurement during pregnancy

An SR has been identified in order to evaluate the routine use of fundal height measurement during perinatal care in improving pregnancy outcome respect to the measurement of foetal size through examination by abdominal palpation only (Jp, 2009). The main outcomes, analysed the complications associated with foetal growth restriction such as stillbirth, foetal distress during labour, and neonatal hypoglycaemia; complications associated with foetal macrosomia (cephalopelvic disproportion resulting in a caesarean section for failure to progress, or shoulder dystocia) and complications associated with multiple pregnancy (preterm childbirth, perinatal mortality). Secondary outcomes included others as maternal and perinatal mortality or some related to health care (hospital admission).

SFH measurement during pregnancy versus no measurement

Pregnant women who underwent a fundal height measurement during pregnancy showed no significant differences in hospital admissions before delivery due to intrauterine growth restriction (IUGR), compared to pregnant women to whom periodic abdominal palpation was performed (1 RCT, 1,639 pregnant women; Peto Odds Ratio [Peto OD] 1.93, 95% CI 0.85 to 1.39) (A Lindhard et al., 1990). **Very low quality**

Pregnant women who underwent a fundal height measurement during pregnancy showed no significant differences in the induction of labour by IUGR, compared to pregnant women to whom periodic abdominal palpation was performed (1 RCT; 1,639 pregnant women; Peto Odds Ratio [Peto OD] 0.84, 95% CI 0.44 to 1.59;) (A Lindhard et al, 1990). **Very low quality**

In turn, no significant differences were found in terms of caesareansection delivery for IUGR in pregnant women who underwent fundal height measurement during pregnancy with respect to pregnant women to whom periodic abdominal palpation was performed (control group) (1 RCT, 1,639 pregnant women; Peto Odds Ratio [Peto OD] 0.72, 95% CI 0.031 to 1.67) (A Lindhard et al., 1990). **Very low quality**

No significant differences were found in the presence of a birth weight below the 10th percentile among the children of pregnant women who underwent periodic measurements of fundal height, compared to that of children of pregnant women who underwent periodic abdominal palpation (1 RCT, 1,639 pregnant women; Peto Odds Ratio [Peto OD] 1.34, 95% CI 0.91 to 1.98) (A Lindhard et al, 1990). **Very low quality**

No differences in perinatal mortality were detected in pregnant women who underwent periodic SFH measurements compared to pregnant women who underwent periodic abdominal palpation (1 RCT, 1639 pregnant women; Peto Odds Ratio [Peto OD] 1.25, 95% CI 0.38 to 4.08) (A Lindhard et al., 1990). **Very low quality**

The children of women who underwent SFH measurement during pregnancy showed no significant differences in terms of obtaining a score under four in the Apgar score, after one and five minutes, compared to children from women within the control group (who underwent abdominal palpation) (1 RCT, 1639 pregnant women; Peto Odds Ratio [Peto OD] 0.93, 95% CI 0.38 to 2.31; 1.04; 95% CI 0.26 to 4.17 respectively) (A Lindhard et al., 1990). **Very low quality**

No studies assessing the value of the fundal height measurement for outcome variables such as the complications associated with foetal macrosomia and/or associated with multiple pregnancies were found.

Summary of evidence

Very low quality	The measurement of fundal height has not been found useful in detecting abnormalities in foetal growth compared to the measurement through abdominal palpation and / or in improving outcomes in newborns (Jp, 2009).

From evidence to recommendation

The aspects considered to determine the strength and direction of the recommendation were:

1. Quality of the evidence: the evidence comes from an SR aimed at assessing whether the regular use of measuring fundal height in prenatal care improves the pregnancy outcome. One RCT that shows possible potential sources of bias has been identified. It was developed with a relatively small sample of subjects and is quite imprecise in the results (few events or confidence intervals included no effect).
2. Balance between benefits and risks. There is limited evidence of its benefits, although the study found no reported adverse effects of the intervention.
3. No studies on the costs and use of resources, values and preferences of pregnant women were identified.

Finally, the development group considered that the measurement of fundal height is a simple procedure, which involves relatively low costs and few risks to the mother and the newborn. Likewise, it was considered that the results of the studies (an SR that identified one RCT) are insufficient to dismiss the usefulness of measuring fundal height in the control and prediction of foetal growth. The very low quality of the evidence determined the weak strength of the recommendation.

Recommendation

Weak	We suggest carring out the measurement of fundal height during prenatal visits from week 24 of gestation as part of the interventions to assess foetal growth.

Benefits of the Doppler study of uterine arteries

Umbilical and uterine artery Doppler study in low-risk pregnancy

A systematic review (SR) evaluating the effects on obstetric practice and pregnancy outcome of the regular use of the umbilical and foetal Doppler in unselected low-risk pregnancies (Alfirevic, 2010) was identified. The authors defined the unselected pregnancies as pregnant women without identified risk factors or those that could have any risk factor but who were not reported separately in the studies included. Randomised controlled trials (RCTs) and quasi-randomised trials comparing the routine use of foetal and umbilical Doppler regarding its non-performance or performance but with hidden results for health professionals (control group) were included.

Another SR (Stampalija, 2010) that evaluated the use of the utero-placental Doppler improving pregnancy outcomes in women with low and high risk of hypertensive complications was identified. RCTs and qRCTs comparing the use of the utero-placental circulation Doppler (uterine arteries, arcuate, radial, and spiral) in pregnant women without risk factors (not exclusively

hypertensive) during their first or second trimester, compared to their non-performance were identified. Studies involving the combination of the utero-placental Doppler and the foetal or umbilical Doppler were not considered.

Umbilical artery Doppler

No significant differences were found in perinatal deaths from any cause, after randomisation among pregnant women who underwent the foetal - umbilical Doppler compared to pregnant women in the control group (2 RCTs, 5,914 pregnant women, RR 0.51, 95% CI 0.20 to 1.29) (French Doppler, 1997; Mason, 1993). Taking the same variable, no significant differences were found among pregnant women to which thefoetal - umbilical and uterine Doppler was performed, compared to pregnant women in the control group (2 RCTs, 5,276 pregnant women, RR 1.06, 95% CI 0.47 to 2.38) (Davies, 1992; Newnham, 1993). When evaluating all types of Doppler together, no differences were found between the groups (4 RCTs, 11,190 pregnant women, RR 0.85; 95% CI 0.47 to 1.54) (French Doppler 1997; Mason 1993; Davies 1992; Newnham, 1993).	**Low quality**
Regarding preventable perinatal deaths (excluding those caused by chromosomal abnormalities) a lower risk was found in pregnant women where the foetal - umbilical *Doppler* was performed solely compared to the pregnant women in the control group (2 RCTs, 6,884 pregnant women, RR 0.35 95% CI 0.12 to 0.99) (French *Doppler*, 1997; Whittle, 1993). When analysing the results in pregnant women who had undergone thefoetal- umbilical and uterine *Doppler*, an increased risk was observed compared to pregnant women in the control group (1 RCT, 2,475 pregnant women, RR 3.95, 95% CI 1.32 to 11.77) (Davies, 1992). Analysing all types of *Doppler*, the results showed no differences between the groups under study (3 RCTs, 9,359 pregnant women; RR 0.82, 95% CI 0.15 to 4.67) (French *Doppler*, 1997; Whittle, 1993; Davies, 1992).	**Low quality**
Regarding the number of stillbirths, women who underwent the foetal - umbilical vessels Doppler only, had lower risk compared to pregnant women in the control group (2 RCTs, 6,884 pregnant women; RR 0.34, 95% CI 0.12 to 0.95) (French Doppler, 1997; Whittle, 1993). No significant differences were found when comparing pregnant women who had undergone the foetal - umbilical and uterine Doppler to the control group (2 RCTs, 5,276 pregnant women; RR 1.14 95% CI 0.44 to 4.46) (Davies 1992; Newnham, 1993). When evaluating all types of Doppler, no differences were found between the groups (4 RCTs, 12,160 pregnant women; RR 0.79 95% CI 0.32 to 1.97) (French Doppler, 1997; Whittle, 1993; Davies 1992; Newnham, 1993).	**Low quality**
No significant differences were found in the risk of neonatal death in pregnant women who underwent the foetal - umbilical Doppler compared to pregnant women in the control group (1 RCT, 3,898 pregnant women; RR 0.25, 95% CI 0.03 to 2.23) (French Doppler, 1997). No differences were found among pregnant women who underwent the foetal - umbilical and uterine Doppler compared to pregnant women in the control group (2 RCTs, 5,276 pregnant women; RR 1.44 95% CI 0.04 to 54.93) (Davies, 1192; Newnham, 1993) nor when all types of Doppler were analysed(3 RCTs, 9,174 pregnant women; RR 0.69, 95% CI 0.09 to 5.23) (French Doppler, 1997; Davies, 1192; Newnham, 1993).	**Very low quality**

Uterine artery Doppler

The difference in perinatal mortality for any cause was not statistically significant among children of women without risk factors for complications to whom the uterine artery Doppler was performed in the second trimester, compared to thecontrol group (2 RCTs, 5,009 babies; RR 1.61, 95% CI 0.48 to 5.39) (Subtil, 2003; Goffinet 2001).	**Very low quality**
No significant differences were found for the number of preventable perinatal deaths between the two groups (2 RCTs, 5,009 babies, RR 1.29, 95% CI 0.21 to 7.94) (Subtil, 2003; Goffinet, 2001).	**Very low quality**
No statistically significant differences were found in the presence of maternal hypertensive disorders (2 RCTs, 4,987 pregnant women; RR 1.08, 95% CI 0.87 to 1.33) nor in the number of abortions (2 RCTs, 5,009 babies; RR 1.44, 95% CI 0.38 to 5.49) or neonatal deaths (2 RCTs, 5,009 babies; RR 2.39, 95% CI 0.39 to 14.83), between groups (Subtil, 2003; Goffinet, 2001).	**Moderate quality**
Regarding intrauterine growth retardation, no differences were found in the group of pregnant women to whom the uterine artery Doppler was performed compared to pregnant women in the control group (2 RCTs, 5006 babies; RR 0.98, 95% CI 0.64 to 1.50) (Subtil, 2003; Goffinet, 2001).	**Very low quality**

The SR analysing the use of the utero-placental Doppler found no study that evaluated its use during the first trimester of pregnancy or in pregnant women at high risk of developing hypertensive disorders during pregnancy (Stampalija, 2010). Moreover, it emphasized its low strength to detect significant differences in maternal or neonatal morbidity. Furthermore, it states that only two studies evaluating the utero-placental Doppler were identified (Goffinet, 2002; Subtil, 2003), despite being widely introduced in routine medical practice. The authors of this SR refer that the data presented should be interpreted with caution due to the small number of samples and the high heterogeneity of results.

Pooled data from the two studies evaluating the use of the umbilical artery Doppler showed a significant decrease in potentially preventable perinatal deaths (French Doppler, 1997; Whittle, 1994). However, the results of the study by Davies (1992) suggest that the foetal - umbilical and uterine vessel Doppler performed routinely in unselected pregnancies, could present more risk than benefit. In this study, pregnant women who underwent the foetal - umbilical and uterine Doppler showed an increased risk of neonatal deaths compared to the control group (RR 10.85, 95% CI 0.60 to 196.01). The authors of this study indicate that the increased number of perinatal deaths in their study was an unexpected finding and could be due to chance (Davies, 1992). These findings were not associated with increased perinatal morbity and mortality (Newnham, 1996; Newnham, 2004).

Summary of evidence

Low quality	The routine use of the foetal - umbilical Doppler has shown a significant benefit in reducing the risk of perinatal death for any cause or those preventable and has shown no reduced risk of stillbirth (Alfirevic, 2010). In the case of the foetal - umbilical Doppler associated with the uterine Doppler, the risk of preventable perinatal death increases compared to the control group and no significant differences were found between the groups regarding the risk of stillbirth. Analysing the different types of Doppler jointly, (unique umbilical artery Doppler and foetal - umbilical artery Doppler together with uterine Doppler) no significant differences were found in the risk of perinatal death (all causes), preventable perinatal deaths, risk of stillbirth, or risk of neonatal death (Alfirevic, 2010).
Very low quality	Regarding the use of the uterine artery Doppler in pregnant women in their second trimester and at low risk of developing complications, no significant differences were found in the risk of perinatal mortality, preventable deaths, hypertensive disorders and IUGR, with respect to its non-performance (Stampalija, 2010).

From evidence to recommendation

The aspects considered to establish the strength and direction of the recommendations were:

1. Quality of the evidence. The Cochrane SR evaluating the use of the foetal - umbilical Doppler included RCTs with a high risk of bias, with considerable heterogeneity and a major inaccuracy, presenting a small number of participants that would detect small but significant changes in perinatal outcomes (Alfirevic 2010) (low quality). The Cochrane SR evaluating the use of the utero-placental Doppler despite including studies which were generally of good methodological quality, had a significant inconsistency and inaccuracy in the results, lacking in strength to detect clinically important differences in outcomes such as maternal and neonatal morbidity (Stampalija, 2010) (very low quality).
2. Balance between benefits and risks. The use of the uterine arteries and umbilical Doppler in low-risk pregnancies is based on the potential benefit of early screening for potential risk factors that can slow foetal growth and on which to act and thus prevent future complications. However, in the case of a false positive result, this would expose the mother and child, to the performance of unnecessary additional tests.
3. Although the costs and use of resources and values and preferences of pregnant women are considered important factors in the recommendation, no evidence was found thereon.

Finally, the development group considered that there is no evidence that clearly supports the use of the uterine artery and umbilical - artery Doppler improving the outcomes in pregnant women with low risk of developing complications and their children, so a recommendation against this surgery was formulated. On the other hand, the recommendation was considered weak due to the low quality of the evidence and the fact that no studies evaluating the costs and the values, as well as the preferences of women and their families were identified.

Recommendation

Weak	We suggest not performing routinely in pregnancies at low risk of developing complications Doppler utero-placental and umbilical / foetal studies .

Routine monitoring by cardiotocography

Prenatal cardiotocography for the assessment of foetal wellbeing

This summary of the evidence focuses on the analysis of cardiotocography (CTG). Other types of monitoring such as the Doppler (foetal, umbilical, utero-placental), are evaluated in other sections. An SR (Grivell and Alfirevic, 2010) that evaluated the effectiveness of cardiotocography (CTG) both traditional and computerised, in improving outcomes in the mother (with or without risk factors) and the foetus was identified.

The SR included randomised clinical trials (RCTs) and quasi-randomised trials evaluating the traditional prenatal CTG (paper record and interpretation carried out by a health professional) or computed prenatal CTG (performing quantitative analysis with subsequent analysis results carried out by a health professional). The comparisons of interest were: traditional CTG versus control (no performance of CTG; regular controls, test performance without giving the results to health professionals), computerised CTG versus control and comparison between traditional and computerised CTG.

The main variables to be analysed in this study were perinatal mortality and caesarean section delivery and as secondary variables, potentially preventable perinatal mortality, induction of labour, or gestational age at birth.

The SR identified four studies involving 1,636 women comparing the prenatal use of CTG with not using it (VA Brown et al, 1982; Lancaster et al, 2010; Anon; Lumley et al, 1983) and two studies with 469 pregnant comparing computerised CTG with traditional CTG (visual analysis) (Bracero et al., 1999; National et al., 2006). No studies evaluating the use of computerised CGT compared with not using itwere identified.

Two studies included pregnant women with at least 37 weeks of gestation at the time of inclusion (V.A. Brown et al, 1982; Steyn DW) and the other four included pregnant women at any gestational age (Bracero et al, 1999; Flynn et al., 1982; Lumley et al., 1983; Anon).

All studies included in the SR (Grivell et al., 2010) were performed in pregnant women with an increased risk of complications. No details on the prenatal use of CTG in pregnant women without risk factors were found. Therefore, it was considered that these studies provide indirect evidence to answer the question.

Traditional cardiotocography versus control in pregnant women at risk for complications during pregnancy

No significant differences were identified in the risk of perinatal mortality among pregnant women (4 studies; 1627 pregnant women; Risk Ratio (RR 2.05, 95% CI 0.95 to 4.42) (VA Brown et al, 1982; Flynn et al, 1982; Anon; Lumley et al, 1983). Of these, only one study was of good quality (Lumley et al, 1983), the other two were quasi-randomised (Lancaster et al, 2010; Anon) and one was without a clear sequence of randomisation (VA Brown et al. 1982). Taking only the results of the Lumley study (1983), no significant differences were found in perinatal mortality between groups (1 RCT, 530 pregnant women; RR 1.53, 95% CI 0.51 to 4.61).

Very low quality

Regarding the risk of preventable perinatal deaths, their results were similar to those of perinatal mortality, but with wider confidence intervals (2 RCTs, 2 qRCTs; 1627 pregnant women; RR 2.46, 95% CI 0.96 to 6,30) (VA Brown et al, 1982; Lancaster et al, 2010; Anon; Lumley et al, 1983).	**Very low quality**
No significant differences were found in the risk of caesarean section delivery between the groups (2 RCTs, one ECQE, 1,279 pregnant women; RR 1.06, 95% CI 0.88 to 1.28) (VA Brown et al, 1982;. Lancaster et al, 2010; Anon; Lumley et al, 1983).	**Very low quality**
Two qRCTs that evaluated the induction of labour, finding no significant differences between the groups being compared, were found (2 qRCTs; 696 pregnant women; RR 0.97, 95% CI 0.80 to 1.17) (Flynn et al, 1982; Anon).	**Very low quality**
Regarding the mean gestational age at birth, the children of pregnant women to which traditional CTG was performed showed no significant differences compared to the mean gestational age of the children of pregnant women in the control group (1 RCT, 353 pregnant women; Mean Difference (MD) 0.0; 95% CI -0.33 to 0.33) (VA Brown et al, 1982).	**Very low quality**

Computerised versus traditional cardiotocography in pregnant women at risk for complications during pregnancy

A significant reduction in perinatal mortality was found among the group of pregnant women to which computerised CTG was undertaken compared to those pregnant women who underwent traditional CTG (2 RCTs, 259 pregnant women; RR 0.25, 95% CI 0.04 to 0.88) (Bracero et al., 1999; Steyn DW).	**Very low quality**
A significant reduction in perinatal mortality was found among the group of pregnant women to which computerised CTG was undertaken compared to those pregnant women who underwent traditional CTG (2 RCTs, 259 pregnant women; RR 0.25, 95% CI 0.04 to 0.88) (Bracero et al., 1999; Steyn DW).	**Very low quality**
One RCT identified showed no significant differences in caesarean section deliveries among the groups under study (1 RCT, 59 pregnant women; RR 0.86, 95% CI 0.61 to 1.24) (Steyn DW).	**Very low quality**
The mean gestational age was not significantly different between the groups (1 RCT, 405 pregnant women; MD -0.10, 95% CI -0.43 to 0.23) (Bracero et al, 1999).	**Very low quality**

Although the identified SR (Grivell et al., 2010) showed among its goals the analysis of the performance of the CTG prior to childbirth in all pregnant women, no studies to make this assessment were found.

Prenatal CTG is most often performed during the third trimester of gestation (28 weeks). It is used in conjunction with other tools to assess foetal well-being. The CTG acts as a screening test that would identify newborns presenting acute, chronic hypoxia or present a risk of developing it. Thus, early completion of the test would serve to assess changes in foetal heart rate due to stress and would allow early intervention with consequent improvement in results for both the mother and the child.

The CTG is widely used in pregnant women at risk of developing complications during pregnancy. The review authors considered that should benefits for mothers and babies be found, it might be necessary to raise the widespread use of the test. However, the results of the SR do not show benefits for these women and their babies, so the authors reported that it is less likely to provide any benefit for pregnant women without risk factors regarding complications in pregnancy.

Moreover, it is highlighted that the majority of the studies used in this SR were performed over 10 years ago. This period has given the opportunity to improve other tools such as the Doppler in the diagnosis and monitoring of pregnancies at high risk of developing complications.

Given these data, the time at which CTG monitoring should start before childbirth in pregnant women at low risk is not evaluated.

Summary of evidence

Very low quality	There is no direct evidence evaluating the need for routine monitoring of foetal wellbeing through CTG. There is evidence available on the usefulness of CTG (traditional or computerised) in pregnant women with possible complications during pregnancy. This evidence suggests that the CTG (traditional) compared to its non-performance would not affect (in this group of pregnant women) the risk of perinatal mortality, preventable perinatal deaths, nor the risk of induction of labour, caesarean section delivery and mean gestational age at delivery. The computerised versus traditional CTG reduces the risk of perinatal mortality in children of pregnant women with risk factors for complications during pregnancy (Grivell et al., 2010).

From evidence to recommendation

The strength and direction of the recommendation were established based on the following:

1. Quality of the evidence. The evidence is indirect and comes from a Cochrane SR (Grivell et al., 2010) with good methodological quality including studies in a population group(women with pregnancies at high risk for complications) which is different to the target population (women without this risk). The studies included in this SR, showed different sources of potential bias as a loss of important follow-up, lack of specification of the methods of randomisation and concealment of the sequence. Given the nature of the intervention, it was not possible to blind clinicians, with few studies to specify blind participants.
2. Balance between benefits and risks. Although no specific study that assessed the risk-benefit of the intervention, Grivell (2010) (Grivell et al., 2010) was found, the importance of assessing the potential adverse effects of this type of assessment of foetal well-being is to be highlighted. These include the consequences of false negatives, inappropriate interpretation of data and subsequent false sense of safety for the family and the healthcare professional. Likewise, in the case of false positives, which involve a serie of tests and/or additional unnecessary confirmatory interventions for mother and child.
3. Values and preferences of pregnant women. The presumption of a pregnancy at high risk of developing complications is associated with an increased anxiety in the family (Grivell et al., 2010). Therefore, it is important to assess the effect of such test in their emotional wellbeing. Grivell (2010) (Grivell et al., 2010) describes a study evaluating anxiety in women with term pregnancies, who underwent a computerised CTG. The levels of anxiety increased significantly after the completion of the test, compared to the same results before the test. These levels of anxiety seemed to increase in pregnant women presenting obstetric problems.
4. No studies on the cost-effectiveness of this intervention in pregnant women were identified.

Finally, the development group made a recommendation against the intervention considering the fact that the quality of the evidence is very low, mainly because it is indirect evidence from studies carried out in other populations. Furthermore, the studies found have methodological and variability deficiencies in their interventions. The results of the studies included for the variables of interest assessed do not support the use of CTG (traditional or computerised) during pregnancy to improve foetal outcomes. Moreover, many aspects of maternal care have changed since the completion of these studies, thus, further studies to evaluate these tests in the current context would be required. Nor are there any good quality studies that evaluate important aspects such as the risk-benefit and / or preferences of the patients in this type of intervention. Therefore, the recommendation was made against the intervention and with a weak strength.

Recommendation

Weak	We suggest not performing foetal monitoring by cardiotocography before week 40 of gestation in pregnant women without risk of complications.

5.2. Vaccines during pregnancy

Key question:

- What vaccines are indicated and which are contraindicated during pregnancy?

The information collected on vaccination during pregnancy is based on the document of recommendations developed by consensus by the Spanish Society of Preventive Medicine, Public Health and Hygiene (Dominguez, 2010) and the recommendations of the American Centers for Disease Control and Prevention (CDC, 2012). The recommendations for this section are taken from the proposals of the Presentation of Immunisation Registry Program and the Public Health Commission Inter-Territorial Council in its 2004 document (MSC, 2004) and the update of 2009 of diphtheria and tetanus (MSC, 2009).

In this section, vaccines against preventable disease that can affect the foetus or newborn are collected. Vaccines would be given in the presence of certain risk factors such as certain medical co-morbidities, occupational factors, or lifestyle (CDC, 2012), not being covered within the scope of this Clinical Practice Guideline.

Much of the information on vaccines and their potential benefits and iatrogenic effects during pregnancy are derived from observational studies, with varying results and methodological limitations, and can be broadly categorized as low quality evidence. This section does not provide a formal assessment of the quality of the evidence.

Vaccines which can be administered during pregnancy

Tetanus vaccination

Other clinical practice guidelines

Neonatal tetanus occurs because of inadequate or deficient obstetric procedures or postnatal care, and can lead to brain damage in the newborn. To prevent neonatal tetanus, the best strategy is universal vaccination, and if this is not possible, the immunisation of women of childbearing age or pregnant women (Dominguez, 2010; Cherry, 2009; CDC, 2011).

Boys and girls born to mothers who have been vaccinated during pregnancy have adequate levels of circulating antibodies and are protected against the disease. Mothers who received two doses of tetanus toxoid during pregnancy transferred elevated levels of tetanus antitoxin to the newborns.

Although there is no increased risk of teratogenic side effects with the administration of the tetanus vaccine during pregnancy (Dominguez, 2010), its administration is recommended after 20 weeks.

In some documents, the administration of the tetanus vaccine Td (tetanus diphtheria) is recommended after 20 weeks of gestation (during the second and third trimester of pregnancy) in women who have not received vaccination in the last 10 years (CDC, 2012; Domínguez, 2010).

Vaccination against pertussis

Other clinical practice guidelines

The pertussis vaccine is usually administered together with the tetanus vaccine Td becoming the triple bacterial. The protective role of antibodies transferred via the placenta is debatable. Although pertussis has a very high infectivity (up to 90% of the contacts of a case), studies in pregnant women show no increased morbidity or mortality compared to non-pregnant women, nor have shown alterations in foetal development. However, the risk of perinatal death or serious illness is high in children under 6 months; high risk until the child does not receive the first two doses of pertussis vaccine (Tanaka, 2003).

Going through the placental route of antibodies could explain why mortality in children under one month was lower than that of older children, but an alternative explanation is that the parents avoided further exposure to cases with the disease in the first month of life. It was also noted that vaccination of pregnant women could increase the antibody titer in the newborn for the first 6 months of life and confer some protection, although these antibodies interfere with the response to vaccination in children (Dominguez, 2010).

The immunisation of the contacts with the newborn has been proposed as the best strategy to prevent infection (Dominguez, 2010). This immunisation strategy is based on the results of a study from a simulation following a mathematical model which showed that vaccination of 90% of the cohabiting people with the newborn, together with the vaccination in 75% of teenage population could prevent 75% of cases of pertussis in children under 2 years (Van Rie, 2004). Vaccination of the parents and child before leaving the hospital could prevent nearly 40% of cases and deaths in infants (Scuffham, 2004). However, a recent pre- and post-study evaluating the impact of immunisation exclusively for mothers during the puerperium has shown a decrease of the disease in infants up to 6 months of age (Castagnini, 2012). Furthermore, theanalysis of surveillance systems has shown a relative impact of the strategy in settings with a low incidence of the disease (Skowronski, 2012).

Flu Vaccination

Other clinical practice guidelines

The impact of the infection with the influenza virus in the foetus could result in foetal growth retardation and low birth weight. It has also been suggested that infection during pregnancy may cause spontaneous abortion and stillbirth (Stanwell-Smith, 1994).

In newborns, the infection with the influenza virus can be serious, leading to sepsis, pneumonia, cardiac arrhythmia, and sudden death. Infection may be in the form of hospital outbreaks (Dominguez, 2010).

The few available studies on the safety of the influenza vaccine show no serious adverse effects on pregnant women or babies, even when the vaccine is administered during the first trimester of pregnancy (Mak, 2008). In some countries, influenza vaccination is suggested in any trimester exclusively on those pregnant women with any comorbidity, reserving vaccination during the second and third trimester for women without significant health problems.

Infection with the influenza virus in pregnant women, especially when they are in their third trimester of pregnancy has been associated with an increased risk of hospitalisation for cardiorespiratory problems compared to non-pregnant women (Neuzil 1998). This is attributed to an increase in oxygen consumption, decreased lung capacity and changes in the immune function (Dominguez, 2010).

Other clinical practice guidelines

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In newborns, the infection with the influenza virus can be serious, leading to sepsis, pneumonia, cardiac arrhythmia, and sudden death. Infection may be in the form of hospital outbreaks (Dominguez, 2010).

The few available studies on the safety of the influenza vaccine show no serious adverse effects on pregnant women or babies, even when the vaccine is administered during the first trimester of pregnancy (Mak, 2008). In some countries, influenza vaccination is suggested in any trimester exclusively on those pregnant women with any comorbidity, reserving vaccination during the second and third trimester for women without significant health problems.

The administration of the inactivated influenza vaccine during the flu season to all pregnant women at any time during pregnancy because of the risk of cardiac and pulmonary complications in mother (Domínguez, 2011; CDC, 2012; MSSI, 2012; Tamma 2009) is recommended.

The attenuated influenza vaccine is contraindicated during pregnancy.

Vaccines indicated in women of childbearing potential, which should not be used during pregnancy

Rubella vaccination

The rubella virus can affect all the organs of the foetus. The lesions caused by the infection vary depending on the time of pregnancy in which it occurs. If the infection occurs in the first twelve weeks of pregnancy, the frequency of abnormalities is much higher than if it occurs after (Dominguez, 2011).

If the infection takes place between weeks 13 and 16 of the pregnancy, 16.7% of children have injuries, but when the infection occurs between weeks 17 and 20, only 5.9% of them are affected, and if it takes place after week 20, the percentage drops to 1.7% (Best, 2004). The injuries children born to mothers who have had the infection during pregnancy is congenital rubella syndrome, characterised by significant delays in growth and development, microcephaly, cataracts, hepatosplenomegaly, heart defects, deafness and meningoencephalitis among other signs and symptoms.

It is necessary to know the immunity to rubella in women of childbearing age, and in cases where there is no evidence of immunisation. The MMR vaccine should be administered to women who are not pregnant (CDC, 2012). In these cases, it is advisable to avoid pregnancy during the 4 weeks after vaccination.

Other clinical practice guidelines

In the case of pregnant women in whom there is no evidence of immunisation against rubella, a dose of the postpartum triple viral vaccine should be provided (CDC, 2012).

Mumps vaccination

The infection with mumps virus during the first trimester of pregnancy has been associated with foetal mortality (Dominguez, 2011). A case-control study showed that 27.3% of women who had had mumps, foetal deaths occurred compared to 13% in women without early infection (Siegel, 1973). This infection has also been associated with endocardial pathology. Similarly, the virus has been isolated in children born to mothers with mumps, presenting injuries, which can be mild, such as inflammation of the parotid, or more serious, such as pneumonia or respiratory distress.

Other clinical practice guidelines

The mumps vaccine is given as MMR vaccine. A single dose of the mumps vaccine provides adequate protection against mumps. However, as the administration of additional doses is harmless, normally in many countries two doses of the MMR vaccine are administered in childhood. Two doses of the MMR vaccine separated by an interval of 28 days can be administered at any age.

This vaccine is contraindicated in pregnancy. Precautions should be taken to avoid pregnancy during the 4 weeks following vaccination (Dominguez, 2011).

Measles vaccination

Infection with measles during pregnancy is associated with spontaneous abortion, stillbirth, and low birth weight (Chiba, 2003). In women with measles in the late phase of pregnancy, at childbirth or during the first 10 days of life may have congenital rash. Pneumonia is a common complication in pregnant women having this disease (Dominguez, 2011).

Other clinical practice guidelines

The attenuated measles virus used for vaccination, unlike attenuated rubella and mumps has not shown to cross the placenta and cause foetal harm. However, like any attenuated vaccine, this vaccine is contraindicated during pregnancy. (Dominguez, 2011).

Other clinical practice guidelines

It has not been shown that attenuated measles can cross the placenta and cause foetal harm (Strebel, 2008) but like any attenuated virus vaccine, it is contraindicated in pregnant women. Women of childbearing age who are vaccinated should avoid pregnancy during the 28 days following vaccination.

Pregnant women who are inadvertently vaccinated or who become pregnant before the stated 28 days should not perform an abortion (Dominguez, 2011).

Varicella vaccination

Although the incidence of varicella in pregnancy is low, if acquired during pregnancy it can have serious consequences for the mother and the foetus and can lead to spontaneous abortion, stillbirth and premature birth, or congenital varicella syndrome (Domínguez, 2011). The greatest risk of severe embryopathy is in the first 20 weeks of pregnancy, and its frequency is less than 2%. If the infection from the mother occurs at a more advanced stage of the pregnancy, the lesions consist of cutaneous scars, atrophy of limbs, unilateral ocular defects, central nervous system disorders, as well as urinary and gastrointestinal tract disorders. If maternal varicella infection occurs in the last five days of gestation or in the first two days of life, the risk that the newborn suffers from neonatal varicella is high (attack rate 20%). In these children generalised varicella occurs, with a fatality rate reaching 30%.

Other clinical practice guidelines

According to the Spanish vaccination schedule, seronegative adults aged between 15 to 49 should be vaccinated (two separate doses of 1 or 2 months) (Dominguez, 2011). If women of childbearing age are vaccinated, it is advised to avoid pregnancy for 4 weeks after vaccination.

Although there is no evidence that there have been cases of congenital varicella due to the vaccine virus (Shields, 2001), varicella vaccination is contraindicated during pregnancy. If a pregnant woman should inadvertently receive the varicella vaccine, she should not perform an abortion.

A determination of immunity to varicella should be performed in pregnant women. Those pregnant women with no evidence of immunisation against varicella should be administered the first dose of the vaccine as soon as the pregnancy ends before being discharged from the hospital. The second dose of the vaccine should be given between 4 and 8 weeks after the first dose (CDC, 2012).

From evidence to recommendation

The aspects that determined the strength and direction of the recommendation were:

1. Quality of the evidence. The information in this section is derived from observational studies, with varying results and methodological limitations.
2. Balance between benefits and risks. It has been considered in all cases the effect any vaccination can have on the results in the foetus or the newborn. All the considerations made in this section show a positive balance between benefits and risks.
3. The costs and use of resources was not considered crucial to make the recommendation.
4. Values and preferences of users. A study of the Dutch influenza A vaccination campaign (van Lier, 2012) showed that vaccination was more accepted among older women, those who had been pregnant before, than by women with medical comorbidity. The determining factors for vaccination were the prevention of negative consequences for the foetus and the newborn, and the governmental character of the campaign. In most cases, women expressed concern about the lack of sufficient knowledge about vaccine safety. The authors emphasised the need to provide pregnant women and health professional clear and enough information about the severity of the disease and the benefits and safety of vaccination.

The development group made recommendations considering that the benefits to the foetus and the newborn clearly outweigh the potential risks. The fact that health professionals can provide information to women about the risk vaccine-preventable diseases mentioned in this section and the benefits of vaccination pose to the foetus and the newborn were highly evaluated.

Recommendations

√	Healthcare professionals should provide information to women about the risks certain vaccine-preventable diseases pose to the foetus and the newborn. The vaccination schedule should be checked and the benefits of vaccination discussed by the health professional together with the woman during prenatal visits.
Strong	The attenuated influenza vaccine, or vaccines against rubella, mumps, measles and varicella should not be administered during pregnancy as they are contraindicated.

Strong	The administration of inactivated influenza vaccine should be provided during the flu season to all pregnant women during any stage of pregnancy.
Strong	The diphtheria and tetanus vaccine should be administered for those pregnant women who do not have a complete vaccination regimen, avoiding them during the first trimester of pregnancy.
Strong	In the case of pregnant women in whom there is no data of immunisation against rubella, a dose of the MMR postpartum vaccine should be offered, assessing the benefits and risks during the breastfeeding period.
Strong	In pregnant women in whom there is no data of immunisation against varicella, the first dose of the vaccine should be administered as soon the pregnancy ends and, whenever possible, before being discharged from hospital. The second dose of vaccine should be given between 4 and 8 weeks after the first dose.

5.3. Lifestyles during pregnancy

Key question:

- Are specific indications on eating habits and diet during pregnancy necessary?
- What are the recommendations for dietary intake during pregnancy?
- With a varied diet, are micronutrient needs as iron, vitamins or iodine covered?
- What is the effect of iron prophylaxis in women during pregnancy?
- Is a pharmacological iodine supplementation necessary during pregnancy?
- Is a pharmacological folic acid supplementation necessary during pregnancy?
- Is a pharmacological vitamin complex supplementation necessary during pregnancy?
- How safe are food supplements (omega3 fatty acids) during pregnancy?
- What widely used drugs are safe during pregnancy?
- What are the consequences of drinking alcohol during pregnancy?
- Are there programs to reduce alcohol consumption targeting pregnant women?
- What are the consequences of active and passive smoking during pregnancy?
- Are there specific smoking cessation programs targeting pregnant women?
- Is it necessary to perform physical exercise or sport in certain circumstances during pregnancy?
- What are the tools with better performance in the detection of mental disorders during pregnancy?
- Is sexual activity related to the occurrence of problems during pregnancy? Is sexual activity related to the appearance of labour contractions?
- What recommendations are required during pregnancy for women who want to travel?

Eating habits

Specific directions on eating habits

An SR evaluating the effects of advice or guidance to increase or reduce the intake of energy or protein, as well as the supplementation or restriction of energy and protein intake during pregnancy, weight gain and its outcome during pregnancy, was found (Kramer, 2003). This SR included 27 RCTs in which 8,298 women were involved.

The following interventions were evaluated:

– Nutritional advice to increase energy and protein intake (5 RCTs, 1134 women).

– Advice for balanced protein-energy supplementation (13 RCTs, 4665 women).

– Advice for supplementation with high protein intake (2 RCTs, 1076 women).

– Advice for isocaloric protein supplementation (3 RCTs, 966 women).

– Energy and protein restriction in women with overweight or high weight gain (4 RCTs, 457 women).

Nutritional advice to increase the intake of energy and protein

The intervention was evaluated in five RCTs (Kafatos, 1989; Briley, 2002; Hankin, 1962; Sweeney, 1985; Hunt, 1976).

Most studies had a high risk of bias. Most women were healthy and in some cases from a low socio-economic status.

The results of these RCTs showed that nutritional counselling increased the intake of protein and foods with high energy content, albeit not significantly regarding the advice (DM energy intake: 105.61 kcal / day, 95% CI -18.94 to 230.15; DM protein intake: 17.99 g / day, 95% CI -1.48 to 37.45). **Low quality**

In the group of women receiving advice, a reduced risk of preterm birth (RR 0.46, 95% CI .21-.98) was observed, although the result is not consistent with the lack of significant difference in the gestational age at childbirth among women who did not receive counselling and those who did (MD -0.10, 95% CI -0.48 to 0.28). **Moderate quality**

No significant differences in the risk of preeclampsia, foetal or neonatal death were found. **Low quality**

Balanced protein-energy diet

The intervention was evaluated in 13 RCTs (Blackwell, 1973; Mora, 1978; Rush, 1980; Elwood, 1981; Kardjati, 1988; Ceesay, 1997; Girija, 1984; Cambel Brown, 1983; Ross 1938; Viegas, 1982a, 1982b; Atton, 1990). The balanced protein-energy supplements where those whose amount of protein was less than 25% of the total energy content. The studies included healthy mostly non-obese women, in some cases with marginal or vulnerable nutrition from the nutritional point of view and a risk of having infants small for gestational age (Rush, 1980; Mora, 1978; Campbell Brown, 1983).

The results of these RCTs showed that weekly weight gain was significantly higher in the group receiving supplementation (10 RCTs, 2571 women, DM 20.7g, 95% CI 1.46 to 40.02). **Low quality**

The incidence of infants small for gestational age was significantly lower in the group treated with a protein-energy balanced diet (3 RCTs, 3396 women; RR 0.68, 95% CI .56-.84). **Moderate quality**

Although there was no significant difference in the weight of the newborn, a tendency to an increase in the group of the balanced protein-energy diet was observed (DM 37.6 g, 95% CI -0.21 to -75, 45).

The incidence of stillbirth was lower in the intervention group (4 RCTs, 2206 women; RR 0.55, 95% CI 0.31- 0.97), whereas no differences were observed regarding neonatal death, or possible developmental and long-term growth effects in the newborn. **Moderate quality**

There were differences either in the risk of preeclampsia and preterm delivery. **Low quality**

High protein intake diet

High protein supplementation is defined as the amount of supplementation in which the protein provided corresponds to 25% of the total energy content of the regular diet. Two RCTs (Rush, 1980; Iyengar, 1967) included 1,076 women who were at risk of having children with low birth weight.

The group of women who received supplementation showed a significant increase in the risk of having a newborn small for gestational age (Rush, 1980; 505 women, RR 1.58, 95% CI 1.03 to 2.41). **High quality**

No differences were observed in any of the other evaluated outcomes (preterm delivery, foetal and neonatal death, birth weight, maternal weight gain and child growth results in the long term). **Low quality**

Isocaloric protein diet

Isocaloric protein supplements are those balanced supplements in which the protein replaces an equal amount of non-protein energy. Three RCTs with 966 women who underwent this type of intervention were included (Mardones, 1988; Viegas, 1982a, 1982b).

The isocaloric protein supplementation increased the risk of infants small for gestational age (Mardones, 1988; 782 women, RR 1.35, 95% CI 1.12 to 1.61). **Moderate quality**

No differences were observed in any of the other outcomes assessed (birth before 37 weeks gestational age, foetal death, neonatal death, preeclampsia, maternal weight gain, or long-term growth in the newborn). **Low quality**

Energy and protein restriction in overweight or high weight gain during pregnancy

Four RCTs involving 457 women were assessed (Badrawi, 1993; Campbell, 1975, 1983; Wolff, 2008). All women included in these RCTs were obese or had excessive weight gain.

No differences were observed in the incidence of preeclampsia among women who had to follow a restricted diet and those who did not (3 RCTs, 334 women, RR 1.07, 95% CI 0.57 to 2.02). **Very low quality**

The results were similar when the incidence of pregnancy-induced hypertension (4 RCTs, 434 women, RR 0.94, 95% CI 0.72 to 1.22) and gestational diabetes (1 RCT, 53 women, RR 0.18, 95% CI 0.01 to 3.4) were evaluated. **Moderate quality**

Gestational weight gain per week was significantly lower in the group of dietary restriction (3 RCTs, 303 women, DM - 230.3 g; 95% CI -347.7 to -112.89). **Moderate quality**

Summary of evidence

Nutritional advice to increase the intake of energy and protein	
Low quality	Nutritional counselling does not significantly increase the likelihood of increasing the intake (Kramer, 2007).
Moderate quality	Nutritional counselling has shown a significant reduction in the risk of preterm delivery (Kramer, 2007).
Moderate quality	Nutritional counselling does not increase significantly other maternal or foetal variables such as preeclampsia, maternal or foetal death (Kramer, 2007).
Balanced protein-energy balanced diet	
Low quality	A balanced protein-energy diet showed a significant increase in maternal weight (Kramer, 2007).

Moderate quality	A significant reduction in foetal death was observed with balanced protein-energy diets (Kramer, 2007). However, it has been observed that such diets have an impact on blood pressure or the incidence of infants small for gestational age.
High protein intake diet	
High quality	A high protein intake diet has been shown to increase the risk of having a newborn small for gestational age (Kramer, 2007).
Low quality	No differences were observed in any of the other evaluated outcomes (preterm delivery, foetal and neonatal death, birth weight, maternal weight gain and child growth outcomes in the long term).
Isocaloric protein diet	
Moderate quality	The isocaloric protein supplementation has been shown to increase the risk of having a newborn small for gestational age (Kramer, 2007).
Low quality	No differences were observed in any of the other outcomes assessed (risk of delivery before 37 weeks of gestational age, foetal death, neonatal death, preeclampsia, maternal weight gain and child growth outcomes in the long term).
Energy and protein restriction in women with overweight or high weight gain during pregnancy	
Moderate quality	Protein-energy restriction in women with a weight problem during pregnancy has shown a significant reduction in weight during pregnancy (Kramer, 2007).
Low quality	No differences were observed in any of the other outcomes assessed (gestational diabetes, pregnancy-induced hypertension, birth weight, preterm birth and the anthropometric parameters of the child).

From evidence to recommendation

The development group considered the following aspects to discuss the strength and direction of the recommendations:

1. Quality of the evidence. The quality of the evidence is in most cases moderate or high. When the quality of the evidence was reduced, it was due to the presence of heterogeneity in the included studies or the presence of a severe risk of bias mainly by lack of blinding of the randomisation sequence of the studies included.
2. Balance between benefits and risks. The only intervention that showed a benefit, which, exceeded the risks, was the fulfilment of a balanced protein-energy diet as it increased maternal weight, with a reduction in foetal death and infants small for gestational age without other effects identified.
3. The costs and use of resources of this intervention, as well as the values and preferences of the pregnant woman were not assessed.

The positive results regarding the carrying out of balanced protein-energy diets in women with inadequate food intake led to the formulation of a recommendation in favour of the intervention. The low quality of the evidence led to the formulation of weak recommendations.

Recommendations

Weak	We suggest providing of nutritional advice to pregnant women in order to follow a balanced diet and adjust an adequate caloric intake to the needs of the pregnancy.

Weak	We suggest providing advice about a balanced protein-energy diet to those pregnant women to whom an insufficient dietary intake has been identified.
Weak	We suggest not recommending routinely a diet with high protein or isocaloric content to pregnant women.
Weak	We suggest recommending a protein-energy restriction to overweight pregnant women, or those who have gained excessive weight during pregnancy (> 570 g per week).

Recommended diet ary intake

For the development of this section, the recommendations or direction of scientific societies such as the American Dietetic Association (Kaiser, 2008) or the Spanish Society of Community Nutrition (SENC, 2007) have been taken as reference. The reason for selecting these documents is justified by their multidisciplinary and comprehensive search of the literature (Kaiser, 2008) and to provide recommendations on food intake directly applicable to our environment (SENC, 2007).

The aim of the recommendations of these documents is that through a proper weight gain, a rich and varied diet, and physical activity, an adequate nutritional status can be maintained during pregnancy in the context of a lifestyle that optimizes the state of the women's health, helping to reduce the risk to the developing of the foetus and the newborn.

The document of the American Dietetic Association highlights that the main nutritional limitations among women of childbearing age are due to inadequate intake of foods rich in vitamin E, magnesium, potassium, fibre and calcium. Likewise, the intake of vitamins A, C, B-6, and folic acid are moderate, while other nutrients such as sodium or saturated fat are consumed in excess.

Other clinical practice guidelines

The American Dietetic Association advises that the first time when counselling on dietary intake should be performed, is in the preconception visit, since it is an appropriate time to identify the eating habits of women and assess their needs.

At this point, it is recommended to ensure that women consume adequate amounts of folic acid (0.4 mg daily) from the intake of fortified foods or the inclusion of dietary supplements in the diet. Similarly, to avoid problems arising from iron deficiency anaemia during pregnancy, it is necessary to encourage the intake of iron-rich foods and foods that facilitate the absorption of iron as those rich in vitamin C.

Other clinical practice guidelines

This document recommends calculating weight gain during pregnancy according to the BMI of women before pregnancy, based on these parameters:

	Recommended weight gain
BMI<19.8 kg/m2	12.5 to 18 kg
BMI between 19.8 and 26 kg/m2	11.5 to 16 kg
BMI between> 26 and 29 kg/m2	7 to 11.5 kg
BMI> 29 kg/m2	At least 6 kg
Multiple pregnancy	16 to 20.5 kg

The energy intake of pregnant women should increase from the second trimester when an extra amount of energy of 340 kcal may be required, which in the third trimester should be 452 kcal. Most pregnant women need to perform a daily intake ranging between 2,200 and 2,900 kcal.

To achieve this intake a dietary plan should be developed jointly with the woman taking into account her age, activity, and weight gain recommended and the pregnancy trimester. The US Department of Agriculture promotes tools like MyPlate or MyPyramid to facilitate the design of a dietary plan that includes recommended amounts of food for pregnant women to get a full and varied diet (MyPyramid, 2005; MyPlate, 2012). The following is an example of a diet covering a daily intake of about 2000 kcal (Adapted from Foster 2009):

Food (Recommended frequency)	Reference measurement
Oils 6 tablespoons	1 tablespoon of olive oil = 3 teaspoons; 1 tablespoon of margarine or mayonnaise = 2.5 teaspoons; 30 grams of nuts = 3 teaspoons; 2 tablespoons of salad dressing = 3small tablespoons
Low-fat dairy products 3 cups (c.) (1 cup = 226.8 g or ml)	1 cup of skimmed milk or 1 low-fat yogurt= 1cup; 125 gr of fresh cheese = 1 cup; 55 grams of fat cheese = 1 cup; 45 gr of grated cheese = 1 cup.
Vegetables 250 gr	1 bowl of boiled vegetables; 1 large bowl of salad bowl; 1 glass of fresh juice
Meat, poultry and eggs, fish 150 gr	1 fillet of lean meat; 1 chicken quarter; 1 or 2 eggs; 1 fillet of fish;
Fruit 250 gr	2 glasses of juice; 2 large pieces of fruit; 2 servings of fruit in syrup
Cereals 175 gr	Bread, breakfast cereal, rice, or pasta.

This diet plan is accompanied by a number of additional recommendations as eating a varied diet, taking foods rich in fibre, making a little exercise, drinking plenty of water, and doing 3 to 5 meals a day.

Other clinical practice guidelines

For its part, the Spanish Society of Community Nutrition in its Guide to Healthy Eating recommends that nutrition during pregnancy is planned adapting to the needs of each woman, recommending a varied diet that takes into account the groups and the amount to be consumed within a healthy lifestyle. It highlights calcium, folic acid and iron as essential nutrients during this stage so it is very important to control the contributions made by each woman (SENC, 2007).

Other clinical practice guidelines

To ensure adequate nutrition during pregnancy, an extra contribution of about 250 or 300 kcal should be taken during the second half of the pregnancy mainly from dairy products. An extra supply of calcium is also advisable considering that the requirement of this nutrient by the foetus can be up to 250 mg per day in the third trimester. Other nutrients that need strengthening are folic acid in foods such as dark green leafy vegetables, fruit, bread, fortified cereals, or nuts like hazelnuts, or

iron (extra daily intake of 0.9 mg) in foods such as meat, poultry, eggs, seafood, vegetables, and whole grains. Foods rich in vitamin C (citrus, kiwi, strawberries, and vegetables like tomatoes or peppers) enhance the absorption of iron.

The Guide to Healthy Eating recommends the following daily rations for pregnant and lactating women:

Food	Servings (pregnant women)	Reference
Starchy products	between 4 and 5	Bread, pasta, rice, legumes, cereals, whole grains, potatoes
Vegetables	between 2 and 4	Variety depending on the season, included in different types of salads
Fruit	between 2 and 3	Variety depending on the season
Dairy products	between 3 and 4*	Milk, yogurt and cheese
Protein food	2	Meat, poultry, fish, eggs. Pulses and dried fruits / nuts.
Supplement fats	between 3 and 6	Olive or seed oil
Water	between 4 and 8	Tap water, mineral water, herbal teas and drinks with little sugar and no alcohol

Adapted from SENC 2007 *4 to 6 for breastfeeding women

For these servings, the following weight equivalences are recommended:

Food	Recommended serving (in grams)
Starchy (wholegrain bread)	60 gr
Raw rice or pasta	between 60 and 80 gr
Potatoes	200 gr
Raw pulses	entre 60 and 80 gr
Vegetables	250 gr
Fruits	200 gr
Fresh milk or yogurt	200 ml
Fresh cheese	between 60 and 100 gr
Semi-cured cheese	between 30 and 40 gr
Meat	between 100 and 125 gr
Fish	150 gr
Cooked ham	between 80 and 100 gr
Eggs	1 unit
Chicken	1 quarter
Olive oil	1 spoonful

Adapted from SENC 2007

The following recommendations are added:

- Eat quietly, without leaving more than 4 hours between meals.
- Have a varied breakfast and a light lunch, a light snack, have dinner soon, avoid snacking between meals.
- Try to cook the most natural way possible: steam, stir fry, cooked in foil, boiled, grill lightly and well fried.
- Perform a regular weight control.
- Perform moderate physical activity such as walking and swimming and stay outdoors and in contact with the sun with adequate protection (source of vitamin D).

Coverage of micronutrient needs to diet

Three publications with results of the cohort of pregnant women from Valencia participating in the INMA (Childhood and Environment) study have been identified (Ramón, 2009; Navarrete-Muñoz, 2010; Rodriguez-Bernal, 2012). In a first study, the dietary intake of folic acid, supplementations, and the factors associated with the failure to comply with the recommended intake of 0.6 mg / day and 0.4 mg / day were evaluated, using supplements to prevent neural tube defects (Navarrete- Muñoz, 2010). Through an interview and a validated questionnaire, a dietary intake of 782 pregnant women was collected in the period from preconception to the second month of pregnancy and the period between months 3 and 7.

A second study evaluated the intake of nutrients and carried out a follow-up of the dietary recommendations of 822 women with an uncomplicated pregnancy between 10 and 13 weeks of gestation (Rodríguez-Bernal, 2012). Through an interview and validated questionnaires corresponding to the daily intake of food and nutritional supplements of each participant, the nutritional values were collected. These were contrasted with the recommendations of the Spanish Society of Community Nutrition (SENC, 2007) and the nutritional values set by the US Dietary Reference Intakes from the Institute of Medicine.

Finally, another study evaluated data from 787 newborns in this cohort to assess through a multiple linear regression analysis, the possible relationship between the intake of fruits and vegetables with the weight and size of newborns, in addition to the incidence of infants small for gestational age (Ramón, 2009).

In this regard, a study evaluated the possible association between the consumption of fruits and vegetables during pregnancy and birthweight of babies from 43,000 Danish women participating in the Danish National Birth Cohort (Mikkelsen, 2006). In a British cohort, the impact of iron intake (derived from diet or supplementation) was found in the birthweight of newborns of 1,274 pregnant women (Alwan, 2011). In another study the impact of the diet of pregnant women on the risk of preeclampsia in 23,000 participants in the cohort of the Norwegian Mother and Child Cohort Study (Brantsaeter, 2009) was evaluated. Using a validated questionnaire four dietary factors (vegetables, processed foods, potatoes, fish, and sweets) were identified and through a multiple logistic regression model the association of these patterns was evaluated with the risk of preeclampsia. Researchers in this cohort also evaluated the contribution of food supplements on nutrient intake of 40,000 women (Haugen, 2008).

The study by Navarrete-Muñoz (2010) showed that food intake was insufficient for most participants to reach the recommended intake of folic acid, a fact that a considerable percentage of women did not achieve by taking supplements. During the preconception period up to 80% of women did not meet the intake of folic acid considered advisable (0.6 mg/d). The percentage remained high in the first two trimesters of the pregnancy (69%) and was improved in the seventh month of pregnancy, when a third of the women did not achieve the recommended intake. The percentage of women who took supplements increased progressively in early pregnancy (19% in the preconception period, 30% in the first month and 66% in the second), and 30% of women exceeded the tolerable dose of 1 g/d. The analysis by the Norwegian Mother and Child Cohort Study provided similar results (Haugen, 2008). 81% of participants in this cohort indicated that they consumed one or more food supplements (the most common were the fish oil supplements (59%), folic acid (36%) or other multivitamins (31%). Despite this consumption, 63% of women who took supplements did not meet the recommended intake of vitamin D, 34% did not meet the minimal intake of folic acid, and 28% did not do so with the minimal intake of iron.

Very low quality

he study by Rodriguez-Bernal (2012) showed that on average, women met the nutritional recommendations except in the case of the intake of whole grains (recommended daily intake: between four and five; median intake: 3.1; interquartile range: 1.9). The authors also noted that vegetable intake was higher among pregnant women older than 30 years (recommended daily intake: 2 to 4; median intake women <25 years: 1.6 versus 25 to 30 years: 2.1 versus >30 years: 2.3; P <0.001)and that women with higher educational level consumed lower amounts of meat, although all participants did so within the recommended amounts. Foods with a greater noncompliance were cereals (up to 77% of women did not meet the minimum intake recommendations), dairy products (52%) and fruits and vegeta ble (47%), an issue that was observed very evident in pregnant women under 25 years.

Very low quality

When analysing the macronutrient intake, it was observed that 57% of participants consumed a carbohydrate amount below the nutritional values recommended in the Dietary Reference Intakes, while protein intake was adequate in 99% of women. 71% of women consumed more fat than the amount recommended, and more than half of the participants consumed insufficient amounts of n-3 and n-6 fatty acids. When comparing the place of origin of the pregnant women (Spain versus Latin America), Spanish women consumed less carbohydrates (61%, P <0.001) and excessive amounts of fat (74%, P <0.001), whereas the Latin American women consumed less n-3 fatty acids (77%, P <0.001). The younger and less educated women are those who consumed lessn-3 fatty acids.

Regarding the consumption of macronutrients, a significant increase in the intake of folic acid supplements was observed when food supplements were included in the diet (0.298 mg/d derived from food intake versus 2,112 mg/d when a supplement was included). The greatest deficiencies in micronutrient intake were observed in the amount of vitamin D (practically no women consumed the recommended amount in the Dietary Reference Intakes), iron or vitamin E (68% of the sample did not meet the recommendations). Younger women showed greater inadequacy in the consumed amount of vitamins A, C, E, iron and calcium. Although with the inclusion of food supplements the lack of quantity consumed of

some of these nutrients decreased, it remained inadequate in a considerable percentage of women regarding vitamin E (40.8%), iron (50.9%) and vitamin D (88%).

Although the study by Ramón (2009) showed no relationship between the intake of fruit and the weight and size of newborns from the Valencia INMA cohort study, a linear relationship was established between vegetable intake and the incidence of babies weighing few or being small for gestational age. Women who during the first trimester of pregnancy consumed the least amount of vegetables, had a three times greater chance of having a baby with a low birth weight for gestational age than women who consumed more vegetables (OR 3.7; 95% CI 1.5 to 8.9; P <0.001). The chance of having a baby with a small size for gestational age was five times higher among women who consumed fewer vegetables during the third trimester of pregnancy than women who consumed greater amounts of these foods (OR 5 5; 95% CI 1.7 to 17.7; P = 0.04). **Very low quality**

The results of the Danish National Birth Cohort showed a significant association between the consumption of fruits and vegetables during pregnancy and birth divided into quintiles according to their consumption of fruit and vegetables, and an increase of 10.7 gr was observed in the weight of the newborn (95% CI 7.3 to 14.2) for each quintile. In women with a BMI <20 kg / m2 (7,169 participants) the increase in the weight of newborns was higher as fruit and vegetable quintiles of consumption increased (increase of 14.6 grams per quintile; 95% CI 6.4 to 22.9). The results of a cohort of women whose iron intake was collected showed that up to 80% of participants consumed an iron intake below the recommended amounts in the UK (Alwan, 2011). he study showed that the total iron intake was associated with increased birth weight of newborns (an average of 2.5 percentile of weight increase per 10 mg of iron; 95% CI 0.4 4.6), but this result was not observed when analysing the data of iron intake from food alone.

Brantsaeter (2009) showed that women in the *Norwegian Mother and Child Cohort Study* who consumed greater amounts of vegetables, potatoes and fish or vegetable oils had a lower risk of preeclampsia (OR of the third versus first tertiles: 0.72, CI 95% 0.62 to 0.85), whereas the risk was higher in women who consumed greater amounts of processed foods, sweet or savoury snacks (OR of the third versus first tertiles: 1.21; 95% CI 1.03 to 1.42). **Very low quality**

Summary of evidence

Very low quality	In our environment, it has been observed how an inadequate intake of vegetables is associated with a higher risk of having a baby with an inappropriate weight for gestational age (when inadequate intake occurs during the first trimester of pregnancy) or inadequate size (when inadequate consumption occurs during the third trimester) (Ramón, 2009). Other studies have shown an association between an increased consumption of fruits and vegetables and a higher birth weight (Mikkelsen, 2006) or a lower risk of preeclampsia (Brantsaeter, 2009).

Very low quality	In our environment, it has been observed that a considerable number of women do not consume the recommended amounts of some nutrients and foods such as cereals, pulses or vegetables during pregnancy. It was found that age, educational level and the origin of pregnant women is related to food intake and nutrient adequacy (Navarrete-Muñoz, 2010; Rodriguez-Bernal, 2012). In the case of folic acid, a study has shown that the intake is inadequate and sometimes the supplementation is taken late (Navarrete Munoz, 2010). Other studies have also shown that supplementation is sometimes not enough to ensure the recommended nutrients intake such as folic acid, vitamin D or iron (Haugen, 2008).

From evidence to recommendation

Although the quality of the evidence was taken into account, the values and preferences of pregnant women, as well as the cost and use of resources were not considered by the development group as determinants in the strength and direction of the recommendation. Since the only intervention that showed a benefit exceeding the risks was the fulfilment of a balanced protein-energy diet, the development group made a recommendation in favour of the intervention. The available studies are, as a whole, longitudinal studies with methodological limitations. On the other hand, they evaluate different outcomes of interest or nutrients, therefore the consistency of the results of different studies cannot be assessed properly. For this reason, the recommendation was considered weak.

Recommendation

Weak	We suggest carring out an assessment of the dietary habits of pregnant women at the first contact with health professionals. This assessment should estimate the daily food intake in order to quantify its nutritional value, and this way be able to inform women about a proper diet for their needs and about the advisability of supplementing the diet.

Iron supplementation

Iron versus placebo or no treatment

Two studies, a meta-analysis (Szajewska, 2010) and a systematic review (Macedo, 2010) evaluating the prophylactic administration of iron in women during pregnancy have been identified. Both reviews had in common a randomised clinical trial (Zhou et al., 2007). The trials included were conducted in populations from countries with different levels of socioeconomic development (Canada, Indonesia, UK, Turkey, and Australia). All studies included women without anaemia and in various stages of gestation.

The meta-analysis conducted by Szajewska included seven RCTs, of which only two analysed population groups with prenatal iron supplementation. In the remaining studies included, the pregnant women were treated after childbirth. The systematic review by Macedo contained five systematic reviews (of which only three analysed the comparison between that with placebo or no treatment) and seven RCTs using different treatment regimens:

- Daily supplementation with 50 mg.
- Daily supplementation with 30 mg.
- Daily supplementation with 20 mg.

The risk of anaemia (Hb <11 g / L) at the end of the pregnancy was significantly lower in the group receiving oral iron prophylaxis versus the group of pregnant women treated with placebo or where no prophylaxis was performed. (5 RCTs, 3262 women; RR 0.45, 95% CI 0.22 to 0.88) (Cogswell, 2003; Kulier, 1998; Makrides, 2003; Siega-Riz, 2005; Zhou, 2007). **Very low quality**

No significant differences were observed in the number of preterm births among the group of pregnant women treated prophylactically with oral iron and the group treated with placebo (2 RCTs, 547 women; RR 0.73, 95% CI 0.38 to 1.39) (Cogswell, 2003; Siega-Riz, 2005). **Very low quality**

No significant differences were found in the number of caesarean section deliveries for the group of pregnant women treated prophylactically with oral iron and the group of women not treated or treated with placebo (3 RCTs, 932 pregnant women; RR 0.92, 95% CI 0.48 to 1.73) (Harrison, 1985; Fleming, 1986; Ziaei, 2007) **Very low quality**

The risk of suffering from hypertensive problems during pregnancy was significantly higher in the group of women treated with prophylactic iron compared to the group treated with placebo (1 RCT, 727 pregnant women: RR 3.22, 95% CI 0.89 to 11.59) (Ziaei, 2007). **Very low quality**

The risk of giving birth to low birth weight newborns was significantly lower in the group of pregnant women undergoing a prophylactic iron treatment compared to the group of women undergoing a placebo treatment (2 RCTs, 547 women; RR 0.31, 95% CI 0.17 to 0.57) (Cogswell, 2003; Siega-Riz, 2005). **Very low quality**

The average IQ score of children born to mothers who underwent prophylactic iron measured with the *Stanford-Binet Intelligence Scale showed* no significant difference compared to those with no treatment or placebo (1 RCT, 302 pregnant; DM -0.03, 95% CI 2.47 to 2.4) (Zhou, 2006). **Very low quality**

The average score assigned by teachers about problems with peers as measured by the Strengths and Difficulties Questionnaire was significantly higher in children born to women in the group undergoing a treatment with prophylactic iron than in the group of mothers who were not treated or treated with placebo (1 RCT, 299 pregnant women; RR 3.7, 95% CI 1.06 to 12.91) (Parsons, 2008). **Very low quality**

No study evaluated the identified side effects of using iron prophylaxis during pregnancy.

Iron versus other micronutrient compounds (including iron)

Only one systematic review (Allen, 2009) analysing the effects of prophylaxis with iron alone against prophylaxis with multiple micronutrients in pregnant women was identified. Five of the studies included in this review (Caulfield et al., 1999; Friis et al., 2004; Muslimatun et al., 2001; O'Brien et al, 1999; Ramakrishnan et al, 2004) analysed the effects of prophylactic treatment with iron alone compared with the prophylactic use of micronutrients, including one (Muslimatun et al., 2001) which did not provide sufficient data on the results. The iron doses used ranged from 30 mg on a daily basis to 120 mg on a weekly basis.

No significant differences were observed in the relative risk of anaemia among the group of women treated with micronutrients and the group of women taking iron (1 RCT, 296 pregnant women; RR 0.89, 95% CI 0.69 to 1.15). (Ramakrishnan, 2004). **Very low quality**

No significant differences were found in relation to the amount of maternal haemoglobin concentration in those women treated with iron prophylaxis compared with those treated with multiple micronutrients(2 RCTs, 389 pregnant; DM 1.80, 95% CI 1.35 to 2.25) (O'Brian, 1999; Ramakrishnan, 2004). **Very low quality**

Summary of evidence

Very low quality	Oral iron supplementation during pregnancy significantly reduces the risk of anaemia (Hb <11 g / L) in late pregnancy. (Macedo, 2008).
Low quality	Supplementation with oral iron or placebo shows no significant difference in the risk of preterm delivery or caesarean section in pregnant women. (Macedo, 2008).
Low quality	Oral iron supplementation during pregnancy significantly increases the risk of hypertensive problems during gestation. (Macedo, 2008).
Low quality	Oral iron supplementation during pregnancy significantly reduces the risk of giving birth to low weight newborns. (Macedo, 2008).
Very low quality	Oral iron supplementation or placebo during pregnancy showed no significant difference in scores for the IQ of the newborn as measured with the Stanford-Binet intelligence scale. (Szajewska, 2010).
Very low quality	Oral iron supplementation or iron associated with other micronutrients showed no significant differences in the risk of anaemia during pregnancy. (Allen, 2009).

From evidence to recommendation

The aspects considered to establish the strength and direction of the recommendation were:

1. The quality of the evidence: the quality of the evidence for most of the outcome variables evaluated for iron as supplement was low or very low due to the existence of incomplete results and / or imprecision of the results (few events or wide confidence intervals).
2. Balance between benefits and risks: although clinical benefit has been observed with the administration of an oral iron supplement during pregnancy to reduce the risk of anaemia and the risk of low birth weight, a relationship of this type of intervention has been found with the risk of hypertensive pregnancy problems.
3. No studies examining the costs, use of resources, values, and preferences of pregnant women were found.

Finally, the development group made a recommendation against the intervention considering that the benefits of decreased risk of anaemia in late pregnancy and the risk of giving birth to foetuses of low weight for gestational age did not outweigh the risks of suffering hypertensive problems during pregnancy. The low quality of the studies led to the weak force of this recommendation.

Recommendation

Weak	We suggest administering iron supplementation routinely to pregnant women.

Iodine supplementation

Recent epidemiological studies in the pregnant population of different autonomous regions in Spain show that the nutritional status of iodine estimated from urinary iodine is below the range recommended by the WHO during pregnancy (Murcia, 2010).

A systematic review (Gavilán, 2011) evaluating the effects of iodine supplementation in pregnant women has been identified. This systematic review includes, in turn, two systematic reviews (Mahomed et al, 2006; Wu et al, 2008) on study populations from areas with high iodine deficiencies, and only one (Wu et al. 2008) included a study with pregnant women (Romano, 1991) which was analysed as an independent study. The review by Mahomed et al. analysed the effect of iodine supplementation in areas with severe iodine deficiency. This review included three trials carried out in pregnant women. The results showed that the risk of death in children was statistically lower in the group of pregnant women undergoing pharmacological iodine supplementation (RR 0.71; 95% CI, 0.56 to 0.90). Likewise, a decrease was observed in the prevalence of cretinism at the age of four (RR 0.27, 95% CI 0.12 to 0.60) as well as a better psychomotor development of those between 4 and 25 years old. However, due to the limited applicability of these results to our study, an analysis on the quality of the evidence for these results was deemed unnecessary.

Besides these two systematic reviews, the systematic reviews developed by Gavilán included eight studies (five clinical trials and three quasi-experimental studies, two of national origin) carried out in areas of mild to moderate iodine deficit.

Five clinical trials included in the review by Gavilán (2011) analysed the effect of iodine supplementation versus placebo in pregnant women, one using iodized salt, and the remaining four (Pedersen, 1993; Glinoer, 1995; Nohr, 2000; Antonangeli, 2002) using potassium iodide pharmacological supplements. The dose used in these preparations ranged from 100 mg/d and 200 mg/d of potassium iodide and the period of the intake lasted from the diagnosis of pregnancy until delivery or breastfeeding. Two of the five trials were developed double blind and the follow-up period ranged from 14 weeks to 12 months postpartum. These studies valued different results, many biochemicals, both in the mother, the foetus, and the newborn.

Iodized salt versus placebo

Only a clinical trial included in the review by Gavilán analysed the effect of iodized salt versus placebo in women with a normal pregnancy from areas of mild to moderate iodine deficit. The dose of iodine administered was 120-180 mcg per day, which came from iodized salt whose iodine concentration was 20 mg per kg of salt.

The urinary excretion of maternal iodine in the first trimester of pregnancy was higher, albeit not significant, in the group of pregnant women who consumed iodized salt (20 mg of iodine per kilo of salt) compared to the group of pregnant women subject to placebo (1 RCT, 35 pregnant women; mean difference (MD) 6.5, 95% CI -19.7 to 32.37) (Romano, 1991). **Very low quality**

The urinary excretion of maternal iodine during the third trimester of pregnancy

was significantly higher in the group of pregnant women who consumed iodized salt (20 mg of iodine per kilo of salt) compared to the group of pregnant women subject to placebo (1 RCT; 35 pregnant women; mean difference (MD) 50.00 mcg/l, 95% CI 24.78 to 75.22) (Romano, 1991).

In the first trimester of pregnancy, the thyroid volume of pregnant women subject to iodized salt (20 mg of iodine per kilo of salt) was lower, although not significantly, than in the group of pregnant women subject to placebo(1 RCT, 35 pregnant women; mean difference (MD) - 0.30 mcg / l, 95% CI -1.69 to 1.09) (Romano, 1991). **Very low quality**

No significant differences were observed for maternal blood levels of TSH among the group of pregnant women subject to iodized salt (20 mg of iodine per kilo of salt) and the group of pregnant women subject to placebo (1 RCT, 35 pregnant; No numerical data are provided) (Romano, 1991). **Very low quality**

Pharmacological iodine supplementation versus placebo

Four clinical trials (Romano, 1991; Pedersen, 1993; Glinoer, Nohr 1995 and 2000) of the five included in the review by Gavilán (2011) studied the effects of oral supplementation with potassium iodide drug versus placebo in pregnant women and the newborn for a period of time ranging from 14 weeks of gestation and the year after birth.

Two of the three observational studies (Velasco, 2009 and Berbel, 2009) that included the review by Gavilán, were carried out in Spain (Seville and Alicante, respectively). Both studies examined outcomes related to the neurophysiological development of children born to mothers who underwent pharmacological supplementation with iodine.

The study by Berbel (2009) examined the effects of supplementation with potassium iodide in children divided into three groups of study: children of mothers with free T4 levels during pregnancy to term above 20th percentile (n = 13), children of mothers with mild hypothyroxinaemia at 12 to 14 weeks of gestation and free T4 levels above the 20th percentile (n = 12) and children of mothers with term hypothyroxinaemia not receiving pharmacological iodine supplementation during pregnancy (comparison group) (n = 19). The mothers of the first two groups of study were supplemented with 200 mcg of potassium iodide during pregnancy. In order to meet the neurocognitive development in these groups of study the Brunet-Lézine scale was used at 18 months of age.

The study by Velasco (2009) assessed the psychological development of children between 3 and 18 months of age born to mothers pharmacologically supplemented with 300 mcg of potassium iodide (n = 133) versus another group of children whose mothers did not receive pharmacological supplementation with iodine during pregnancy (n = 61). The assessment of the psychological development was performed in a single session by interviewing the parents and the use of the Bayley Scales of Infant Development medical scale consisting, in turn, of three scales: The Scale of Mental Development (SMD), the Scale of Psychomotor Development (SPD), and the Behavioural Scale (BRS).

Maternal outcomes

Maternal urinary excretion of iodine was higher in the group of pregnant women subject to supplementation with potassium iodide (100-200 mg/day) compared to pregnant women belonging to the group subject to placebo. (2 RCTs, 89 women; No numerical data were provided) (Glinoer, 1995 and Pedersen, 1993). **Very low quality**

The increase in the volume of maternal thyroid during late pregnancy was significantly lower in the group of pregnant women undergoing pharmacological supplementation with potassium iodide (100-200 mg/day) compared to the group of pregnant women subject to placebo. (Two RCTs, data corresponding to Glinoer since Pedersen does not provide numerical data, 120 pregnant women; DM 15, 95% CI 22.24 to 7.76) (Glinoer, 1995 and Pedersen, 1993).	**Very low quality**
No significant differences in relation to maternal serum levels of TSH were detected at 35 weeks of gestation between the group of pregnant women undergoing pharmacological supplementation with potassium iodide (100-200 mg / day) and the group of pregnant women subject to placebo. (3 RCTs, data from the study by Nohr as the rest do not provide numerical data, 66 pregnant women; DM 0.04, 95% CI 0.49 to 0.57) (Nohr, 2000; Glinoer, 1995 and Pedersen, 1993).	**Very low quality**
Thyroglobulin levels in maternal serum at week 35 of pregnancy were lower though not significantly, in the study group of pregnant women undergoing pharmacological supplementation with potassium iodide (100-200 mg/day) compared to the group of pregnant women subject to placebo (3 RCTs, data from the study by Nohr because the rest did not provide numerical data, 66 pregnant women, MD -5.30, 95% CI -16.59 to 5.99) (Nohr, 2000; Glinoer, 1995 and Pedersen, 1993)	**Very low quality**
Iodine levels in breast milk in the group of pregnant women who underwent pharmacological supplementation with potassium iodide (100 - 200 µg / day) were significantly higher compared with the levels of iodine in breast milk of pregnant under placebo. (2 RCTs, 174 pregnant women, DM 31.66 , 95% CI 29.1 to 34.2) (Glinoer , 1995 and Pedersen, 1993).	**Very low quality**
As side effects, the risk of postpartum thyroid dysfunction was analysed. The results showed a non-significant trend in relation to the risk of thyroid dysfunction in the group of pregnant women undergoing pharmacological supplementation with potassium iodide (150 g / day) compared to the group of pregnant women subject to placebo. (One RCT, 46 pregnant women, OR 1.71, 95% CI 0.53 to 5.50) (Nohr, 2000).	**Very low quality**
Neonatal outcomes	
The serum thyroglobulin levels of infants in the group of pregnant women undergoing pharmacological supplementation with potassium iodide (100-200 mg/day) were significantly lower compared to the levels of serum thyroglobulin levels in infants of pregnant women subject to placebo (2 RCTs, 174 pregnant women, DM 47.8, 95% CI 50.52 to 45.08) (Glinoer, 1995 and Pedersen, 1993).	**Very low quality**
The levels of TSH in infants in the group of pregnant women undergoing pharmacological supplementation with potassium iodide (100-200 mg / day) were significantly higher compared with the TSH levels in newborns of pregnant women subject to placebo (2 RCTs, 174 pregnant women, DM 0.97, 95% CI 0.62 to 1.33) (Glinoer, 1995 and Pedersen, 1993).	**Very low quality**
The level of urinary iodine excretion in infants of pregnant women undergoing pharmacological supplementation with potassium iodide (100-200 mg/day) was significantly higher compared to the group of infants whose mothers were subjected to placebo (2 RCTs, 174 pregnant women, DM 34.04, 95% CI 31.8 to 36.2) (Glinoer, 1995 and Pedersen, 1993).	**Very low quality**

The thyroid volume in newborns whose mothers were subjected to pharmacological supplementation with potassium iodide (100 mg/day) during pregnancy was significantly lower compared to the group of infants whose mothers were subjected to placebo (1 RCT, 120 pregnant women, DM 0.29, 95% CI 0.31 to 0.27) (Glinoer, 1995). **Very low quality**

Free T4 levels in newborns whose mothers were subjected to pharmacological supplementation with potassium iodide (100-200 mg/day) during pregnancy was significantly higher compared to the group of newborns whose mothers were subjected to placebo (2 RCTs, 120 pregnant women, DM 0.58, 95% CI 0.41 to 0.76) (Glinoer, 1995 and Pedersen, 1993). **Very low quality**

No significant differences were observed in independent mental development or psycho-mental development (according to the Bayley Scales of Infant Development) jointly between the group of children whose mothers received pharmacological supplementation during pregnancy with 300 mcg of potassium iodide and the group of children of mothers who did not receive such supplementation during pregnancy (1 observational study with comparison group, 194 children, DM: 0.32; 95% CI 4.4 to 3.40 and DM 0.18, 95% CI 2.74 to 2.38, respectively) (Velasco, 2009). **Very low quality**

The average score on the Psychomotor Developmental Index scale measuring child psychological development was significantly higher in the group of children born to mothers taking 300 mcg of potassium iodide during pregnancy compared to the group of children born to mothers without pharmacological iodine supplementation during gestation (1 observational study with comparison group, 194 children, DM 6.09, 95% CI 1.75 to 10.43) (Velasco, 2009). **Very low quality**

The average score on the Brunet-Lézine scale measuring children's neurocognitive development was significantly higher in the group of children born to mothers taking 200 mcg of potassium iodide during pregnancy compared to the group of children born to mothers without pharmacological iodine supplementation during pregnancy (1 observational study with comparison group, 52 children, DM 14.30, 95% CI 7.68 to 20.92) (Berbel, 2009) **Very low quality**

Pharmacological iodine supplementation at doses of 200 mg versus 50 mg

A randomised clinical trial included in the review by Gavilán (2011) compared the effects of pharmacological supplementation with 200mg of potassium iodide versus 50 mg of potassium iodide in 67 pregnant women.

Maternal urinary excretion of iodine between weeks 18 and 26 of gestation was significantly higher in the group of pregnant women subject to supplementation with 200 mg of potassium iodide compared to the group of pregnant women subject to 50 mg of iodine (1 RCT, 67 pregnant women; DM 19.0, 95% CI 12.73 to 25.27) (Antonangeli, 2002). **Very low quality**

No significant differences were found in relation to maternal thyroid volume between weeks 18 and 26 of gestation from the group of pregnant women subject to supplementation with 200 mg of potassium iodide and the group of pregnant women subject to 50 g of this compound (1 RCT, 67 pregnant women; DM 19.0, 95% CI 12.73 to 25.27) (Antonangeli, 2002). However, a progressive increase was detected at the end of the pregnancy in both groups, showing significant differences in the group of pregnancy in both groups, showing significant differences in the group of pregnant women subject to 200 mcg of potassium iodide (1 RCT, 67 pregnant women; no numerical data were provided) (Antonangeli, 2002). **Low quality**

No significant differences were found in maternal TSH levels between weeks 18 and 26 of gestation in the group of pregnant women subject to supplementation with 200 mg of potassium iodide and the group of pregnant women who took 50 g of this compound (1 RCT, 67 pregnant women; DM 0.00, 95% CI -0.04 to 0.04) (Antonangeli, 2002). **Very low quality**

No significant differences were found in relation to maternal thyroglobulin levels between weeks 18 and 26 of gestation in the group of pregnant women subject to supplementation with 200 mg of potassium iodide and the group of pregnant women who took 50 g of this compound (1 RCT, 67 pregnant women; DM 1.00, 95% CI 2.28 to 4.28) (Antonangeli, 2002). **Very low quality**

Regarding side effects, the risk for postpartum thyroid dysfunction was analysed. No significant differences were observed between the group of pregnant women undergoing pharmacological supplementation with potassium iodide and group of pregnant women subject to placebo (1 RCT, 46 pregnant women, RR 0.73, 95% CI 0.13 to 4.09) (Antonangeli, 2002). No other side effects were detected. **Very low quality**

Moreover, recent epidemiological studies conducted in the whole of Spain and in some regions have revealed that both the child and the adult population have surpassed the mild to moderate iodine deficiency which they had been suffering for a long time and have achieved adequate intakes of iodine in the entire child population and in the subgroup of the population which includes adults who consume iodized salt, including women of childbearing age (Delgado, 2004; Donnay, 2012; Soriguer, 2012; Arrizabalaga, 2012 and Arena, 2012). This change in the nutritional status with respect to iodine is attributable to the increased use of iodized salt and, particularly, to the increase of iodine in cow milk (Soriguer, 2011). **Very low quality**

The group of Iodine Deficiency Disorders and Thyroid Dysfunction of the Spanish Society of Endocrinology and Nutrition (Soriguer, 2013) recommended that in cases in which no iodine nutritional requirements are met through the diet (in pregnant women, 3 servings of milk and dairy products +2 g of iodized salt cover about 100% of the recommended daily allowances (RDA) of iodine and in nursing mothers, 90%), pharmacological supplements of potassium iodide associated with folic acid should be administered.

Summary of evidence

Iodized salt versus placebo	
Very low quality	Iodized salt supplementation during pregnancy (20 mg of iodine per kilo of salt) increases significantly the amount of maternal urinary excretion of iodine during the third trimester of pregnancy, compared to not using any type of supplementation (Romano, 1991).
Very low quality	Iodized salt supplementation during pregnancy (20 mg of iodine per kilo of salt) increases, although not significantly, the amount of maternal urinary excretion of iodine and decreases maternal thyroid volume, although not significantly, during the first trimester of gestation. (Romano, 1991).
Very low quality	No significant differences were observed for maternal blood levels of TSH among the group of pregnant women subjected to iodized salt (20 mg of iodine per kilo of salt) and the group of pregnant women subject to placebo (Romano, 1991).
Pharmacological supplementation with potassium iodide versus placebo	
Maternal outcomes	
Very low quality	Pharmacological supplementation with 100-200 mcg / day of iodine from potassium iodide preparations during pregnancy significantly increases the concentrations of iodine in breast milk compared to not using any type of supplementation (Glinoer, 1995 and Pedersen, 1993).
Very low quality	Pharmacological supplementation with 100-200 mcg / day of iodine from potassium iodide preparations during pregnancy significantly reduces the increase in the volume of maternal thyroid at the end of the pregnancy compared to not using any type of supplementation (Glinoer, 1995 and Pedersen, 1993).
Very low quality	No significant differences were observed in maternal blood levels of TSH and thyroglobulin at 35 weeks of gestation or in maternal urinary excretion of iodine in the group of pregnant women undergoing pharmacological supplementation with 150 mg / day of iodine from potassium iodide preparations and the group of pregnant women subjected to placebo (Nohr, 2000; Glinoer, 1995 and Pedersen, 1993).
Very low quality	The pharmacological supplementation with 150 mg / day of iodine from potassium iodide preparations during pregnancy increased, although not significantly, the risk of postpartum thyroid dysfunction compared to not using any type of supplementation. (Nohr, 2000).
Neonatal outcomes	
Very low quality	Pharmacological supplementation with 100-200 mcg / day of iodine from potassium iodide preparations during pregnancy significantly reduces the levels of serum thyroglobulin in newborns compared to not using any type of supplementation. (Glinoer, 1995 and Pedersen, 1993).
Low quality	Pharmacological supplementation with potassium iodide (100 mg / day) during pregnancy significantly reduces neonatal thyroid volume compared to not using any type of supplementation. (Glinoer, 1995).

Very low quality	Pharmacological supplementation with 100-200 mcg / day of iodine from potassium iodide preparations during pregnancy significantly increases the levels of TSH and free T4 as well as the amount of urinary excretion of iodine in infants, compared to not using any type of supplementation. (Glinoer, 1995 and Pedersen, 1993).
Very low quality	Pharmacological supplementation with 200-300 mcg / day of iodine from potassium iodide preparations during pregnancy significantly increases the psychological development (as measured with the Bayley Scales of Infant Development) and neurocognitive development (measured with the Brunet-Lézine scale) compared to not using any type of supplementation. However, the joint assessment of mental and psychological development provided no significant differences. (Velasco, 2009 and Berbel, 2009).
Pharmacological iodine supplementation at doses of 200 mcg / day versus 50 mcg / day	
Very low quality	Pharmacological supplementation with 200 mcg / day of potassium iodide during pregnancy significantly increases the urinary excretion of iodine maternal compared to not using any type of supplementation (Antonangeli, 2002).
Low quality	Pharmacological supplementation with 200 mcg / day of potassium iodide during pregnancy significantly increases maternal thyroid volume at the end of the pregnancy compared to not using any type of supplementation. (Antonangeli, 2002).
Very low quality	No significant differences were observed in maternal blood levels of free T4, TSH and thyroglobulin between weeks 18 and 26 of gestation in the group of pregnant women undergoing pharmacological supplementation with potassium iodide (150 mcg / day) and the group of pregnant women subjected to placebo (Antonangeli, 2002).

From evidence to recommendation

The aspects considered by the development group to establish the strength and direction of the recommendation were:

1. Quality of the evidence. The quality of evidence has decreased in most of the outcome variables assessed due to the limitations in the study design (lack of information on the existence of blinding), indirect data (intermediate variables) and / or imprecision of results (few events or wide confidence intervals).
2. Balance between benefits and risks. A clinical benefit with iodine supplementation during pregnancy has been observed regarding improvements in the psychological and neurocognitive development child. Moreover, as a side effect of iodine supplementation only the existence of postpartum thyroid dysfunction was collected and it has not shown significant differences compared to those supplemented study groups included in the studies. However, these clinical results come from observational studies in areas with moderate or mild deficiency, not from areas where enough levels of iodine are taken.
3. No studies examining the results on the use of resources and costs or on the values and preferences of pregnant women were identified.

Finally, the development group considered a recommendation in favour of the intervention in a specific subgroup of the population, given that there is an association between pharmacological iodine supplementation during pregnancy and positive clinical results on the psychological and

neurocognitive development in children from mild to moderate iodine deficient populations, and that in Spain, in women of childbearing age who do not use iodized salt, the intake of iodine is in a borderline situation. The recommendation was made as weak due to the low quality of the evidence that supports it.

Recommendation

Weak	We suggest administering a pharmacological supplementation with potassium iodide at a dose of 200 mg / day during pregnancy to women who do not meet the recommended daily intake of iodine in their diet (3 servings of milk and dairy products + 2 g of iodized salt).

Supplementation with folic acid

Folic acid (alone or in combination with other supplements) versus placebo / no treatment / other micronutrients

Two systematic reviews (SR) (De-Regil, 2010 and Wolff, 2009) evaluating the effect and safety of supplementation with folic acid in the prevention of neonatal defects versus placebo have been identified. The first one is based on randomised trials (RCTs) or quasi-randomised (qRCTs), while the second one has been developed from observational studies. The SR by De-Regil (2010) (CochraneSR) has been selected as it is the most updated and includes the highest methodological quality (measured using the AMSTAR tool).

The SR by De-Regil (2010) included five RCTs containing comparisons where besides placebo or the lack of treatment, the administration of other micronutrients was considered. In all of them folic acid was administered daily. In one trial women received doses below 400 mcg, while in the rest women consumed 0.8 mg and 4 mg. In three of all the studies included,pregnant women began taking supplementation with folic acid before pregnancy and stopped after 12 weeks of pregnancy.

The risk of giving birth to babies with neural tube defects was significantly lower in the study group of pregnant women subject to daily supplementation of folic acid than in the study group subjected to placebo, did not follow any treatment or received supplementation from other micronutrients (5 RCTs, 6,105 pregnant women, RR 0.28, 95% CI 0.15 to 0.52) (De-Regil, 2010). **Low quality**

The risk of giving birth to babies with cleft palate was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid than in the study group which was subjected to placebo, did not follow any treatment or received supplementation from other micronutrients (3 RCTs, 5,715 pregnant women, RR 0.66, 95% CI 0.11 to 3.92) (De-Regil, 2010). **Very low quality**

No significant differences were found in the risk of giving birth to babies with cleft lip in the study group of pregnant women subject to daily supplementation of folic acid and the study group subject to placebo, did not follow any treatment or received supplementation from other micronutrients (3 RCTs, 5,715 pregnant women, RR 1.00, 95% CI 0.27 to 3.74) (De-Regil, 2010). **Very low quality**

The risk of giving birth to babies with congenital cardiovascular defects was higher, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid than in the study group subject to placebo, did not follow any treatment or received supplementation from other micronutrients (3 RCTs, 5,715 pregnant women, RR 0.55, 95% CI 0.27 to 1.14) (De-Regil, 2010).	**Very low quality**
The risk of giving birth to babies with other birth defects was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid than in the study group subjected to placebo, did not follow any treatment or received supplementation from other micronutrients (3 RCTs, 5,715 pregnant women, RR 0.72, 95% CI 0.48 to 1.07) (De-Regil, 2010).	**Very low quality**
The risk of abortion was higher, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid than in the study group subjected to placebo, did not follow any treatment or received supplementation from other micronutrients (5 RCTs, 7,618 pregnant women, RR 1.10; confidence interval 95% CI 0.97 to 1.26) (De-Regil, 2010).	**Very low quality**
The risk of foetal death was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid than in the study group subjected to placebo, did not follow any treatment or received supplementation from other micronutrients (4 RCTs, 5,994 pregnant women, relative risk RR 0.96, 95% CI 0.51 to 1.83) (De-Regil, 2010).	**Very low quality**
The risk of termination of the pregnancy due to foetal abnormalities was significantly lower in the study group of pregnant women subject to daily supplementation of folic acid than in the study group subjected to placebo, did not follow any treatment or received supplementation from other micronutrients (4 RCTs, 5,908 pregnant women, RR 0.30, 95% CI .16-.54) (De-Regil, 2010).	**Very low quality**
The risk of giving birth to low birth weight babies was lower, although not significantly, in the study group of pregnant women subjected to daily supplementation of folic acid than in the study group subjected to placebo, did not follow any treatment or received supplementation from other micronutrients (1 RCT, 186 pregnant women, RR 0.80, 95% CI 0.39 to 1.64) (De-Regil, 2010).	**Very low quality**
The risk of multiple pregnancy was higher, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid than in the study group subjected to placebo, did not follow any treatment or received supplementation from other micronutrients (3 RCTs, 6,239 pregnant women, RR 1.32, 95% CI 0.88 to 1.98) (De-Regil, 2010).	**Very low quality**

Folic acid alone versus placebo or not following any treatment

A systematic review (SR) (De-Regil, 2010 and Wolff, 2009) evaluating the effect and safety of supplementation with folic acid in the prevention of neonatal defects versus placebo has been identified. This review included five RCTs containing comparisons where besides placebo or the lack of treatment, the administration of other micronutrients was considered. In all of them, folic acid was administered daily. In one trial, the women received doses below 400 mcg, while the rest of women received 0.8 mg and 4 mg. In three of all the studies included, the pregnant women began taking supplementation of folic acid before pregnancy and stopped after 12 weeks of pregnancy.

The risk of giving birth to babies with neural tube defects was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid than in the study group that was subjected to placebo or did not follow any treatment (2 RCTs, 299 pregnant women, RR 0.32; confidence interval (CI) 95% 0.08 to 1.34) (De-Regil, 2010). **Very low quality**

The risk of giving birth to babies with congenital cardiovascular defects was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid than in the study group that was subjected to placebo or did not follow any treatment (1 RCT, 188 pregnant women, RR 0.40; confidence interval (CI) 95% 0.02 to 9.77) (De-Regil, 2010). **Very low quality**

The risk of giving birth to babies with other birth defects was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid than in the study group that was subjected to placebo or did not follow any treatment (1 RCT, 188 pregnant women, RR 0.61; confidence interval (CI) 95% 0.06 to 6.57) (De-Regil, 2010). **Very low quality**

The risk of abortion was higher, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid than in the study group that was subjected to placebo or did not follow any treatment (2 RCTs, 299 pregnant women, RR 1.66; confidence interval (CI) 95% 0.66 to 4.18) (De-Regil, 2010). **Very low quality**

The risk of foetal death was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid than in the study group that was subjected to placebo or did not follow any treatment (1 RCT, 188 pregnant women, RR 0.13; confidence interval (CI) 95% 0.01 to 2.46) (De-Regil, 2010). **Very low quality**

The risk of termination of pregnancy due to foetal abnormalities was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid than in the study group that was subjected to placebo or did not follow any treatment (1 RCT, 111 pregnant women, RR 0.28; confidence interval (CI) 95% 0.01 to 6.83) (De-Regil, 2010). **Very low quality**

No more reports on other adverse events related to the treatments assessed have been identified (De-Regil, 2010).

Folic acid in combination with other micronutrients versus placebo or not following any treatment

A systematic review (SR) (De-Regil, 2010 and Wolff, 2009) that evaluates the effect and safety of supplementation of folic acid in the prevention of neonatal defects versus placebo has been identified. This review included five RCTs containing comparisons where besides placebo or the lack of treatment, the administration of other micronutrients was considered. In all of them, folic acid was administered daily. In one trial, the women received doses below 400 mcg, while the rest of women received 0.8 mg and 4 mg. In three of all the studies included, pregnant women began taking supplementation with folic acid before pregnancy and stopped after 12 weeks of pregnancy.

The risk of giving birth to babies with neural tube defects was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group that was subjected to placebo or did not follow any treatment (1 RCT, 190 pregnant women, RR 0.17, 95% CI 0.01 to 3.22) (De-Regil, 2010).	**Very low quality**
The risk of giving birth to babies with congenital cardiovascular defects was significantly lower in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group that was subjected to placebo or did not follow any treatment (1 RCT, 190 pregnant women, RR 0.39, 95% CI 0.02 to 9.55) (De-Regil, 2010).	**Very low quality**
The risk of giving birth to babies with other birth defects was higher, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group that was subjected to placebo or did not follow any treatment (1 RCT, 190 pregnant women, RR 1.18, 95% CI 0.17 to 8.23) (De-Regil, 2010).	**Very low quality**
The risk of abortion was higher, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group that was subjected to placebo or did not follow any treatment (1 RCT, 190 pregnant women, RR 5.91, 95% CI 0.29 to 121.46) (De-Regil, 2010).	**Very low quality**
The risk of foetal death was lower although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group that was subjected to placebo or did not follow any treatment (1 RCT, 190 pregnant women, RR 0.13, 95% CI 0.01 to 2.41) (De-Regil, 2010).	**Very low quality**

No more reports on other adverse events related to the treatments assessed have been identified (De-Regil, 2010).

Folic acid in combination with other micronutrients versus other micronutrients

An SR (De-Regil, 2010) evaluating the effect and safety of supplementation with folic acid in the prevention of neonatal defects versus placebo has been identified. This review included five RCTs containing comparisons where besides placebo or the lack of treatment, the administration of other micronutrients was considered. In all of them, folic acid was administered daily. In one trial, the women received doses below 400 mcg, while the rest of women received 0.8 mg and 4 mg. In three of all the studies included, the pregnant women began taking supplementation with folic acid before pregnancy and stopped after 12 weeks of pregnancy.

The risk of giving birth to babies with neural tube defects was significantly lower in the study group of pregnant women subject to daily supplementation of folic acid than in the study group receiving other micronutrient supplementation (4 RCTs, 5,806 pregnant women, RR 0.9, 95% CI 0.15 to 0.56) (De-Regil, 2010).	**Very low quality**
The risk of giving birth to babies with cleft palate was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group receiving other micronutrient supplementation (3 RCTs, 5,527 pregnant women at risk; RR 0.66, 95% CI 0.11 to 3.92) (De-Regil, 2010).	**Very low quality**

The risk of giving birth to babies with cleft lip was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group receiving other micronutrient supplementation (3 RCTs, 5,527 pregnant women, RR 0.99, 95% CI 0.27 to 3.65) (De-Regil, 2010).	**Very low quality**
The risk of giving birth to babies with congenital cardiovascular defects was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group receiving other micronutrient supplementation (3 RCTs, 5,527 pregnant women, RR 0.98, 95% CI 0.43 to 2.22) (De-Regil, 2010).	**Very low quality**
The risk of giving birth to babies with other birth defects was lower in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group receiving other micronutrient supplementation (3 RCTs, 5,715 pregnant women, RR 0.75, 95% CI 0.50 to 1.12) (De-Regil, 2010).	**Very low quality**
The risk of abortion in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients was significantly lower, than in the study group receiving other micronutrient supplementation (5 RCTs, 7,319 pregnant women, RR 1.10, 95% CI 0.96 to 1.26) (De-Regil, 2010).	**Very low quality**
The risk of foetal death was higher, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group receiving other micronutrient supplementation (4 RCTs, 5,994 pregnant women, RR 1.36, 95% CI 0.68 to 2.75) (De-Regil, 2010).	**Very low quality**
The risk of multiple pregnancy was higher, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group receiving other micronutrient supplementation (3 RCTs, 6,239 pregnant women, RR 1.32, 95% CI 0.88 to 1.98) (De-Regil, 2010).	**Very low quality**
The risk of termination of pregnancy due to foetal abnormalities was significantly lower in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group receiving other micronutrient supplementation. (3 RCTs, 5,797 pregnant women, RR 0.30, 95% CI 0.16 to 0.55) (De-Regil, 2010).	**Very low quality**
The risk of giving birth to low birth weight babies was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid in combination with other micronutrients than in the study group receiving other micronutrient supplementation (1 RCT, 186 pregnant women, RR 0.80, 95% CI 0.39 to 1.64) (De-Regil, 2010).	**Very low quality**

Folic acid in combination with iron versus multiple micronutrients

Two SRs (Haider, 2009 and Haider, 2011) evaluating the effect and safety of supplementation with folic acid associated to iron in the prevention of neonatal defects versus placebo have been identified. All are based on randomised trials (RCTs).

The SR by Haider (2009) included nine RCTs, six of which evaluated the multiple micronutrient supplementation versus supplementation with one or two micronutrients. The multiple micronutrient composition differed between studies, and although all supplements were administered orally to pregnant women, time tracking was different between studies (first trimester, second trimester or both). The SR carried out by the same author in 2011 included a total of 14 RCTs. Twelve of the studies included used as multiple micronutrient comparator a formula called UNIMMAP, while the rest were similar except for a small variation in the dose of iron and folic acid. Three of the outcome variables used in the aforementioned SR were considered in this study.

The SR developed by Imdad et al. (2011), included 13randomised or quasi-randomised trials that examined the risk of stillbirth as an outcome variable.

The risk of giving birth to preterm babies was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid combined with iron than in the study group subject to multiple micronutrient supplementation (4 RCTs, 3,669 pregnant women, RR 0.88, 95% CI 0.76 to 1.03) (Haider, 2009).	**Very low quality**
The risk of giving birth to babies small for gestational age was significantly lower in the study group of pregnant women subject to daily supplementation of folic acid combined with iron than in the study group subject to supplementation with multiple micronutrients. (14 RCTs, 2,019 pregnant women, RR 0.91; CI 95% 0.86 to 0.96) (Haider, 2011).	**Low quality**
The risk of giving birth to low birth weight babies was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid combined with iron than in the study group subject to multiple micronutrient supplementation (4 RCTs, 3576 pregnant women, RR 0.94, 95% CI 0.83 to 1.06) (Haider, 2009).	**Very low quality**
The risk of perinatal mortality was higher, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid combined with iron than in the study group subject to multiple micronutrient supplementation (9 RCTs, 6,603 pregnant women, RR 1.05, 95% CI 0.92 to 1.19) (Haider, 2011).	**Very low quality**
The risk of maternal anaemia in the third trimester of pregnancy was higher, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid combined with iron than in the study group subject to multiple micronutrient supplementation (1 RCT, 347 pregnant women, RR 1.03, 95% CI 0.87 to 1.22) (Haider, 2011)	**Very low quality**
The risk of congenital malformations (including NTDs) was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid combined with iron than in the study group subject to multiple micronutrient supplementation (1 RCT, 347 pregnant women, RR 0.99, 95% CI 0.14 to 7.05) (Haider, 2009).	**Very low quality**
The risk of foetal death was lower, although not significantly, in the study group of pregnant women subject to daily supplementation of folic acid combined with iron than in the study group subject to multiple micronutrient supplementation (1 RCT, 347 pregnant women, RR 0.98, 95% CI 0.88 to 1.10) (Imdad et al., 2011).	**Very low quality**

Summary of evidence

Folic acid (alone or in combination with other supplements) versus placebo / no treatment / other micronutrients	
Very low quality	Daily supplementation with folic acid during pregnancy, either alone or in combination with other supplements, significantly decreases the risk of giving birth babies with neural tube defects and the termination of pregnancy due to foetal malformations. (De-Regil, 2010).
Very low quality	Daily supplementation with folic acid during pregnancy, either alone or in combination with other supplements, decreases in a non-significant way, the risk of giving birth to babies with cleft palate, congenital defects (cardiovascular or other) or low birth weight and the risk of stillbirth. (De-Regil, 2010).
Very low quality	Daily supplementation with folic acid during pregnancy, either alone or in combination with other supplements, shows no difference in relation to the risk of giving birth to babies with cleft lip. (De-Regil, 2010).
Very low quality	Daily supplementation with folic acid during pregnancy, either alone or in combination with other supplements, increases in a non-significant way, the risk of multiple pregnancy and abortion (De-Regil, 2010).
Folic acid alone versus placebo / no treatment	
Very low quality	Daily supplementation with folic acid alone during pregnancy decreases in a non-significant way, the risk of neural tube defects, birth defects (cardiovascular or otherwise), foetal death, or the termination of pregnancy due to foetal abnormalities. (De-Regil, 2010).
Very low quality	Daily supplementation with folic acid alone during pregnancy increases in a non-significant way, the risk of abortion. (De-Regil, 2010).
Folic acid combined with other micronutrients versus placebo / no treatment	
Very low quality	Daily supplementation with folic acid combined with other micronutrients during pregnancy significantly reduces the risk of giving birth to babies with cardiovascular birth defects. (De-Regil, 2010).
Very low quality	Daily supplementation with folic acid combined with other micronutrients during pregnancy, decreases in a non-significant way, the risk of giving birth to babies with neural tube defects and foetal death. (De-Regil, 2010).
Very low quality	Daily supplementation with folic acid combined with other micronutrients during pregnancy increases in a non-significant way, the risk of giving birth to babies with other congenital defects and an abortion. (De-Regil, 2010).
Folic acid combined with other micronutrients versus other micronutrients	
Very low quality	Daily supplementation with folic acid combined with other micronutrients during pregnancy significantly reduces the risk of giving birth to babies with neural tube defects as well as the risk of termination of pregnancy due to congenital defects of the newborn versus other micronutrient supplementation (De-Regil, 2010).
Very low quality	Daily supplementation with folic acid combined with other micronutrients during pregnancy, decreases in a non-significant way, the risk of giving birth to babies with cleft palate, cleft lip, congenital defects (cardiovascular or otherwise), of abortion or low weight for gestational age versus other micronutrient supplementation. (De-Regil, 2010).

Very low quality	Daily supplementation with folic acid combined with other micronutrients during pregnancy increases in a non-significant way, the risk of stillbirth, and multiple gestations versus supplementation with other micronutrients. (De-Regil, 2010).
Folic acid combined with iron versus multiple micronutrients	
Low quality	Daily supplementation with folic acid combined with iron during pregnancy significantly reduces the risk of giving birth to babies small for gestational age versus supplementation with other micronutrients (Haider, 2009, 2009 2 / id, 2011, 2011 8 / id}).
Very low quality	Daily supplementation with folic acid combined with iron during pregnancy, decreases, though not significantly, the risk of giving birth to low birth weight babies, preterm babies with birth defects (including neural tube defects) and stillbirth compared to supplementation with other micronutrients. (Haider, 2009 and Hayder, 2011).
Very low quality	Daily supplementation with folic acid combined with iron during pregnancy, increases, though not significantly, the risk of perinatal death and maternal anaemia in the third trimester compared to supplementation with other micronutrients (Haider, 2009 and Hayder, 2011).

From evidence to recommendation

The strength and direction of the recommendation were established based on the following aspects:

1. Quality of the evidence. The quality of the evidence has decreased in most of the outcomes of interest assessed for folic acid supplementation due to limitations in the design of the study, and a great inconsistency between its results, in addition to the imprecision of the results (few events or wide confidence intervals).
2. Balance between benefits and risks. There has been a clinical benefit with supplementation of folic acid during pregnancy although there is still limited evidence regarding the optimal regimen to be followed (route of administration, dosage, and duration of treatment) or adverse events regarding the drug and the treatment regimen.
3. Costs and use of resources: two studies on the cost-effectiveness of folic acid supplementation during pregnancy have been identified (Yi et al, 2011, and Wolf et al, 2009a) in which it is concluded that the benefits of prevention of neural tube defects with folic acid outweighed the cost derived.
4. No studies examining the values and preferences of pregnant women in relation to folic acid supplementation were identified.

The development group made a recommendation in favour considering that daily supplementation with folic acid has shown to significantly decrease the incidence of newborns with neural tube defects and the termination of pregnancy due to foetal malformations. Although the possibility of an association between folic acid intake and colorectal cancer has been considered (Eurocat, 2009), the lack of evidence in the studies analysed does not justify that this undesirable effect implies any limitation when determining the strength of the recommendation. Although the findings that relate daily supplementation of folic acid with an increased risk of abortion could decrease the strength of the recommendation, these findings were not significant.

Recommendations

Strong	A daily supplementation at a dose of 0.4 mg / day (400 mg / day) of folic acid should be administered during the first twelve weeks of pregnancy.
√	In patients using AEDs (antiepilepticdrugs), a daily dose of 5 mg is recommended regardless of the type of antiepileptic used.

Supplementation with multivitamins

Vitamin A

Vitamin A versus placebo or no treatment

A systematic review (van den Broek, 2010) published in 2011, which includes 16 studies, of which nine assess the effectiveness of vitamin A versus placebo or no treatment in pregnant women using different variables has been identified. The studies included in this review are from the following countries: 3 from Malawi, 1 from South Africa, 2 from Ghana, 1 from Tanzania, 5 from Indonesia, 1 from Nepal, 1 from India, 1 from the US and 1 from the UK with great heterogeneity in the clinical characteristics of the population under study (three studies included pregnant women diagnosed with HIV).

Most of the participants in the included studies were considered moderately deficient in vitamin A, except the population participating in 3 studies: a study conducted in Nepal where the population had severe vitamin A deficiency and two studies, one conducted in the US and one in the UK, where the population was not considered deficient in vitamin A. Vitamin A deficiency in these studies was determined by biochemical analysis. There are problems associated with the biochemical assessment of deficiency of vitamin A. The serum retinol levels due to homeostatic control by the liver, are not a good general indicator of the state of vitamin A. Retinol serum levels reflect the status of vitamin A storage in the liver only when these are severely depleted (less than 0.07 mmol / g liver) or extremely high (more than 1.05 mmol / g liver). Between these two extremes, serum retinol is controlled homeostatically and therefore does not always correlate with the intake or clinical signs of vitamin A deficiency. Therefore, serum retinol is not useful for assessing the level of vitamin A in individuals. Rather, the distribution of serum retinol in populations and the prevalence of individuals with serum retinol values below a cut-off, can provide important information about the status of vitamin A levels of the population and can indicate the severity of vitamin A deficiency as a public health problem. Serum retinol concentrations of 1.05, 0.70 and 0.35 mol / l have been used in the literature to indicate whether hepatic reserves are inadequate, moderate and very inadequate, respectively. (Sommer, 1995; WHO, 1996; Underwood, 1990).

The review (van den Broek, 2010) showed that supplementation with vitamin A does not affect the risk of maternal mortality (three studies were included); RR 0.78; 95% CI 0.55 to 1.10. **High quality**

The review (van den Broek, 2010) showed that supplementation with vitamin A does not affect the risk of perinatal mortality (one study was included); RR 1.01; 95% CI 0.95 to 1.07. **High quality**

The review (van den Broek, 2010) showed that supplementation with vitamin A does not affect the risk of neonatal mortality (three studies were included); RR 0.97; 95% CI 0.9 to -1.05. **High quality**

The review (van den Broek, 2010) showed that supplementation with vitamin A does not affect the risk of stillbirth (one study was included); RR 1.6; 95% CI 0.98 to 1.14.	**High quality**
The review (van den Broek, 2010) showed that supplementation with vitamin A significantly reduces the risk of maternal anaemia (three studies were included); RR 0.64; 95% CI 0.43 to 0.94.	**High quality**
The review (van den Broek, 2010) showed that supplementation with vitamin A significantly reduces the risk of maternal infection (three studies were included); RR 0.37; 95% CI 0.18 to 0.77.	**Low quality**
The review (van den Broek, 2010) showed that supplementation with vitamin A significantly reduces the risk of maternal night blindness (one study was included); RR 0.7 95% CI 0.6 to 0.82.	**High quality**
The review (van den Broek, 2010) showed that supplementation with vitamin A does not affect the risk of preterm childbirth (four studies were included); RR 0.77; 95% CI 0.57 to 1.04.	**High quality**
The review (van den Broek, 2010) showed that supplementation with vitamin A does not affect the risk of neonatal anaemia (one study was included); RR 0.99; 95% CI 0.92 to 1.08.	**High quality**
The review (van den Broek, 2010) showed that supplementation with vitamin A does not affect the risk of low birthweight (three studies were included); RR 0.98; 95% CI 0.62 to 1.54.	**Moerate quality**

Vitamin A versus micronutrient supplementation without vitamin A

No studies have been found in relation to this comparison.

Vitamin A with other micronutrients versus micronutrient supplements without vitamin A

A systematic review (van den Broek, 2010) including five studies assessing the efficacy of vitamin A combined with micronutrients versus micronutrient supplements without vitamin A in pregnant women (Dijkhuizen et al. 2004: iron, folic acid and zinc; Fawzi et al., 1998: multivitamin complex; Kumwenda et al, 2002: iron and folate; Muslimatun et al., 2001: iron and folic acid; Semba et al., 2001. iron and folate) using the measurement of different variables, has been identified.

Vitamin A supplements along with other micronutrients showed a lower proportion of neonatal deaths (12/285, 4.2%) compared with micronutrients without vitamin A (20/309, 6.5%), however, it has no significant effect on the reduction of neonatal mortality risk (one study was included); RR 0.65; 95% CI 0.32 to 1.31.	**High quality**
Vitamin A supplements along with other micronutrients showed a higher proportion of stillbirths (11/428, 2.6%) compared with micronutrients without vitamin A (8/438, 1.8%), however, it has no significant effect on the risk of foetal mortality (two studies were included); RR 1.41; 95% CI 0.57 to 3.47.	**Low quality**
Vitamin A supplements along with other micronutrients showed a lower proportion of maternal anaemia (86/360, 23.9%) however, it has no significant effect on the reduction of the risk of maternal anaemia (three studies were included); RR 0.86; 95% CI 0.68 to 1.09.	**Low quality**

Vitamin A supplements along with other micronutrients showed a lower proportion of preterm births (2/69, 2.9%) compared with micronutrients without vitamin A (5/67, 7.5%), however, it has no significant effect on the reduction of the risk of preterm birth (one study was included); RR 0.39; 95% CI 0.08 to 1.93. **Low quality**

Vitamin A supplements along with other micronutrients showed a lower proportion of neonatal anaemia (254/516, 49.2%) compared with micronutrients without vitamin A (314/536, 58.6%), however, it has no significant effect on the reduction of the risk of neonatal anaemia (two studies were included); RR 0.75; 95% CI 0.38 to 1.51. **High quality**

Vitamin A supplements along with other micronutrients showed a lower proportion of infants with low birthweight (40/285, 14%) compared with micronutrients without vitamin A (65/309, 21%), having an effect on the risk of low birth weight (one study was included); RR 0.67; 95% CI from 0.47 to 0.96. **High quality**

Vitamin B6

Oral vitamin B6 versus Control

A systematic review (Thaver et al, 2006) including five studies evaluating the efficacy of oral vitamin B6 versus control in pregnant women using different variables has been identified.

The review (Thaver et al., 2006) showed that oral supplementation with vitamin B6 does not affect the risk of eclampsia (three studies were included), as it does not produce any event on the intervention or the control. **Low quality**

The review (Thaver et al., 2006) revealed that supplementation with oral vitamin B6 showed a higher proportion of pre-eclampsia events (21/604, 3.5%) versus control (12/593, 2.0%), not having a significant effect in the reduction of the risk of preeclampsia (two studies were included); RR 1.71; 95% CI 0.85 to 3.45. **Low quality**

The review (Thaver et al., 2006) revealed that supplementation with oral vitamin B6 showed a lower proportion of dental caries (112/198, 56.6%) versus control (117/173, 67.6%), having a significant effect in the reduction of the risk of dental caries (1 study was included); RR 0.84; 95% CI 0.71 to 0.98 **Moderate quality**

The review (Thaver et al., 2006) revealed that supplementation with oral vitamin B6 showed lower production of maternal milk (100.8 g / kg / day, SD 12.8) versus control (103.1 g / kg / day, SD 21.5), however, it has no significant effect in the reduction of breast milk (one study was included); MD -2.30; 95% CI -16.46 to 11.86. **Very low quality**

The review (Thaver et al., 2006) revealed that supplementation with oral vitamin B6 showed a lower weight in newborns (2.9 kg, SD 0.28) compared to control (3.13 kg, SD 0.28) however, it had no significant effect on the lower weight of newborns (one study was included); MD -0.23; 95% CI -0.42 to -0.04. **Very low quality**

The review (Thaver et al., 2006) revealed that supplementation with oral vitamin B6 showed a higher proportion of low scores in the Apgar score test at one minute (4/38, 10.5%) versus control (0/7, 0%), not having a significant effect (one study was included); RR 1.85; 95% CI 0.11 to 31.00. **Low quality**

The review (Thaver et al., 2006) revealed that supplementation with oral vitamin B6 showed no variation of low scores in the Apgar score test at 5 minutes (0/12, 0%) versus control (0/12; 0%) (one study was included). **Very low quality**

Multivitamin with vitamin B6 versus control

A systematic review (Thaver et al., 2006) including five studies, of which two evaluated the efficacy of multivitamin with oral vitamin B6 versus control in pregnant women using different variables, has been identified.

The review (Thaver et al., 2006) revealed that the vitamin complex with oral vitamin B6 showed no change in the number of eclampsia events (one study was included), not producing any event on the intervention or the control. **Low quality**

The review (Thaver et al., 2006) revealed that the vitamin complex with oral vitamin B6 showed a higher proportion of preeclampsia events (11/368, 3%) versus control (12/576, 2.1%), no having a significant effect (one study was included); RR 1.43; 95% CI 0.64 to 3.22. **Low quality**

The review (Thaver et al., 2006) revealed that supplementation with oral vitamin B6 showed a lower proportion of dental caries (78/169, 46.2%) versus control (117/173, 67.6%), having a significant effect in the reduction of the risk of dental caries (one study was included); RR 0.68; 95% CI 0.56 to 0.83. **Moderate quality**

Intramuscular Vitamin B6 at childbirth

A systematic review (Thaver et al., 2006) including five studies, of which one evaluates the effectiveness of intramuscular vitamin B6 at childbirth versus control using different variables, has been identified.

The review (Thaver et al., 2006) revealed that intramuscular vitamin B6 at childbirth showed lower production of maternal milk (96.9 g / kg / day, SD 17.8) versus control (103.1 g / kg /day, SD 21.5), however, it has no significant effect in the reduction of breast milk (one study was included); MD -6.20; 95% CI -21.99 to 9.59. **Very low quality**

The review (Thaver et al., 2006) revealed that intramuscular vitamin B6 at childbirth showed no variation in the number of low score in the Apgar score test at minute (one study was included), not producing any events on the intervention or the control. **Very low quality**

The review (Thaver et al., 2006) showed that intramuscular vitamin B6 at childbirth showed no change in the number of low score events in the Apgar score test in 5 minutes (one study was included), not producing any event on the intervention or the control. **Very low quality**

Vitamin D

Vitamin D versus placebo or no treatment

A systematic review (De-Regil et al., 2012) including six studies, of which five evaluated the efficacy of vitamin D versus placebo or no treatment in pregnant women using different variables has been identified.

Vitamin D showed increased levels of maternal vitamin D at term versus no treatment or placebo, with a significant effect in the increase of these levels (four studies were included); MD 47.08; 95% CI 23.76 to 70.39. **Low quality**

In the sensitivity analysis it was found that women who received vitamin D daily (four studies were included) (MD 49.70, 95% CI 21.86 to 77.54) reached higher concentrations of vitamin D at the end of the pregnancy than older women who received a single dose (two studies were included) (MD 12.19, 95% CI 2.82 to 21.57).

The results did not vary considering the dose of vitamin D and the season in which the study was conducted.

The review (De-Regil et al., 2012) suggested a tendency for women who took vitamin D during pregnancy to have less frequently children of low birthweight (<2,500 g) (24/249, 9.6 %) than those who received no treatment or placebo (42/214, 19.6%) (three studies were included); RR 0.48; 95% CI 0.23 to 1.01. **Low quality**

The review (De-Regil et al., 2012) showed that women who take vitamin D are less likely to report nephritic syndrome (0/90, 0%) as a side effect than women who received no supplements or placebo (1/45, 2.2%) (one study was included); RR 0.17; 95% CI 0.01 to 4.06), but given the lack of data for this result and the wide confidence interval, no conclusions can be drawn. **Low quality**

The review (De-Regil et al, 2012) showed that children of women who take vitamin D are similar in length to the children of women taking no treatment or placebo (two studies were included); MD 0.97; 95% CI -0.41 to 2.34. **Low quality**

The review (De-Regil et al., 2012) showed that children of women who take vitamin D have a greater head circumference at birth than that of children of women who do not take any treatment or placebo (two studies were included); MD 0.43; 95% CI 0.06 to 0.79. **Moderate quality**

The review (De-Regil et al., 2012) showed no differences in birth weight for children of women who take vitamin D compared with the children of women who do not take any treatment or placebo (three studies were included); MD 39.55; 95% CI -240.68 to 319.78. **Low quality**

The review (De-Regil et al., 2012) showed that women receiving vitamin D are less likely to suffer stillbirth than women who do not receive treatment or placebo (one study was included); RR 0.17; 95% CI 0.01 to 4.06. However, given the lack of data for this result, no conclusions can be obtained. **Low quality**

The review (De-Regil et al, 2012) showed that newborns of women receiving vitamin D are less likely to die in the neonatal period than those of women who receive no treatment or placebo (one study was included); RR 0.17; 95% CI 0.01 to 4.06. However, given the lack of data for this result, no conclusions can be obtained. **Low quality**

Calcium + vitamin D versus no treatment

A systematic review (De-Regil et al., 2012) including six studies, one of which evaluated the efficacy of vitamin D + calcium versus no treatment in pregnant women using preeclampsia as an outcome has been identified.

The review (De-Regil et al, 2012) showed that women receiving calcium + vitamin D are less prone to preeclampsia than women who do not receive any treatment (one study was included); RR 0.67; 95% CI 0.33 to 1.35. However, given the lack of data for this result, no conclusions can be obtained. **Very low quality**

Calcium + vitamin D versus calcium

No studies have been found in relation to this comparison.

Vitamin D + Calcium + other vitamins and minerals compared to calcium + other vitamins and minerals

No studies have been found in relation to this comparison.

Vitamin E

Vitamin E + vitamin C versus placebo

Three systematic reviews (Rumbold et al, 2005a and Polyzos et al, 2007, which included four studies; Rahimi et al, 2009, which included seven studies) evaluating the efficacy of vitamin E + vitamin C versus placebo in pregnant women using different variables have been identified.

The review (Rumbold et al., 2005a) found no difference between pregnant women taking vitamin E + vitamin C (8/168, 4.8%) and placebo (11/171, 6.4%) for the risk of foetal deaths (two studies were included); RR 0.77; 95% CI 0.35 to 1.71. **Low quality**

No significant differences or the sensitivity analysis based on the state of gestation of the participants were located.

The review (Polyzos et al., 2007) found no significant difference in the risk of foetal or neonatal deaths among women taking vitamin E + vitamin C supplements (2.6%) compared to those taking placebo (2.3%); RR 1.10; 95% CI 0.78 to 1.56.

The review (Rahimi et al., 2009) found no differences in the risk of preeclampsia among pregnant women at risk of preeclampsia taking vitamin E + vitamin C supplements (306/2982, 10.3%) and those supplemented with placebo (342 / 2887, 11.8%) (seven studies were included); RR 0.7, 95% CI 0.58 to 1.08.

The review (Rumbold et al., 2005a) found no differences in the risk of neonatal deaths between pregnant women taking vitamin E + vitamin C supplements (5/20, 25%) and placebo (1/25, 5%) (one study was included); RR 5; 95% CI 0.64 to 39.06. **Low quality**

The review (Rumbold et al., 2005a) found no difference in the risk of perinatal deaths between pregnant women taking vitamin E + vitamin C supplements (12/27, 44.4%) and placebo (10/29, 34.5%) (one study was included); RR 1.29; 95% CI 0.67 to 2.48 **Moderate quality**

The review (Rumbold et al., 2005a) found no difference in stillbirths between pregnant women taking vitamin E + vitamin C supplements (26/193, 13.5%) and those supplemented with placebo (19/190, 10%) (two studies were included); RR 1.29; 95% CI 0.78 to 2.15. **Low quality**

No significant differences or the sensitivity analysis based on the state of gestation of the participants were found.

The review (Polyzos et al., 2007) found no significant difference in the risk of preterm birth between women taking vitamin E + vitamin C supplements (19.5%) compared to those taking placebo (18%); RR 1.07; 95% CI 0.96 to 1.20.

The review (Rahimi et al., 2009) found no difference in stillbirths between pregnant women taking vitamin E + vitamin C supplements (279/2612, 10.7%) and those supplemented with placebo (246/2620, 9.4%) (five studies were included); RR 1.13; 95% CI 0.96 to 1.32. **Moderate quality**

The review (Rumbold et al., 2005a) showed that women who received vitamin E + vitamin C supplements (21/256, 8.2%) are less prone to episodes of preeclampsia than women receiving placebo (47/254 18.5%) using the fixed effects model (three studies were included); RR 0.44; 95% CI 0.27 to 0.71. However, the result shows some statistical heterogeneity. Using the random effects model, no difference was found between both groups of pregnant women; RR 0.44; 95% CI 0.16 to 1.22 **Moderate quality**

No significant differences or the sensitivity analysis based on the state of gestation of the participants were found.

The review (Polyzos et al, 2007) found no significant difference in the risk of preeclampsia between women taking vitamin E + vitamin C supplements (11%) and those taking placebo (11.4%); RR 0.97; 95% CI 0.82 to 1.13.

The review (Rumbold et al., 2005a) found no differences in intrauterine growth restriction among pregnant women with vitamin E + vitamin C (35/195, 17.9%) and those supplemented with placebo (49/190, 25.8%) (two studies were included); RR 0.72; 95% CI 0.49 to 1.04. **Moderate quality**

No significant differences or the sensitivity analysis based on the state of gestation of the participants were found.

The review (Rumbold et al, 2005a) showed that children of women who take vitamin E + vitamin C have similar birthweight to children of women taking placebo (one study was included); MD 139.00; 95% CI -517.68 to 239.68. **Low quality**

The review (Rumbold et al., 2005a) found no differences regarding maternal deaths between pregnant women taking vitamin E + vitamin C supplements (0/27, 0%) and those supplemented with placebo (0/29, 0%) (one study was included); RR 0.00; 95% CI 0.00 to 0.00. **Moderate quality**

The review (Rumbold et al., 2005a) found no differences in the number of caesareans sections between pregnant women taking vitamin E + vitamin C supplements (16/27, 59.3%) and those supplemented with placebo (11/28, 39, 3%) (one study was included); RR 1.51; 95% CI 0.86 to 2.63. **Moderate quality**

The review (Rumbold et al., 2005a) found no differences in the number of bleeding episodes between pregnant women taking vitamin E + vitamin C supplements (3/168, 1.8%) and those supplemented with placebo (9/171, 5.3%) (two studies were included); RR 0.35; 95% CI 0.10 to 1.23. **Low quality**

The review (Rumbold et al., 2005a) found no differences in the number of women with eclampsia between pregnant women taking vitamin E + vitamin C supplements (1/27, 3.7%) and those supplemented with placebo (1/29, 3.4%) (one study was included); RR 1.07; 95% CI 0.07 to 16.33. **Low quality**

The review (Rumbold et al., 2005a) found no differences in the number of maternal renal failure and disseminated intravascular maternal coagulation between pregnant women taking vitamin E + vitamin C supplements (0/27, 0%) and those supplemented with placebo (1/29, 3.4%) (one study was included); RR 0.36; 95% CI 0.02 to 8.41.	**Low quality**
The review (Rumbold et al., 2005a) found no differences in the number of episodes of maternal pulmonary oedema between pregnant women taking vitamin E + vitamin C supplements (1/27, 3.7%) and those supplemented with placebo (2 / 29, 6.9%) (one study was included); RR 0.54; 95% CI 0.05 to 5.59.	**Low quality**
The review (Rumbold et al, 2005a) showed that children of women who take vitamin E + vitamin C supplements have a gestational age at birth which is similar to that of children of women taking placebo (one study was included); MD 0.40; 95% CI -1.87 to 1.07.	**Low quality**
The review (Rumbold et al., 2005a) found no differences in the number of children with scores less than 7 in the Apgar test at 5 minutes, between pregnant women taking vitamin E + vitamin C supplements (4/20, 20%) and those supplemented with placebo (6/19, 31.6%) (one study was included); RR 0.63; 95% CI 0.21 to 1.90.	**Low quality**
The review (Rumbold et al., 2005a) found no differences in the number of acne and skin rashes side effect episodes between pregnant women taking vitamin E + vitamin C supplements (1/27, 3.7%) and those supplemented with placebo (0/29, 0%) (one study was included); RR 3.21; 95% CI 0.14 to 75.68.	**Low quality**
The review (Rumbold et al., 2005a) found no differences in the number of episodes of transient weakness side effects between pregnant women taking vitamin E + vitamin C supplements (2/27, 7.4%) and those supplemented with placebo (0/29, 0%) (one study was included); RR 5.36; 95% CI 0.27 to 106.78.	**Low quality**
The review (Rumbold et al., 2005a) found no differences in admissions to neonatal intensive care between pregnant women taking vitamin E + vitamin C supplements (5/20, 25%) and those supplemented with placebo (6/20 30%) (one study was included); RR 0.83; 95% CI 0.30 to 2.29.	**Moderate quality**
The review (Rumbold et al., 2005a) found no differences in the use of mechanical ventilation in newborns between pregnant women taking vitamin E + vitamin C supplements (2/20, 10%) and those supplemented with placebo (6/20, 30 %) (one study was included); RR 0.33; 95% CI 0.08 to 1.46.	**Moderate quality**
The review (Rahimi et al., 2009) found no differences in the risk of hypertension between pregnant women at risk of preeclampsia taking vitamin E + vitamin C supplements (222/2210, 10%) and those supplemented with placebo (172/2222, 7.7%) (three studies were included); RR 1.3; 95% CI 1.08 to 1.57.	**Low quality**
The review (Rahimi et al., 2009) found no differences in the risk of small size at birth between pregnant women taking vitamin E + vitamin C supplements (554/2612, 21.2%) and those supplemented with placebo (534/2620 , 20.4%) (five studies were included); RR 1.04; 95% CI 0.94 to 1.15.	**Low quality**
The review (Rahimi et al., 2009) found no differences in the risk of low birth weight between pregnant women taking vitamin E + vitamin C supplements (449/1795, 25%) and those supplemented with placebo (396/1787, 22, 2%) (three studies were included); RR 1.13; 95% CI 1.004 to 1.27.	**Moderate quality**

Vitamin C

Vitamin C alone versus placebo

A systematic review (Rumbold et al., 2005b) including five studies, of which four evaluated the efficacy of vitamin C + Vitamin E versus placebo in pregnant women getting the same results as Rumbold et al., 2005b was identified. However, a single study evaluating the efficacy of vitamin C alone versus placebo in pregnant women using different variables is included. The data from this study are obtained by a sensitivity analysis based on the type of supplement.

The review (Rumbold et al., 2005b) found no differences in the risk of stillbirth between pregnant women taking vitamin C supplements (1/100, 1%) and placebo (0/100, 0%) (one study was includ ed); RR 3.00; 95% CI 0.12 to 72.77. **Moderate quality**

The review (Rumbold et al. 2005b) found no differences in the risk of neonatal death between pregnant women taking vitamin C supplements (1/89, 1.1%) and placebo (3/92, 3.3%) (one study was included); RR 0.34; 95% CI 0.04 to 3.25. **Moderate quality**

The review (Rumbold et al., 2005b) found no differences in the risk of perinatal death between pregnant women taking vitamin C supplements (1/90, 1.1%) and placebo (2/92, 2.2%) (one study was included); RR 0.51; 95% CI 0.05 to 5.54. **Moderate quality**

The review (Rumbold et al., 2005b) found no differences in the risk of intrauterine growth restriction between pregnant women taking vitamin C supplements (0/100, 0%) and placebo (0/100, 0%) (one study was included); RR 0.00; 95% CI 0.00 to 0.00. **Moderate quality**

The review (Rumbold et al., 2005b) showed that women who received vitamin C supplements (50/100, 50%) are more prone to premature births than women receiving placebo (35/100, 35%) (one study was included); RR 1.43; 95% CI 1.03 to 1.99. **Moderate quality**

The review (Rumbold et al, 2005b) found no differences in the risk of preeclampsia between pregnant women taking vitamin C supplements (3/100, 3%) and placebo (3/100, 3%) (one study was included); RR 1; 95% CI 0.21 to 4.84. **Moderate quality**

Summary of evidence

Vitamin A	
Low quality	Vitamin A supplementation in pregnant women does not reduce the risk of maternal mortality, perinatal mortality, neonatal mortality, foetal mortality, or neonatal anaemia compared to placebo or no treatment (van den Broek et al., 2010).
Low quality	Vitamin A supplementation in pregnant women does not reduce the risk of preterm birth compared to placebo or no treatment (van den Broek et al., 2010).
Moderate quality	Vitamin A supplementation in pregnant women does not reduce the risk of low birth weight of the newborn compared to placebo or no treatment (van den Broek et al., 2010).
High quality	Vitamin A supplementation in pregnant women reduces the risk of maternal anaemia and maternal night blindness compared to placebo or no treatment (van den Broek et al., 2010).

Low quality	Vitamin A supplementation in pregnant women reduces the risk of maternal infection compared to placebo or no treatment (van den Broek et al., 2010).
High quality	Vitamin A supplementation along with other micronutrients was associated with a reduced risk of low birth weight of the newborn compared to other micronutrients without vitamin A (van den Broek et al., 2010).
High quality	Vitamin A supplementation along with other micronutrients has no significant effect on the risk of neonatal mortality and neonatal anaemia compared to other micronutrients without vitamin A (van den Broek et al., 2010).
Low quality	Vitamin A supplementation along with other micronutrients has no significant effect on the risk of foetal mortality, maternal anaemia and preterm birth compared to other micronutrients without vitamin A (van den Broek et al., 2010).
Vitamin B6	
Moderate quality	Oral vitamin B6 supplementation in pregnant women reduces the risk of dental caries versus control (Thaver et al., 2006).
Low quality	Oral vitamin B6 supplementation in pregnant women does not reduce the risk of eclampsia, preeclampsia, a low score in the Apgar test at 1 minute versus control (Thaver et al., 2006).
Very low quality	Oral vitamin B6 supplementation in pregnant women reduces the risk of lower birth weight of the newborn compared to control (Thaver et al., 2006).
Very low quality	Oral vitamin B6 supplementation in pregnant women does not reduce the risk of producing less maternal milk, a low score in the Apgar test at 5 minutes compared to control (Thaver et al., 2006).
Moderate quality	Oral multivitamin B6 supplementation in pregnant women reduces the risk of dental caries compared to control (Thaver et al., 2006).
Low quality	Oral multivitamin B6 supplementation in pregnant women does not reduce the risk of eclampsia or preeclampsia compared to control (Thaver et al., 2006).
Very low quality	Intramuscular vitamin B6 at birth does not reduce the risk of producing less maternal milk, a low score in the Apgar test at 1 minute and a low score in the Apgar test at 5 minutes compared to control (Thaver et al., 2006).
Vitamin D	
Low quality	Vitamin D supplementation in pregnant women produces a significant increase in the levels of vitamin D in women in late pregnancy, mainly when taken at daily doses compared to no treatment or placebo (De-Regil et al., 2010).
Moderate quality	Vitamin D supplementation in pregnant women causes an increase in the head circumference of the child at birth compared to placebo or no treatment. However, this increase is at the edge of non-statistical significance (De-Regil et al., 2010).
Low quality	Vitamin D supplementation in pregnant women has no significant effect on the length and weight of the child at birth compared to placebo or no treatment (De-Regil et al., 2010).
Low quality	Vitamin D supplementation in pregnant women reduces the risk of low birth weight compared to placebo or no treatment. However, this reduction in risk is at the edge of statistical significance (De-Regil et al., 2010).

Low quality	Vitamin D supplementation in pregnant women does not reduce the risk of side effects, stillbirths and neonatal deaths compared to placebo or no treatment (De-Regil et al., 2010).
Low quality	Vitamin D supplementation plus calcium in pregnant women does not reduce the risk of preeclampsia compared to no treatment (De-Regil et al., 2010).
Vitamin E + vitamin C	
Low quality	Supplementation with vitamin E + vitamin C in pregnant women does not reduce the risk of stillbirth, neonatal death, preterm delivery (a review of moderate quality, Rahimi et al., 2009), episodes of maternal bleeding, eclampsia, maternal renal failure, disseminated intravascular maternal coagulation, maternal pulmonary oedema, children with a low score in the Apgar test score at 5 minutes, small size for gestational age and side effects such as acne, rashes and maternal weakness compared to placebo (Rumbold et al., 2005a).
Low quality	Supplementation with vitamin E + vitamin C in pregnant women does not significantly alter either the weight or gestational age at birth of the child compared to placebo (Rumbold et al., 2005a).
Moderate quality	Supplementation with vitamin E + vitamin C in pregnant women does not reduce the risk of perinatal death, preeclampsia (low quality reviews, Rahimi et al., 2009), intrauterine growth restriction, maternal death, caesarean section, admissions to neonatal intensive care unit, use of mechanical ventilation compared to placebo (Rumbold et al., 2005a).
Low quality	Supplementation with vitamin E + vitamin C in pregnant women at risk of preeclampsia increases the risk of gestational hypertension compared to placebo (Rahimi et al, 2009; Conde-Agudelo et al., 2011).
Moderate quality	Supplementation with vitamin E + vitamin C in pregnant women at risk of preeclampsia increases the risk of low birth weight compared to placebo (Rahimi et al., 2009).
Vitamin C	
Moderate quality	Supplementation with vitamin C alone in pregnant women does not reduce the risk of stillbirths, neonatal deaths, perinatal deaths, intrauterine growth restriction, and preeclampsia compared to placebo (Rumbold et al., 2005b).
Moderate quality	Supplementation with vitamin C alone in pregnant women increases the risk of preterm birth compared to placebo (Rumbold et al., 2005b).

From evidence to recommendation

The aspects considered to establish the strength and direction of the recommendation were:

1. Quality of the evidence:

   a. Vitamin A: the quality of the evidence is variable depending on the results evaluated for vitamin A supplementation with or without micronutrients. However, the quality of the evidence was considered high in those key outcomes for decision-making, as these failed to identify major limitations. Within the review, each of the outcome variables is assessed by different studies, being the quality of the latter different in each case. There are limitations in the design of some studies (lack of clarity in the method of randomisation, blinding), attrition bias and inaccuracy of the results.

b. Vitamin B6: the quality of the evidence for most of the variables evaluated in the vitamin B6 is low. The number of studies is small and includes some of the outcome variables within a single study. There are significant limitations in most studies including the lack of clarity in the method of randomisation, allocation concealment, attrition bias, and size of the population under study.

c. Vitamin D: the quality of the evidence for most of the variables evaluated in the vitamin D is low. The number of studies is small and contains some of the outcome variables within a single study. There are significant limitations in most studies including the lack of clarity in the method of randomisation, allocation concealment, attrition bias, size of the population under study, blinding, and wide confidence intervals.

d. Vitamin E + Vitamin C: the quality of evidence for most of the variables evaluated in the vitamin E + vitamin C supplements is low. The number of studies is small and contains some of the outcome variables within a single study. There are significant limitations in most studies including the lack of clarity in the method of randomisation, allocation concealment, type of population, size of the population under study, blinding and wide confidence intervals.

e. Vitamin C: the quality of the evidence in the variables evaluated in vitamin C supplementation is moderate; the main limitation is the small number of studies included, as only one has been identified and the fact that there is a low number of participants in the study.

2. Balance between benefits and risks:

a. Vitamin A: Vitamin A supplementation showed a clinical benefit over placebo or no treatment in some secondary variables, which are important but not critical, such as:

   i. Maternal anaemia and maternal night blindness, in which the quality of the evidence on which the result is based is high, although the number of studies included is small.

   ii. Maternal infection, although the quality of the evidence is low.

Vitamin A supplementation with micronutrients reduces the risk of low birth weight in newborns compared to micronutrients without vitamin A. The quality of evidence is high, although the number of studies included is low, as there is only one.

b. Vitamin B6: Oral vitamin B6 and vitamin supplements decrease the risk of suffering from dental caries, although this variable is considered unimportant.

c. Vitamin D: vitamin D supplementation in pregnant women produces a significant increase in the levels of vitamin D in women in late pregnancy; however, the quality of evidence is low.

d. Vitamin E + Vitamin C: no benefit from supplementation with vitamin E + vitamin C has been identified in pregnant women compared with placebo in any of the many different variables used both for the mother and the baby, and may even increase the risk of gestational hypertension and low birthweight babies of pregnant women at risk of preeclampsia.

e. Vitamin C: no benefit from vitamin C supplementation has been identified in pregnant women compared to placebo in any of the variables used both for the mother and the baby, and may even increase the risk of preterm birth compared to placebo.

3. No studies on the costs and use of resources, the values, and preferences of pregnant women in terms of multivitamin supplementation during pregnancy were identified.

The development group considered that the benefits shown for vitamin A supplementation during pregnancy in no case exceeded the risk of teratogenicity in the associated foetus. It was also considered that other vitamin supplements have shown limited benefits or limited clinical relevance to be recommended.

Recommendations

√	Pregnant women should be informed to avoid taking vitamin A supplements in doses higher than 2,500 IU or 750 mcg due to their teratogenicity.
√	Women should not take multivitamin supplements during pregnancy.

Safety of supplementation with omega 3 fatty acids

An SR evaluating the effect of polyunsaturated fatty acid supplementation on the results of pregnant women without risk of complications during pregnancy and the growth of the newborn has been identified (Szajewska, 2006). This SR included six RCTs (with a total of 1,278 newborns) that provided data on the effect of supplementing the diet of pregnant women with polyunsaturated fatty acids at gestational age, number of preterm deliveries (<37 weeks of gestation), low birthweight (<2,500 g), preeclampsia, caesareansection delivery, birth weight, size and head circumference of the newborn. The SR also assessed the adverse effects reported in the six RCTs included.

A subsequent SR included 15 RCTs evaluating the impact of the intake of polyunsaturated fatty acids, included in the food diet of pregnant women (with or without risk of complications during pregnancy) or as a supplement, on the same outcomes of the SR by Szajewska (2006) plus some additional complications like high blood pressure, or neonatal death of the newborn (Imhoff-Kunsch, 2012).

No observational studies with an appropriate design to assess the possible adverse effects arising from the diet supplements of pregnant women with polyunsaturated fatty acids have been identified.

The variability of the 6 RCTs included in the SR by Szajewska (2006) did not allow a combined analysis of their results. Therefore, the results collected adverse events of the 3 RCTs that described this outcome. **Low quality**

An RCT comparing the results from taking a dietary supplement of cod liver oil versus corn oil showed a similar dropout rate between the two groups due to the discomfort caused by the intervention (590 participants, 43% in the supplement group versus 38% in the corn oil group) (Helland, 2001). In another RCT comparing a supplement of fish oil versus olive oil in the diet of pregnant women, it was observed that a higher proportion of women in the supplement group described discomforts due to the frequency of belching and the flavour of the supplement (533 participants, belching: 70% versus 20%; taste: 42% versus 4%; P <0.001). The RCT found no significant differences between the groups in terms of bleeding during delivery, the duration of labour or the need for surgery (Olsen, 1986). A third RCT with a small sample (52 participants) compared the effect of supplementing the diet with eggs fortified with docosahexaenoic acid versus a diet with a regular intake of eggs (Smuts, 2003). In this RCT the proportion of pregnant women who reported an adverse event was higher in the control group than in the group of women who supplemented their diet (38% versus 25%; P <0.01). The adverse effects reported in these RCTs are related to nausea, vomiting, or diarrhoea.

On the other hand, the latter SR by Imhoff -Kunsch (2012) showed that supplementing the diet with polyunsaturated fatty acids increases the risk of high blood pressure during pregnancy (5 RCTs, 1,831 participants; RR 1.09, 95% CI 0.90 to 1.33), preeclampsia (4 RCTs, 1,683 participants; RR 0.86, 95% CI 0.59 to 1.27), neonatal death (8 RCTs, 7,038 participants; RR 0.80; 95 % 0.50 to 1.26), or of the newborn (6 RCTs, 6,235 participants; RR 0.69, 95% CI 0.38 to 1.23). **Low quality**

Summary of evidence

Low quality	The RCTs available have shown a rate of adverse effects associated with supplements of polyunsaturated fatty acids when compared to diets in which the intake of these fatty acids is encouraged through food (Szajewska, 2006). Women taking supplements in the RCTs described with great frequency discomforts related to taste of these products or an increased frequency of belching. None of the available studies has shown that these food supplements increase the risk of serious complications for the mother or the newborn (Imhoff-Kunsch, 2012).

The development group considered not to make a recommendation on the consumption of omega 3 fatty acids during pregnancy as it is a question related to the safety of fatty acids, whose effectiveness has not been assessed.

Medication during pregnancy

The use of drugs during pregnancy should be managed by a rational use of drugs which the pregnant woman may require during this stage, always discouraging self-medication, and thoroughly assessing the balance between the benefit for women and the risk to the foetus (NICE, 2008).

It must be considered that most drugs cross the placental barrier and their teratogenic effects (effects which can cause structural or functional abnormalities in embryonic or foetal

development) will depend on factors such as gestational age or the dose and duration of the treatment (SEMFet to ., 2002).

In the first 2 weeks after conception (between 3 and 4 weeks from the date of last menstrual period), the teratogenic effect increases the number of abortions. The third and fourth weeks (5 or 6 weeks after the last menstrual period in which many women do not know they are pregnant) can cause severe malformations at the structural level. In the following weeks, all organs develop until the eighth week when the embryo becomes a foetus, which develops its maturation and growth for the remainder of the gestation (Protocols SEGO, 2005). Therefore, the increased risk of teratogenicity is concentrated between the third and eleventh weeks of gestation, and during the second and third trimesters of pregnancy drugs can affect the growth and development of the foetus or have toxic effects on foetal tissues (Larrubia, 2010). The drug metabolism will also depend on the physiological changes that pregnancy includes mainly due to the involvement of the absorption and distribution of drugs (NICE, 2008).

There are very few drugs that have been shown to be safe during pregnancy and some which were considered safe and had to be withdrawn subsequently, while others produce damage in a given period of the pregnancy (NICE, 2008; Protocols SEGO, 2005). Tables 6 and 7 show drugs that have shown to be safe during pregnancy and others with a teratogenic effect.

There are risk ratings of different drugs to the foetus. The most widespread is the proposal by the Food and Drug Administration (FDA) which classifies drugs into five categories based on the risk of teratogenicity, set in relation to studies and the information derived from records available (Brigg, 1994) (see Table 8).

Multiple sources refer to the risk of drugs during pregnancy. For example, the Therapeutic Prescription Guide offers the possibility of consulting the drugs to be avoided or used with caution during pregnancy (AEMPS – Spanish Medicines and Health Products Agency, 2012).

On the other hand, the Spanish Administration offers a consultation service aimed at health professionals on any agent potentially teratogenic for the foetus. The Spanish Telephone Information Service on Teratologic Agents (SITTE) is an agency belonging to the Instituto de Salud Carlos III which provides telephone service at 913 941 594. There is also a call centre for the public within the Telephone Information Service for Pregnant Women (phone number 918 222 436) (MSSSI, 2012). Outside the national level, there are websites available such as http://www.motherisk.org/prof/drugs.jsp and www.perinatology.com, which provide update information on medication during pregnancy and breastfeeding.

From evidence to recommendation

The strength and direction of the recommendation were established considering the following aspects:

1. Quality of the evidence. The information in this section is derived from observational studies, sometimes uncontrolled, or even carried out in animals.
2. Balance between benefits and risks. Very few drugs have shown to be safe during pregnancy. At this stage it is always taken into account that the benefits for the mother derived from the administration of a drug do not outweigh the risks to the embryo or foetus. It is imperative to consult an information system to clarify this risk to the foetus and indicate which drugs are contraindicated.
3. No studies on the costs and the use of resources, the values, and the preferences of pregnant women in relation to this question were identified.

The following recommendation was formulated as good clinical practice, since these are guidelines aimed at achieving an adequate indication of drugs during pregnancy.

Recommendation

√	During pregnancy, the least amount of drugs should be prescribed and the lowest possible dose, limiting its use to those circumstances in which the expected benefits to the mother and foetus outweigh the known risks to the foetus.

Risks associated with alcohol consumption during pregnancy

Alcohol consumption versus abstinence

An SR (Henderson, 2007) assessed the relationship of a low-moderate consumption of alcohol (less than 12 g per day) or intensive consumption (more than five standard drinks) before or during pregnancy with complications and malformations in the newborn. The SR included 46 studies in a search for studies until 2005.

A subsequent SR (Patra, 2011) evaluated the effect of alcohol consumption before and during pregnancy in the newborn. It included cohort and case-control studies comparing women with different patterns of alcohol versus abstinent women. The review included a regression analysis to demonstrate a relation with the dose (alcohol consumption in grams) and the outcomes evaluated. The SR included 36 studies in a search for studies until June 2009.

In the SR by Henderson (2007),six studies evaluated the association between low or moderate alcohol consumption and the risk of malformations, including foetal alcohol syndrome (although no specific results are provided in this regard). The review does not perform a joint analysis of the results and only one study, with methodological limitations, showed a significant association.	**Very low quality**
In the SR by Patra (2011),28 studies evaluated the weight of the newborn. Overall, the consumption of alcohol before or during pregnancy showed a significant increase in the risk of low birth weight (<2500 g) (RR 1.12, 95% CI 1.04 to 1.20), with a marked variability in the results. A sensitivity analysis regarding the studies which adjusted the results according to confounding factors showed no significant difference (RR 1.06, 95% CI 0.99 to 1.13) (17 studies).	**Low quality**
In the SR by Patra (2011),21 studies evaluated newborns before 37 weeks of gestation. Overall, the consumption of alcohol before or during pregnancy was not associated with an increased risk of prematurity (RR 1.03, 95% CI 0.91 to 1.16), with a marked variability in the results. A sensitivity analysis regarding the studies, which the results adjusted according to confounding factors, did not show significant differences	**Low quality**

In the SR by Patra (2011) 11 studies evaluated the weight of the newborn in relation to gestational age, considering the rate of infants small for gestational age (<10th percentile weight for gestational age). Overall, the consumption of alcohol before or during pregnancy was not associated with a significant reduction of weight in relation to gestational age (RR 1.11, 95% CI 0.95 to 1.30), with a marked variability in the results. A sensitivity analysis regarding the studies, which the results adjusted according to confounding factors, did not show significant differences

Low quality

The SR by Patra (2011) included a regression analysis to show a relation of the variables considered with the dose. The risk of low birth weight was not apparent until a consumption of more than 10 g/day (one unit of standard drink per day). The risk doubles from 52 g/day (4 to 5 units of standard drinks per day). The risk of prematurity is statistically significant from a consumption of 36 g/day (three units of standard drinks per day). In addition, the risk of infants small for gestational age is significant from a consumption more than three units of standard drink per day.

Low quality

Summary of evidence

Low quality	The consumption of alcohol before or during pregnancy shows a relationship with alterations in the newborn such as low birth weight, prematurity or low birth weight for gestational age. Although the joint analysis of the results shows a significant association only for underweight newborns, this result may be influenced by those cases of reduced alcohol consumption so there is a strong association as consumption increases.
Very low quality	The lower alcohol consumption to 12 g day before or during pregnancy does not appear to be associated with an increase in malformations in the newborn.

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The evidence on complications in the newborn comes from observational studies without serious limitations in the design or implementation but with marked variability in the results. The results show a clear relation between dose - effect on all the assessed variables. The evidence on malformations in the newborn comes from observational studies with limitations in the design or implementation.
2. Balance between benefits and risks. There is no apparent risk in the reduction or abstinence of alcohol consumption during pregnancy. High alcohol consumption also has a negative impact on maternal health.
3. No studies on the costs and use of resources, values, and preferences of pregnant women regarding the consumption of alcohol during pregnancy were identified.

The development group made these recommendations considering that the effect estimators show a strong association between the consumption of several units of alcohol per day and low birth weight, prematurity or low birth weight of the newborn for gestational age.

Recommendations

Weak	We suggest that women who are pregnant or planning pregnancy do not consume alcohol.
√	Women should be informed that excessive drinking during pregnancy (defined as more than 5 units or 7.5 standard drinks on a single occasion) is a risk to the foetus.
Strong	Women who decide to consume alcohol during pregnancy, should avoid drinking more than one unit of alcohol a day (equivalent to half a pint of beer, or 25 ml of liquor or a 125 ml glass of wine).

Interventions related to the consumption of alcohol

Psychological or educational interventions

An SR (Stade, 2009) evaluated the effectiveness of psychological or educational interventions aimed at reducing alcohol consumption in pregnant women or women planning to become pregnant. In the studies included, all women received routine medical advice or an assessment of consumption. The SR included four RCTs in a search for studies until November 2007. The review does not perform meta-analysis due to the differences between the interventions and the variables analysed in various trials.

Psychological or educational interventions versus no intervention (all women received routine medical advice or assessment of consumption)

Women abstinent after the intervention **Low quality**

None of the studies included in the SR by Stade (2009) showed a significant effect after the intervention although the timing and form of measurement were highly variable. Two studies showed an increase in the number of abstinent women after the intervention (RR 1.11; RR, 1.25) but in no case was it significant. A third study showed no difference in the days of abstinence after the intervention or control (57.5 ± 6.2 versus 55.1 ± 8.3, respectively). A recent study showed that 98.3% and 91.3% of women in the intervention and control groups respectively were abstinent at the third trimester.

Women who remain abstinent during the study **Low quality**

One study included in the SR by Stade 2009 showed that 20% more women remained abstinent during the study (up to puerperium) (RR1, 20, 95% CI 1.01 to 1.42) (122 events).

Alcohol consumption before childbirth **Low quality**

Of the studies included in the SR by Stade (2009), one study showed a significant reduction in the number of episodes of alcohol consumption (DM 0.30, 95% CI -0.68 to 0.08); another study showed no significant reduction in the number of alcoholic drinks per month (DM: - 0.78, 95% CI -1.58 to 0.02); a third study showed no significant reduction in the number of units at the start of the study.

The study by Chang (2005) showed no significant difference in the number of days with alcohol consumption or the number of units consumed after the intervention.

Psychosocial interventions in pregnant women enrolled in treatment programs for alcohol abuse or dependence

An SR (Lui, 2008) did not locate any randomised clinical trials evaluating psychosocial interventions in pregnant women enrolled in treatment programs for alcohol abuse or dependence.

Pharmacological interventions

An SR (Smith, 2009) did not locate any randomised clinical trials evaluating pharmacological interventions (commonly used to treat alcohol dependence) in pregnant women.

Summary of evidence

Low quality	Evidence suggests that psychological and educational interventions can help reduce the consumption of alcohol or maintain women abstinent during pregnancy. There is not enough evidence to assess the potential effects of the intervention on the health of mothers and newborns. The differences between the evaluated interventions also impede knowing the best strategy (in terms of type, intensity, duration) to be applied to pregnant women who consume alcohol.

From evidence to recommendation

The strength and direction of the recommendation were established considering the following aspects:

1. Quality of the evidence. Although the evidence comes from an RCT, the studies showed different sources of potential bias such as a loss of important follow-up, lack of specification of the methods of randomisation and concealment sequence or no blinding of the intervention with only one study with a blinded assessment of the variable. The information on alcohol consumption was self-reported. The variability between the interventions evaluated as well as the outcome variables analysed make the evidence not directly applicable in most cases.
2. Balance between benefits and risks. There is no apparent risk in the reduction or abstinence from alcohol consumption during pregnancy. High alcohol consumption also has a negative impact on maternal health.
3. Costs and use of resources. It should be assessed if there is trained staff available to perform this type of intervention.
4. No studies on the values and preferences of pregnant women were identified with regard to this question.

The development group made this recommendation considering that the psychological and educational interventions may help reduce alcohol consumption in pregnant women. The quality of the evidence is weak mainly due to methodological shortcomings and the variability of the interventions. Any benefit of the evaluated interventions would mean a net profit due to the absence of risk, but the capacity of the centres to conduct this type of intervention must be considered.

Recommendation

Weak	We suggest implementing some sort of measure aimed at reducing alcohol consumption in women where hazardous drinking is detected during pregnancy

Smoking during pregnancy

1.1. Exposure versus non-exposure to smoke

Several systematic reviews, all observational studies evaluating smoking during pregnancy and its association with complications in the pregnancy or the newborn, have been identified. The evaluation of those more up-to-date and larger in terms of studies included has been prioritised.

In the SR by Shah (2000), 20 cohort studies evaluated the risk of preterm birth (mainly defined as before the 37th week) and smoking in pregnant women. Overall, exposure to tobacco during pregnancy showed a significant increase in preterm births (RR 1.27, 95% CI 121 to 1.33), with a marked variability in the results. **Very low quality**

The review pooled the results by smoking (mild to 10 cigarettes a day; moderate between 11 and 20 cigarettes a day and important more than 20 cigarettes per day). The results were significant in all cases without a clear relationship to the intensity of consumption (mild RR 1.25; moderate RR 1.38; significant RR 1.31).

In the SR by Ananth (1999),13 observational studies evaluated the risk of placental abruption and smoking in pregnant women. Overall, exposure to smoke during pregnancy showed a significant increase of placental abruption (RR 1.9, 95% CI 1.8 to 2.0), with a marked variability in the results. A subgroup analysis showed a similar relationship according to the design of the study (cohort or case-control), the country of study or the prevalence of consumption. **Very low quality**

Five of the 13 studies evaluated the relationship with the intensity of smoking. Although all seem to have a relationship regarding the intensity of consumption, the review does not provide a set estimator. All studies show a statistically significant relationship from 20 cigarettes a day.

Although the studies did not allow adjusting for other risk factors (age, parity or cocaine consumption), the review shows a strong association in women with hypertension and / or eclampsia.

In the SR by Castles (1999), eight case-control studies assessed the risk of ectopic pregnancy and smoking in pregnant women. Overall, exposure to smoke during pregnancy showed a significant increase of ectopic pregnancy (RR 1.74, 95% CI 1.21 to 2.27), with a marked variability in the results. **Very low quality**

Various subgroup analyses of the studies carried out in hospitals or specifically adjusted for the use of intra-uterine device, pelvic inflammatory disease or a history of ectopic pregnancy showed a similar association. Only five studies that evaluated strictly the use of tobacco in early pregnancy showed an increased risk of 51% without being statistically significant (RR 1.51, 95% CI 0.88 to 2.15).

In the SR by Castles (1999), four case-control studies assessed the risk of preterm premature rupture of membranes and smoking in pregnant women. Overall, exposure to smoke during pregnancy showed a significant increase in preterm premature rupture of membranes (RR 1.81, 95% CI 1.36 to 2.26), with a marked variability in the results. **Very low quality**

Summary of evidence

Very low quality	Smoking during pregnancy increases the risk of complications such as preterm delivery, placental abruption, ectopic pregnancy, or preterm premature rupture of membranes.
Very low quality	The results of the studies suggest a possible relationship of the assessed complications (especially preterm labor and premature rupture of membranes) with the intensity of consumption. Some studies show a relationship even with low smoking levels (between 1 and 5 cigarettes a day).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The evidence about pregnancy complications derived from smoking comes from observational studies. Diminishing the quality was considered due to limitations in the design and implementation when there was evidence that the primary studies did not adjust the results correctly according to the main confounders. Similarly, most of the reviews did not provide statistical heterogeneity even if the estimates of primary studies showed high variability. In some reviews, the search strategy of the literature suggested a potential publication bias by excluding unpublished literature in English or did not make an effort to locate potential studies published in the gray literature studies (with negative results). Although for some of the variables analysed the results suggest a dose – effect, increasing the quality of the evidence was not considered due to the existence of the previously described limitations.
2. Balance between benefits and risks. There is no apparent risk in quitting smoking during pregnancy. Smoking also has (respiratory, vascular, cancer risk) negative consequences on maternal health and exposes passively smoke to those around.
3. No studies on the costs and use of resources, the values, and preferences of pregnant women were identified.

The development group made the following recommendations considering that the effect estimators show a strong association between the smoking and pregnancy complications. Although the confidence in the results is low, there is no counterpart to quitting smoking and even has numerous beneficial effects.

Recommendations

Strong	Pregnant women should be strongly recommended to give up smoking.
Strong	Women planning pregnancy should be recommended to give up smoking completely.

Treatingsmoking

An SR (Lumley, 2009) evaluating the effectiveness of different interventions and programs aimed at quitting smoking in pregnant women has been identified. These strategies were compared with a control, which in most of the studies consisted of information about the risks of smoking during pregnancy. Although for the primary outcome (quitting) the results are shown separately by various interventions, for those outcomes related to complications in the newborn, the results are presented jointly for any strategy.

Additionally an RCT (Coleman, 2012) involving 1,050 pregnant women (between 12 and 24 weeks) who were randomised to receive transdermal nicotine patches or placebo for 8 weeks, has been identified.

Treatment for addiction

Treatments for addiction versus control

In the SR by Lumley (2009),72 trials evaluated smoking addiction treatments against a control for more than 25,000 women. The trials included randomised and quasi-randomised studies as well as studies randomised by groups.

In 55 of the 72 studies, women were informed about the risks of smoking and the benefits of abstinence during pregnancy as part of a "regular advice" (control). In the intervention group, the women involved also received interventions (often combined) which consisted of cognitive-behavioural therapy, based on the model of behaviour change stages, information on the health of the foetus, financial rewards, drug treatments or other miscellaneous interventions.

In the SR by Lumley (2009), the studies included evaluated the effect of smoking during pregnancy. Thisevaluation assessed the most advanced stage of the pregnancy. The combined results show that cessation treatments achieved a significant reduction in the smoking habit (RR 0.94, 95% CI 0.93 to 0.96) (65 trials, 21,258 participants) with a marked heterogeneity in the results. A sensitivity analysis with the 14 RCTs (5,691 participants) with a lower risk of bias showed a slightly lower but significant effect (RR 0.97; CI 95% 0.94 to 0.99).	**Low quality**
The combined results in SR by Lumley (2009) show that cessation treatments achieved a significant increase of qutiing smoking up to 5 months after delivery (RR 1.65, 95% CI 1.22 to 2.24) (20 trials, 6097 participants) with a marked heterogeneity in the results.	**Low quality**
The combined results in SR by Lumley (2009) show that cessation treatments do not significantly increase smoking cessation rates until 12 months after delivery (RR 1.39, 95% CI 0.82 to 2.38) (8 trials, 2,624 participants) with a marked heterogeneity in the results.	**Low quality**
The combined results in theSR by Lumley (2009) show that cessation treatments reduce the number of children with low birth weight (<2500 g) (RR 0.83, 95% CI 0.73 to 0.95) (16 trials, 9916 participants) with consistent results.	**Low quality**
The combined results in SR by Lumley (2009) show that cessation treatments reduce the number of preterm births (RR 0.86, 95% CI 0.74 to 0.98) (14 trials, 11,930 participants) with consistent results.	**Low quality**
The SR by Lumley (2009) showed no significant differences among the various treatments to quit smoking, compared to a control, regarding the number of newborns with very low birth weight (<1,500 g), perinatal mortality, neonatal mortality, abortions or admission to a neonatal intensive care unit.	**Very low quality**

Pharmacological treatment

Pharmacological treatment versus control

In the SR by Lumley (2009),five RCTs evaluated the pharmacological treatment (all with nicotine substitution treatment) versus control in a total of 1147 women.

Additionally an RCT (Coleman, 2012) involving 1,050 pregnant women (between 12 and 24 weeks) who smoked at least five cigarettes a day was identified. All participants received behavioural support for smoking cessation and were randomised to receive transdermal nicotine patches or placebo for 8 weeks. The women involved in this trial agreed to set a date to quit within two weeks after inclusion in the study.

In the SR by Lumley (2009), the studies included evaluated the effect of smoking during pregnancy. This evaluation assessed the most advanced stage of the pregnancy. The combined results show that cessation treatments achieved a significant reduction in the smoking habit (RR 0.95, 95% CI 0.92 to 0.98) with consistent results. **Moderate quality**

The combined results of the SR by Lumley (2009) show no significant differences in the two groups regarding the weight of the newborn (3 RCTs, 1,078 participants). **Low quality**

In the RCT by Coleman (2012), the evaluation of abstinence was conducted through a questionnaire and was validated with the determination of exhaled carbon monoxide. The nicotine substitution treatment showed no significant increase in smoking abstinence (RR 1.27, 95% CI 0.82 to 1.98). Women who achieved abstinence in the treatment group were 9.4% and 7.6% in the control group. **Moderate quality**

Abstinence rates were higher in the evaluation in the first month, these being 21.3% and 11.7% in the control group with significant differences, although this variable was obtained in a post hoc analysis of the results.

Cognitive Behavioural Therapy

Cognitive behavioural therapy versus control

In the SR by Lumley (2009), 30 trials assessed the cognitive behavioural therapy versus control in 9,570 participants. The combined results show a significant reduction of the smoking habit (RR 0.95, 95% CI 0.93 to 0.97) with mixed results. **Low quality**

The combined results of the SR by Lumley (2009) show a significant increase in birth weight of 47 g (MD 47.01, 95% CI 12.22 to 81.80) (nine trials, 3809 participants), with consistent results. **Moderate quality**

Interventions basedon the behavioural change stage model

Interventions based on the behavioural change stage model versus control

In the SR by Lumley (2009), 11 trials evaluated the interventions based on the behavioural change stage model versus control in 5,073 participants. The combined results show no significant reduction of the smoking habit (RR 0.99, 95% CI 0.97 to 1.00) with consistent results. **Moderate quality**

The combined results of the SR by Lumley (2009) show no significant differences between the two groups regarding the weight of the newborn (2 trials, 1312 participants). **Low quality**

Information about the health of the foetus

Information about the health of the foetus versus control

In the SR by Lumley (2009), four trials with 572 participants showed a significant reduction in the smoking habit. **Low quality**

The combined results of the SR by Lumley (2009) show no significant differences between the two groups regarding the weight of the newborn (3 trials, 6611 participants). **Low quality**

Financial reward

Financial reward versus control

In the SR by Lumley (2009), four trials evaluated the financial rewards versus control in 1,285 participants. The combined results show no significant reduction of the smoking habit (RR 0.76, 95% CI 0.71 to 0.81) with consistent results. **Moderate quality**

The combined results of the SR by Lumley (2009) show no significant differences between the two groups regarding the weight of the newborn (2 trials, 1008 participants). **Low quality**

Summary of the evidence

Cessation treatments	
Low quality	The treatment of quitting smoking as a whole (including drug treatments, cognitive behavioural therapy and other non-pharmacological interventions) were beneficial, compared to control, to reduce smoking during pregnancy. In addition, these interventions showed some beneficial effects on the newborn, reducing the number of infants with low birth weight and increasing the average birth weight. No differences were shown for the number of newborns with very low birth weight, perinatal mortality, neonatal mortality, abortions, and admission to a neonatal intensive care or smoking habit cessation in the long term.
Pharmacological treatments	
Moderate quality	The interventions assessed were in all cases the nicotine replacement therapy. The studies showed benefits compared to a control, to reduce smoking during pregnancy, but showed no effect on the maintenance of abstinence or birth weight.
Cognitive Behavioural Therapy	
Low quality	The cognitive behavioural therapy proved beneficial, compared to a control to reduce smoking during pregnancy and to increase the average weight of newborns.
Interventions based on the behavioural change stage model	
Low quality	The interventions based on the behavioural change stage model were not effective to reduce smoking during pregnancy or to increase the average weight of newborns versus control.
Information about the health of the foetus	
Low quality	The interventions based on information about the health of the foetus were not effective to reduce smoking during pregnancy or to increase the average weight of newborns versus control.
Financial reward	
Low quality	The financial rewards proved beneficial to reduce smoking during pregnancy, but showed no effect on the maintenance of abstinence or birth weight.

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The main causes that limit the confidence in the results are the methodological limitations in the studies considered as well as the wide variability of results. In assessing cessation treatments together, the diversity and variability of the interventions considered determines that the evidence be indirect.
2. Balance between benefits and risks. The absence of associated risks to non-pharmacological interventions condition a favourable balance while the lack of information on the risks of nicotine addiction treatments, together with its limited effectiveness do not allow to consider a clear balance.
3. No studies on the costs and use of resources or the values and preferences of pregnant women were identified.

The development group made the following recommendations considering that the pharmacological interventions and based on the education and motivation have certain benefits on quitting smoking (in the short term) and this is reflected in a reduction of certain harmful effects in the newborn. The absence of risks and costs associated limited to non-pharmacological interventions were considered to make a strong recommendation.

Recommendations

Strong	Pregnant women who smoke should be provided detailed information about the effects of smoking on their health and that of the foetus, as well as the benefits of giving it up.
Strong	Pregnant women who smoke should be provided measures based on education and motivation (including participation in smoking cessation programs) to give up smoking.
Weak	For pregnant women who do not want to give up smoking and do not accept non-pharmacological interventions we suggest providing information on the risks and benefits of nicotine replacement based therapies (NRT).

Exercise during pregnancy

Physical Activity

An SR (Kramer, 2010) on the effects of recommending regular aerobic exercise (more than two or three times a week) in pregnant women who had no complications or risk factors has been identified. This SR assessed the effect of both the recommendations to start physical activity in pregnant women who previously did not perform any activity (sedentary) and the increase or decrease in the intensity, duration, or frequency of those already engaged in some activity.

The SR included 14 studies, both randomised and quasi-randomised clinical trials (qRCTs). The studies in which the intervention was considered low frequency and / or the duration of the prescribed aerobic exercise (less than two sessions or that lasted less than 30 minutes per week) were excluded. The studies took into account different results, both in the mother and in the foetus and newborn such as the change in maternal anthropometric measures, the development of preeclampsia, preterm delivery, caesarean sections; gestational age or birth weight, among others.

Impact of physical activity in the mother

No changes were detected in the mean total weight gain in pregnant women who initiated physical activity during pregnancy compared to those who did not initiate any activity (control group) (3 RCTs, 1 RCT; 65 pregnant; DM 0.79 kg, 95% CI -0.73 to 2.31) (Clapp, 2000; Collings, 1983; Martin, 2000; Prevedel, 2003), or changes in the maternal adipose tissue (1 RCT, 22 women; DM 1.51 95% CI -3.06 to 0.04) (Prevedel, 2003) or fat-free maternal mass (1 RCT, 22 pregnant women; relative risk (RR) 1.59, 95% CI 1.59 0.38 to 2.80) (Prevedel, 2003). **Very low quality**

No significant differences were found in the development of preeclampsia in pregnant women who initiated physical activity during pregnancy compared to those who did not initiate any activity (1 RCT, 1 ECCAQ; 43 pregnant women; RR 1.17, 95% CI 0.44 3.08) (Collins, 1983; Erkkola, 1976). **Very low quality**

Impact of physical activity in childbirth

No significant differences were found in the number of preterm births between the group of pregnant women who initiated physical activity compared to those who did not initiate any activity (2 RCTs and 1 qRCT; 59 pregnant women; RR 1.82, 95% CI 0.35 to 9.57) (Clapp, 2000; Collings, 1983; Prevedel, 2003). **Very low quality**

No significant differences were found in relation to the number of caesarean section deliveries carried out for the group of pregnant women who initiated physical activity compared to those who did not initiate any activity during pregnancy (1 RCT and 2 qRCTs; 195 pregnant women; RR 0.96, 95% CI 0.60 to 1.53) (Collings, 1983; Lee, 1986; Marquez, 2000). **Very low quality**

Impact of physical activity in the newborn

Regarding the average gestational age at birth, no significant differences were found between the group of pregnant women who initiated physical activity during pregnancy compared to those who did not initiate any activity (2 RCTs and 2 qRCTs were found; 249 pregnant women; 0.10 DM; 95% CI -0.11 to 0.30) (Collings, 1983; Erkkola, 1976; Lee, 1986; Memari, 2006). **Very low quality**

No significant differences were found regarding the average birth weight in newborns of mothers who initiated physical activity during pregnancy compared to those who did not initiate any activity (4 RCTs and 2 qRCTs were found; 280 pregnant women; DM 49 496 grams; 95% CI -27.74 to 126.73) (Clapp, 2000; Collings, 1983; Erkkola, 1976; Lee, 1996; Marquez, 2000; Memari, 2006). **Very low quality**

Regarding the increase or decrease in physical activity in women before pregnancy who already performed some activity, the SR identified one small trial (Bell, 2000) in which no differences were found between pregnant women who were previously involved in physical exercise and continued performing it with the same intensity (> 5 times a week) and those that reduced it (<= 3 times a week) in terms of developing preeclampsia (1 RCT, 61 pregnant women; RR 1.18, 95% CI 0.08 to 17,99) and the mean birth weight (grams) (1 RCT, 61 pregnant women; DM -135.00, 95% CI -368.66 to 98.66).

The same SR identified another RCT which reported that pregnant women who had practiced physical activity previously (were physically fit) and had increased the duration of their exercise in early pregnancy (60 minutes, >5 times a week 20

of gestation) and then had reduced it (20 minutes, 5 times a week until delivery) gave birth to infants with higher weight (1 RCT, 49 pregnant women; DM 460.00 grams, 95% CI 251.63 to 668.37 g) compared to pregnant women in the control group who maintained a moderate-intensity physical activity (40 minutes, 5 times a week) throughout the pregnancy. The group of pregnant women who performed a pattern opposite to the previous one (reduced the duration of physical activity in early pregnancy and subsequent increase) had similar results regarding the mean weight of the newborn than the pregnant women within the control group (1 RCT, 50 pregnant women, DM -100.0; 95% CI -308.39 to 108.39) (Clapp, 2002).

In relation to the mean Apgar score at five minutes, no significant differences were found in newborns of sedentary mothers who initiated physical activity during pregnancy compared to those who did not initiate any activity (2 RCTs 2ECQ; 233 pregnant women; DM 0.15, 95% CI -0.10 to 0.39) (Collings, 1983; Lee, 1996; Marquez, 2000; Memari, 2006). **Very low quality**

An SR evaluating the rate of occurrence of adverse effects (both maternal and foetal) related to the exercise in pregnant women without complications was identified. Seventy-four studies (9 RCTs, 65 observational studies, 3,766 pregnant women, and 63,592 hours of exercise) were included, of which only 35 reported the presence or absence of adverse effects. The rate of serious adverse effects (preterm labour, bleeding from placenta previa, abortion, uterine contractions) is 1.4 events per 10,000 hours of exercise performed (35 studies, 49,665 hours of exercise) (Charlesworth, 2001). **Very low quality**

The two SRs included indicate that the quality and consistency of the data reported in the literature vary enormously and is poor. This finding hinders the work of analysis of the information found. Overall, it is emphasized that, the studies found, include few participants, and do not have a very high methodological quality. In the case of adverse effects e.g., non-reporting of some studies makes it unclear whether this lack is due to its non-occurrence, or if they occur and have not been connected or have not been considered important enough to be reported (e.g. muscle pain).

Summary of evidence

Very low quality	Starting a physical activity during pregnancy does not affect weight gain during pregnancy (Clapp, 2000; Collings, 1983; Marquez, 2000; Prevedel, 2003) and the risk of preeclampsia (Collins, 1983; Erkkola, 1976).
Very low quality	Starting a physical activity during pregnancy does not increase the risk of preterm delivery (Clapp, 2000; Collings, 1983; Prevedel, 2003), or caesarean section delivery (Collings, 1983; Lee, 1986; Marquez, 2000).
Very low quality	Starting a physical activity during pregnancy does not alter the gestational age of the newborn at childbirth (Collings, 19835; Erkkola, 1976; Lee, 1986; Memari, 2006), neither the APGAR score at five minutes (Collings, 1983; Lee, 1996; Marquez, 2000; Memari, 2006) nor the birth weight (Clapp, 2000; Collings, 1983; Erkkola, 1976; Lee, 1996; Marquez, 2000; Memari, 2006).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The quality of the evidence has decreased in most outcome variables assessed for physical exercises, as most studies are done with very small samples with risk of bias, with incomplete results and / or imprecision in the results (few events or wide confidence intervals).
2. Balance between benefits and risks. Performing regular physical activity during pregnancy appears to improve (or maintain) physical fitness. However, as the evidence available is limited, the data are insufficient to infer the balance risk – benefit to the mother and the child.
3. No studies on the costs and use of resources or the values and preferences of pregnant women were identified.

The development group made the following recommendations considering that the results of the studies were insufficient to conclude the risks involved to both the mother and the child, when performing physical exercise during pregnancy. Although for events such as preterm birth, caesareansection delivery, weight gain during pregnancy (mother), gestational age and birth weight, the results seem consistent, the small size of the samples and other methodological limitations studies, prevent to extract conclusive data.

Recommendations

√	Individualised advice on starting or maintaining physical activity as well as its intensity, duration and frequency should be provided.
√	Pregnant women should be informed of the potential dangers of certain activities during pregnancy, for example, contact sports, high impact sports and racquet sports that may involve risk of abdominal trauma; falls or excessive joint stress as well as diving can cause problems at birth and provoke the decompression illness (DCI) of the foetus.

Physiological changes of pregnancy. Psychosocial stress and affective disorders

Evaluation of the psychosocial status during pregnancy

There is extensive literature on the role and impact of psychosocial factors in perinatal outcomes such as prematurity or low birth weight. The two factors, which have undergone more interventions, are stress and those related to depression.

An SR evaluated the results of prospective observational studies showing a statistically significant relationship between the level of stress and the negative perinatal outcomes, although the size of this association was clinically irrelevant (35 studies; 31,323 women r=-0.04, 95% CI -0.08 to -0.01). In particular, stress levels during pregnancy were associated more with birth weight (14 studies, 2,786 women r=-0.07, 95% CI -0.13 to -0.01) and the risk of low birthweight (5 studies; 3,261 women r = 0.07, 95% CI 0.03 to 0.1). These results suggest that factors such as stress can have a greater impact when they interact with other psychosocial factors (Littleton, 2010). Another SR containing 18 longitudinal studies showed that prenatal stress could have a negative impact on the cognitive, psychomotor, and behavioural development of newborns (Kingston, 2012).

Other reviews of the literature have suggested that in the long-term, the stress experienced by mothers during pregnancy could affect the neurocognitive and emotional development of

the child increasing the risk of some behavioural problems, language delays or attention deficit disorder with hyperactivity (Talge, 2007; Glover, 2011).

A Cochrane SR evaluating whether the universal assessment of psychosocial aspects helped to identify pregnant women with an affective or emotional problem and its possible impact on other perinatal outcomes was identified (Austin, 2008). **Low quality**

This SR included two RCTs with different objectives. In the first one, 600 women to whom an important psychosocial risk was identified, were randomised into three possible groups: i) assessment according to the Edinburgh Postnatal Depression Scale (EPDS) and speaking with the woman on the test result and the possible risk of postnatal depression; ii) offering women an informative book on postnatal depression and sending a letter to her GP to be informedof the potential risk to women, and iii) routine prenatal care (Webster, 2003).

The other RCT was intended to discriminate whether the use of the ALPHA instrument by health professionals contributed to better identification of the psychosocial risk of pregnant women and better prevention of possible emotional problems (Carroll, 2005). The Prenatal Psychosocial Health Assessment (ALPHA) incorporates in its assessment 15 risk factors associated with the abuse to women, children, puerperiumdepression, and poor relationship with their partner that can be grouped into the areas of family, maternal factors, consumption of toxic substances and family violence. In this RCT, the ability to identify psychosocial risk factors and to determine the possibility that pregnant women may suffer from postpartum depression was compared by 60 midwives, obstetricians and family physicians which were distributed between a group using the ALPHA instrument and another which offered routine prenatal care.

Both studies had significant methodological restrictions that limit the validity of their conclusions. Webster (2003) only performed the procedure to which 75% of the participants had been assigned, as there were communication problems about the psychosocial risk with the GPs of pregnant women, or the distribution of information materials on the postpartum depression. Besides, a loss of 27% of the participants was accumulated. In the case of the study by Carroll (2005) up to 67% of health professionals who were proposed to participate in the study declined to do so, therefore the results could be attributed to the participation of professionals more motivated on this topic, thus limiting the external validity of these results.

Identification of pregnant women at high psychosocial risk **Low quality**

In the study by Carroll (2005) the health professionals who had used the ALPHA instrument identified a higher proportion of pregnant women with high psychosocial risk than the professionals following a routine prenatal care, although the differences were not significant (139 women; RR 4.61, 95% CI 0.99 to 21.39). When the number of women with any relevant psychosocial aspect was evaluated, no difference was observed between the groups (RR 1.32, 95% CI 0.82 to 2.11 139 women). The ALPHA instrument only contributed to a better detection of pregnant women suffering from domestic violence compared to pregnant women who received routine prenatal care.

Other clinical practice guidelines

As discussed in the "Content of the medical history" section, it is important to assess the existence of personal or family problems, and in particular, it is necessary to identify possible abuse following the protocols available.

Prenatal visits provide an opportunity to identify those women who suffer domestic violence (WHO, 2011). These visits allow providing care to women on a regular and ongoing basis throughout the pregnancy. This may facilitate the establishment of an environment in which to explore this aspect. Some guidelines recommend asking all women about possible domestic violence at different times of the pregnancy (first prenatal visit, quarterly and during the postpartum review) (NICE, 2008, ACOG, 2012).

Screening for postpartum depression during pregnancy

Depressive disorder is one of the most common emotional problems among women of reproductive age. Recent studies have shown that one in seven women had been treated for depression in the period between the pre- and the post-pregnancy year (ACOG, 2010; Dietz, 2007). In a prenatal program in the Community of Valencia a higher proportion of depression was observed during pregnancy in women (10.3%) than in their partners (6.5%), with an increased risk in those couples dissatisfied with their relationship or in which one member had a history of depression (Escribè-Agüir, 2008).

The identification and treatment of depression in pregnancy carries a potential benefit to the mother and her family. Children of mothers with depression have shown a delay in the development of their psychological, cognitive, neurological and motor skills (Gjerdingen, 2007). Although with variations, depending on the socioeconomic status, depression during pregnancy has been linked with an increased risk of giving birth to an infant with low birth weight, which is much lower among European countries (RR 1.16, CI 95% 0.92 to 1.47) than in the US (RR 1.10, 95% CI 1.01 to 1.21), but is much more pronounced in the developing countries (RR 2.05, CI 95% 1.43 to 2.93) (Grote, 2010).

Regarding risk factors, an SR of 57 observational studies showed that stress, lack of support network and gender violence are the factors most associated with depression during pregnancy (Lancaster, 2010). To a lesser extent, depression during pregnancy was also associated with the anxiety of the mother, a history of depression, unwanted pregnancies, low income, or smoking.

The period between pregnancy and postpartum are ideal moment to carry out a proper assessment of risk of postpartum depression in women, since it is a time during which women maintain a more intense contact with the healthcare services.

A report of health technology assessment (Hewitt, 2009a) evaluating the methods available to identify women at risk of postpartum depression, acceptability of these methods, their effectiveness in improving outcomes for mothers and their children, was identified. An economic evaluation of its use was conducted. The results on the effectiveness to improve outcomes for mothers and their children and the study of economic evaluation were described in a later publication (Hewitt, 2009b). Other SRs of literature with a similar approach to this HTA report have arrived to similar conclusions, but have some methodological limitations and an older search date; therefore, they have not been considered in this guide (Austin, 2003; Boyd, 2005).

The SR on the performance of the methods available to identify pregnant women at risk of postpartum depression (Hewitt, 2009a) included 64 yield studies of diagnostic tests, 10 of which focused on the prenatal assessment of the risk of depression (including 4,236 women).

Most studies (5) evaluated the performance of the Edinburgh Postnatal Depression Scale (EPDS) to identify pregnant women at risk of postpartum depression, in which a score of 13 points

was established as the threshold for identification of a pregnant woman at risk of postpartum depression. As a benchmark for evaluating the performance of this instrument, the DSM diagnostic criteria were used in most studies.

When the results of all studies using the EPDS scale to diagnose major depression were combined, the sensitivity of the instrument ranged from 0.60 (CI 95% 0.47 to 0.71) to 0.96 (95% CI 0 90 to 0.98) and specificity from 0.45 (95% CI 0.26 to 0.66) to 0.97 (95% CI 0.92 to 0.99). **Low quality**

The combined analysis of these results determined that the most appropriate cut-off of the EPDS instrument to diagnose a major depression, using the Youden index was 12 points (sensitivity 0.86 (95% CI .81-.89) and specificity 0.87 (CI 95% 0.80 to 0.92) although the heterogeneity of this estimate was very high (I2: 63%).

A review of the diagnostic performance of screening tools for depression in Spanish language (Reuland, 2009) identified a single study which evaluated a Spanish version of the EPDS scale on 321 Peruvian women during the first year after childbirth, taking the DSMIV diagnostic criteria as the gold standard, and setting the cut-off for the diagnosis of postpartum depression in 13 points (Vega-Dienstmaier, 2002). The study showed a good balance between the sensitivity and specificity of the Spanish version of this scale: sensitivity 0.89 (95% CI 0.67 to 0.99) and specificity 0.72 (95% CI 0.67 to 0.77).

In the review on the effectiveness of screening women at risk of postpartum depression (Hewitt, 2009a, 2009b) four RCTs were identified, one of them the RCT by Webster (2003) mentioned in the previous section, which compared if using a method of identifying risk of postnatal depression, followed or not by a monitoring of pregnant women with risk, could improve health outcomes of pregnant women and newborns. In all RCTs assessed, the tool to identify pregnant women at risk of postpartum depression was the Edinburgh Postnatal Depression Scale (EPDS).

An RCT compared the rate of women at high risk of postpartum depression identified by the EPDS against opportunistic identification as part of regular prenatal care in an American hospital (Evins, 2000). This study had some very significant losses, since only 37% of women in the intervention group completed the EPDS and half of women in the control group attended the follow-up visit 6 weeks after childbirth as was planned in the study. Women with a score of 10 points or higher in the EPDS were considered to be at risk of suffering from postpartum depression.

The remaining studies focused on the detection of pregnant women at risk of postpartum depression and subsequent reduction in the number of women at risk. Besides the RCT by Webster (2003), Kung (2002) evaluated at a Chinese university hospital, the impact of coordinated intervention by midwives on the incidence of depression 6 weeks after childbirth. These consisted of identifying women at risk of depression by the EPDS followed by an intensive monitoring of midwives to those women with a score higher than 10 points on the scale. Women in the control group were not assessed until 6 weeks after childbirth.

The last RCT included in this SR, compared a number of health care centres including a special prenatal program to a more direct contact with midwives who coordinated all the care extended up to 28 days after childbirth. They also gave women the opportunity to receive visits. The program included an evaluation with the EPDS. The women from the control group attended in healthcare centres received regular health care (MacArthur, 2002).

Moderate quality

The RCT by Evins (2000) showed that regular administration of EPDS helped identify a greater number of women at risk of postpartum depression than by opportunistic identification (165 women, 35.4% versus 6.3%; P <0.0001). In the RCT by Kim (2002) fewer women who had been assessed with the EPDS and had been closely monitored if they showed a higher risk of depression, had a score above 9 points in the EPDS against women who had received regular care (400 women, 5.9% versus 11.8%; P = 0.03). The RCT by MacArthur (2002) also showed better scores on the EPDS between women attending healthcare centres offering an prenatal program than women who received standard care (2,064 women; OR 2.68 95% CI 1.89 to 3.46) and a lower proportion of women the in improved care group with the EPDS score of 13 points or more (2,064 women; OR 0.47, 95% CI 0.31 to 0.76).

The combined analysis of the results of the studies from the SR by Hewitt (2009) showed that the use of a formal method to identify pregnant women at risk helps to reduce the percentage of women with scores on the EPDS that would indicate the presence of postpartum depression compared to pregnant women receiving regular prenatal care (3 RCTs, 3064 women; OR 0.64, 95% CI 0.52 to 0.78).

Summary of evidence

Evaluation of the psychosocial status during pregnancy	
Low quality	No adequate data on the value of prenatal universal screening for psychosocial factors has been identified, although in a study with important methodological limitations, the use of an instrument for assessing psychosocial risk (ALPHA) has shown to contribute to the identification of pregnant women with high psychosocial risk (Carroll, 2005).
Low quality	Stress levels during pregnancy are associated more with the risk of low birthweight (Littleton, 2010) and a negative impact on the cognitive, psychomotor, and behavioural development of the newborns (Kingston, 2012).
Other clinical practice guidelines	Prenatal visits are an opportunity to identify those women who suffer domestic violence (WHO, 2011). Therefore, it is necessary to ask all women about possible abuse at different times of the pregnancy (NICE, 2008, ACOG, 2012).
Screening for postpartum depression during pregnancy	
Low quality	In pregnant women, the Edinburgh Postnatal Depression Scale (EPDS) is the most commonly used and has shown good performance for identifying women at risk of postpartum depression and its diagnosis (Hewitt, 2009a), although the impact of a systematic screening with this scale is limited (Hewitt, 2009b).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. For the assessment of the psychosocial state, the quality of the evidence has decreased due to serious methodological limitations of the available RCTs related to the inadequate implementation of the interventions in the RCT by Webster (2003) and the participation of more motivated healthcare professionals in

the RCT by Carroll (2005). Furthermore, both studies show very inaccurate results suggesting a possible benefit of the intervention or its absence. The literature on the performance of the Edinburgh Postnatal Depression Scale (EPDS) for identifying women at risk of postpartum depression and its diagnosis is poor due to limitations in the design of most studies (related to patient selection, determination of the test results evaluated, or the presence of bias in disease progression), and a high variability between the results of the studies (I2 values reaching between 63% and 83%). For the assessment of postpartum depression risk, the quality of the evidence has decreased due to serious methodological limitations of the RCTs available: Webster (2003) had a considerable loss of participants in its study, and Kung (2002) and MacArthur (2002) could have used biased randomisation methods.

2. Balance between benefits and risks. The identification of pregnant women at risk of postpartum depression can ensure the proper approach to this affective disorder with a potential impact on women's health, development of their children, and the relationship with their environment. No relevant side effects of a screening of these features, beyond the possible impact the determination of false positives may have, have been derived.

3. Costs and use of resources. The HTA report by Hewitt (2009a) conducted a literature SR to identify economic evaluation studies, but found no studies. The authors developed their own analytical model. Their results did not show that regular identification is cost effective for the parameters in the NHS. Although no studies have been identified on this matter, the amount of workload involved in routine monitoring of pregnant women and the availability of trained health personnel for proper evaluation should be assessed.

4. Values and preferences of pregnant women. The HTA report by Hewitt (2009a) and a subsequent publication of its results (Brealey, 2010) developed an SR on qualitative studies and observational studies to rate the acceptability of the EPDS scale among pregnant women and healthcare professionals. The results of 16 studies, synthesized from a narrative and textual approach, showed that in general the EPDS is accepted by women and healthcare professionals, although there are some factors to be considered related to its administration. Women need to feel comfortable in the screening process to assess the risk of postpartum depression, so it is important that the test is carried out by a person having a link previously established and is familiar to her. If possible, the opportunity to complete it at home should be provided. The review showed that women expressed their difficulty responding to the last item of the instrument related to the possibility of self-injurious behaviours.

The development group made the following recommendations considering that the results of the studies are insufficient to make a favourable recommendation for the universal screening of the psychosocial status of pregnant women. For example, regarding the results available on the benefit derived by the EPDS identification of women at risk of postpartum depression, it is unclear that it can be attributed to this procedure, or to the additional care which women subsequently receive. However, in cases where the health professionals suspect that the mother may have any risk factors that may affect her psychosocial status or can lead to postpartum depression, the EPDS has shown good performance for a good diagnosis.

Recommendations

Weak	We suggest carring out a screening of the psychosocial status of the pregnant woman when there is suspicion of a material factor that may affect the course of pregnancy or postpartum.
√	Health professionals should be alert to the signs and symptoms of domestic violence during pregnancy, asking women about possible abuse in an environment where they feel safe, at least at the first prenatal visit, on a quarterly basis and in the postpartum visit.

Sexual activity during pregnancy

The clinical practice guideline on pregnancy by NICE (NICE, 2008) collected the results of three observational studies (Klebanoff, 1984; Read, 1993; Berghella, 2002) which assessed to what extent sexual intercourse could cause problems during pregnancy.

The results from two cohort studies conducted in the USA (Klebanoff, 1984; Read, 1993) showed an inverse association between frequency of intercourse and the risk of preterm delivery. A third study showed that in pregnant women with bacterial vaginosis the risk of preterm delivery among women was similar regardless of how often they had sexual intercourse (Berghella, 2002). **Low quality**

For the cohort Collaborative Perinatal Project case, which included 40,000 women (Klebanoff, 1984), intercourse frequency (one or more penetrative intercourses a week) at weeks 28 and 29, 32 and 33, and 36 and 37 was associated with a longer gestation. This same study did not show that women who had sexual intercourse during the weeks of gestation mentioned previously, had an increased risk of perinatal mortality than women who did not have sexual penetrative intercourse.

Pregnancy is a stage associated with many changes that may affect the perception of intimacy and sexuality in pregnant women, being a subject to which special attention is not paid during regular prenatal care. This can lead to the misconception that sex during pregnancy can harm the development of the foetus. The most common fears are related to the possibility of harm to the foetus, premature birth, break of the amniotic sac or bleeding and infection. **Other clinical practice guidelines**

The second trimester is a period in which the couple can have sex regularly, although the appearance of symptoms during the first trimester (nausea, breast tenderness) or physiological changes in the third trimester (mobility limitations related to increased abdominal girth) may interfere with the interest and desire for sexual activity.

In any case, the pregnant mother should be able to discuss with the healthcare professionals any possible concerns or doubts. A review of the literature has shown that the lack of adequate information about sex during pregnancy and the potential impact to the foetus is the most important factor leading to avoid sex at this stage (Serati, 2010). Throughout the process of prenatal care healthcare professionals should promote the open discussion and provide guidance to pregnant women about the expected changes in sexual health (Johnson, 2001). **Low quality**

Summary of evidence

Low quality	The frequency with which sex is practiced during pregnancy does not increase the risk of preterm delivery or perinatal mortality (Klebanoff, 1984; Read, 1993; Berghella, 2002).
Low quality	The lack of adequate information about sexuality during pregnancy and the potential impact to the foetus during sexual intercourse can encourage the emergence of misconceptions and make sex be avoided at this stage (Serati, 2010; Millheiser, 2012).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The literature assessed in this section corresponds to observational studies and in no case has been considered to increase the quality of the evidence.
2. Balance between benefits and risks. The frequency with which sex is practised during pregnancy has not shown an increased risk of preterm delivery or perinatal mortality.
3. No studies examining the costs and use of resources of this intervention or the values and preferences of pregnant women have been identified.

The development group made the following recommendation considering the information derived from the absence of risk of preterm birth or perinatal mortality related to the frequency of sexual intercourse that available observational studies have shown. The quality of evidence determined the strength of the recommendation.

Recommendation

Weak	We suggest providing information to pregnant women and their partners about the possibility of having sexual relations regularly during pregnancy because these are not associated with any risk to the foetus.

Travelling abroad during pregnancy

A recent publication in which a synthesis of the literature and recommendations available aimed at pregnant women wishing to travel (Hezelgrave, 2011) has been identified. This review of the literature contains a number of considerations to be taken into account when pregnant women wish to travel during the different stages of gestation or in certain circumstances.

The authors differentiate the risks arising from the very fact of travelling from the risks related to the places where to travel, highlighting the fact that the limited literature available on this subject makes it difficult to provide generalized advice to any woman. In any case, given the need to counsel pregnant women about their trip, the best strategy is to make a detailed assessment of the risks (Hezelgrave, 2011).

This review highlights in broad terms that travelling during pregnancy may cause some risk, especially if travelling by plane, but in any case, the safest time to do so is during the second trimester. It is advisable to inquire about the possible restrictions that certain airlines may have before planning a trip, and ensure that health services are accessible if necessary at the destination (Hezelgrave, 2011).

Moreover, pregnant women who are travelling abroad should know about the risks and benefits of vaccination or prophylaxis recommended and the sanitary conditions of the country they are visiting. They would have to go to an international vaccination centre in their area. Information can be found in the following website: http://www.msssi.gob.es/profesionales/saludPublica/sanidad Exterior / health /centrosvacu.htm.

Possible restrictions on airlines to travel during pregnancy

Other clinical practice guidelines

Most airlines establish a series of restrictions for pregnant women, which are variable, but are concentrated in the advanced stage of the pregnancy. Generally no restrictions are placed until 28 weeks, and as of this week, companies usually request a medical certificatestating that pregnancy is not subject to risks and include the expected date of delivery. Travelling is banned from week 36 (Hezelgrave, 2011). The best strategy in this regard is that pregnant women who wish to travel consult the conditions of each airline.

While other carriers such as rail or bus are less restrictive, it is also necessary to inquire about possible restrictions.

Risks derived from air travel during pregnancy

Very low quality

The special environmental conditions involved in air travel, combined with the physiological changes associated with pregnancy, make that under certain conditions the risk of some complications may increase. However, these complications do not always imply an excessive risk to the pregnant woman and her foetus and can be avoided by following the instructions given by the healthcare professionals and the indications of the different airlines.

For example, several observational studies have shown an increased risk of abortion among flight attendants versus controls, or an increased risk of preterm delivery among aeroplane travellers versus controls (Hezelgrave, 2011; Magann, 2010).

On the other hand, the risk of venous thromboembolism is ten times higher in pregnant women than in non-pregnant women, causing a complication in one in 1,000 pregnancies (Rodger, 2003). In this sense, air travel may involve situations where the risk of thromboembolism increases, due to issues such as little mobility during journeys. It is important to inform pregnant women of this fact, especially when planning long distance trips (NICE, 2008). On the other hand, there are some simple tips for the prophylaxis of deep vein thrombosis such as sitting in an aisle seat, performing some movements every 30 minutes, increasing water consumption and reducing coffee, wearing elastic compression stockings in very long flights (RCOG, 2008).

A woman with a singleton pregnancy with a normal course of gestation can fly safely until week 36 of gestation (ACOG, 2009). Women should be advised to wear the seat belt fastened below the abdomen, in the upper thighs (RCOG, 2008). This indication is to be applied to all means of transport.

Specific considerations depending on the time of pregnancy when wishing to travel

Other clinical practice guidelines

There is no scientific literature that establishes an absolute contraindication for travelling during pregnancy, although given certain obstetric situations it should be discouraged (for example, if there has been an amniocentesis recently, the risk of spontaneous abortion increases, or multiple pregnancy may increase the risk of preterm delivery) (Hezelgrave, 2011).

A number of issues depending on the trimester during which the pregnant woman wishes to travel should be considered. For example, it may be important to identify women at increased risk of ectopic pregnancy during the first trimester, while complications from traveling during the second trimester are less frequent. Therefore, it is considered the safest trimester to travel (ACOG, 2009). The greatest risk to consider during the third trimester is pre-term delivery.

If the pregnant woman expresses her intention to travel during the first trimester of pregnancy, the condition of the foetus will be confirmed previously, to identify women who may be at increased risk of ectopic pregnancy or abortion. If any abnormal symptom is detected, the trip should be deferred until the first ultrasound results are evaluated (Hezelgrave, 2011).

Summary of evidence

Other clinical practice guidelines	The risks derived from travelling during pregnancy may vary depending on the time in which the journey and the destination have been planned. It is important to conduct a risk assessment in each case and circumstance to plan a safe trip (Hezelgrave, 2011).
Other clinical practice guidelines	Although it is advisable to consult the conditions of each airline, pregnant women can generally fly safely until week 36 of gestation (Hezelgrave, 2011, ACOG, 2009).
Other clinical practice guidelines	The second trimester is considered the safest to travel. If women express their desire to travel during the first trimester, it will be necessary to assess in advance the risk of ectopic pregnancy or abortion (Hezelgrave, 2011).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The literature assessed in this section was provided by a review of the literature and the recommendations from other clinical practice guidelines. All available studies evaluating the risks associated with flying during pregnancy are observational, retrospective on many occasions; therefore, there is no reason to consider increasing the quality of the evidence.
2. No studies examining the costs and use of resources of this intervention or the values and preferences of pregnant women were located.

The development group made the following recommendations considering the information collected on recommendations from other CPGs, since there is no available quality scientific literature that can provide definitive recommendations about which specific advice should be given to a woman who wishes to travel.

Recommendations

√	An assessment of the potential risks arising from a trip should be carried out depending on the mother's circumstances and the point of the pregnancy when she wishes to go.
√	When the pregnant woman states that she would like to travel, she should be advised of the possible restrictions for pregnant women established by travel companies.
√	When the pregnant woman states that she would like to travel, she should be informed about the increased risk of venous thromboembolism in long-distance travels.

5.4. Managing common problems during pregnancy

Key question:

- What is the effect of interventions for the treatment of nausea and vomiting during pregnancy?
- What is the effect of interventions to prevent or treat heartburn during pregnancy?
- What is the effect of interventions for the prevention or relief of constipation during pregnancy?
- What is the effect of interventions for the prevention or relief of haemorrhoids during pregnancy?
- What is the effect of interventions for the prevention or treatment of low back pain during pregnancy?

Managing nausea and vomiting

Acupressure

Acupressure versus placebo or control

Three systematic reviews (SRs) by Jewell D (2008), Helmreich RJ (2006) (one of them with its corresponding update by Matthews A, (2012)) and two randomised clinical trials (RCTs) were identified(NM Steele, 2001; Can Gurkan O, 2008). The first SR evaluated the effects of acupressure and acupuncture in the treatment of nausea and vomiting in the early stages of pregnancy and combined the results of both procedures. However, only the results from acupuncture independently were included in this section. This review identified three RCTs comparing acupressure in 500 women versus placebo. The remaining systematic review examined the effects of acupressure, acupuncture and electrical stimulation and identified nine RCTs comparing acupressure versus a control group. This second review included three RCTs identified in the first systematic review described.

Furthermore, an additional document updating the literature search (conducted in February 2012) has been identified. It is a clinical review article published in 2011 in the *British Medical Journal*.

After one day, six days and two weeks of follow-up, significant improvement was observed regarding the intensity of nausea symptoms measured by the Visual Analogue Scale (VAS) for acupressure compared to the untreated group (1 RCT; Werntoft, 2001; 60 women; mean difference (MD) of -2.40 points; 95% CI -3.78 to -1.02; 1RCT; Werntoft, 2001; 60 women; mean difference (MD) -2.00 points, 95% CI -3.37 to -0.63, 1 RCT, Werntoft, 2001; 60 women; mean difference (MD) of -2.30 points; 95% CI -3.79 to -0.81, respectively).	**Very low quality**
The proportion of women who reported nausea was significantly greater in the acupressure group compared with the control group for both digital acupressure and that controlled with a wristband (1 SR; Helmreich RJ, 2006, with 1 and 5 RCTs, 350 and 273 women; RR 0.41 and 0.55, 95% CI from 0.28 to 0.60 and from 0.38 to 0.77, respectively)	**Very low quality**

For the intensity of nausea measured with VAS, one RCT (Can Gurkan O, 2008) did not detect significant differences between acupressure and the group undergoing placebo wristband acupressure (1 RCT; 75 women, the absolute results were not reported). **Very low quality**

The proportion of women who reported the occurrence of vomiting was significantly lower in the group receiving wristband acupressure compared to the control group (1 SR; Helmreich RJ, 2006 2 / id with 5 RCTs, 250 women; RR 0.45; 95% CI 0.32 to 0.63). **Very low quality**

No significant differences were found in terms of the intensity of vomiting measured by VAS after 4 and 6 days of treatment between acupressure wristband and placebo. (1 RCT, Can Gurkan O, 2008; 75 women, the absolute results were not reported). **Very low quality**

The proportion of women who reported morning sickness (without further definition) was lower in the acupressure group compared to the group receiving placebo acupressure (1 SR, Jewell D, 2008, 2 RCTs, RR 0.57, 95% CI 0.38 to 0.86). **Very low quality**

The duration of nausea and vomiting was lower in the group receiving active wristband acupressure than in the control group with placebo acupressure(1 RCT Norheim AJ, 2001; 97 women, WMD -1.89 hours / 12-hour cycle, 95% CI -3.45 hours / cycle 12 hours to 0.33 hours / 12-hour cycle). **Very low quality**

No significant differences were detected in the intensity of nausea and vomiting jointly by the group of women undergoing wristband acupressure and the group with placebo wristband acupressure (1 RCT, Norheim AJ, 2001; 97 women, WMD -0.25, 95% CI -0.62 to +0.12). **Very low quality**

A systematic review Helmreich RJ (2006) reported on adverse effects in the acupressure occurred in a clinical trial that included pain, numbness and swelling of the hands (1 SR; Helmreich RJ, 2006; the number of women included in this analysis or the absolute results were not reported). **Very low quality**

Acupressure against pyridoxine (vitamin B_6)

No significant differences were detected in the intensity of nausea and vomiting measured by the Rhodes rating scale on the fifth day of treatment between the group treated with wristband acupressure on the P6 point compared to the group receiving 50 mg of pyridoxine twice on a daily basis (1 RCT, Jamigorn M, 2007; 66 women; absolute results were not reported). **Very low quality**

No significant differences were found between the groups in terms of the intensity of nausea and vomiting measured by the Rhodes rating scale after seven days of treatment (1 RCT; Jamigorn M, 2007; 66 women; absolute results were not reported)

A clinical trial tested the adverse effects of wristband acupressure at the P6 point and 50 mg of pyridoxine twice a day. This trial reported that both procedures were well tolerated and only one woman suffered irritation resulting from use of the wrist that forced her to abandon the treatment(1 RCT; Jamigorn M, 2007; 66 women; absolute results were not reported). No data on maternal mortality, admission rates, and hospital readmission were provided. **Very low quality**

Antihistamines (H1 antagonists)

Antihistamines versus placebo

Two SRs by Mazzotta P, 2000 and Jewell D, 2008 were identified. Both reviews have five RCTs in common. The antihistamines evaluated in the RCTs and identified by the reviews were buclizine, dimenhydrinate, hydroxyzine, and doxylamine meclicine.

The incidence of nausea was lower in the group of women treated with antihistamines compared with the placebo group (1 SR, Jewell D, 2008, 6 RCTs, OR 0.20, 95% CI 0.06 to 0.63). **Very low quality**

Treatment failure defined as the treatment that provides very mild or no benefit in reducing vomiting was lower in the group treated with antihistamines (1 SR; Mazzotta P, 2000, 7 RCTs, RR 0.34, 95% CI 0.27 to 0.43). **Very low quality**

No data on maternal mortality, admission rates, and hospital readmission were provided.

As a side effect, sleepiness was significantly more frequent in the group of women treated with dimenhydrinate 50 mg twice a day for one week compared to placebo. No significant differences were found between groups in the occurrence of heartburn 1 RCT, Pongrojpaw D (2007) 170 women; absolute scores were not reported. **Low quality**

Antihistamines versus ginger

Ginger or kion (Zingiber officinale) is a plant from the family of gingers, whose underground stem is a horizontal rhizome that has been proposed as a treatment for nausea associated with pregnancy.

One RCT by Pongrojpaw D (2007) comparing the effect of ginger versus dimenhydrinate for 7 days was identified.

No significant differences were observed on mean daily scores of nausea measured with the visual analogue scale between the group of women treated with ginger 0.5g twice a day and dimenhydrinate 50 mg twice a day for a week of treatment (1 RCT; Pongrojpaw D, 2007; 170 women, the absolute results were not reported). **Very low quality**

The average daily episodes of vomiting per day and two days of treatment was lower in the group treated with dimenhydrinate 50 mg twice a day versus the group treated with 0.5 g of ginger twice a day (1 RCT; Pongrojpaw D, 2007; 170 women; absolute results were not reported). **Very low quality**

However, no significant differences were detected between the study groups after 3 and 7 days of treatment (1 RCT; Pongrojpaw D, 2007; 170 women; absolute results were not reported).

No data on maternal mortality, admission rates, and hospital readmission were provided.

Antihistamines against phenothiazines

An SR by Jewell D (2008) with two RCTs and reviews focused on adverse effects by Mazzotta P (2000) were identified.

No significant differences were detected in the incidence of nausea among the group of women treated with phenothiazines and the group of women treated with placebo (1 SR, Jewell D, 2008; RR 0.28, 95% CI 0.06 to 1.29). **Very low quality**

No data on maternal mortality, admission rates, and hospital readmission were provided.

Ginger

Ginger versus placebo

An SR (Borrelli F, 2005) which did not include a meta-analysis was identified.

The intensity of nausea was higher in the group of women treated with placebo compared to the group of women treated with 125 mg of oral ginger capsules four times a day for four days (1 RCT, Willetts K, 2003; 120 women; the absolute results were not provided). **Low quality**

The proportion of women with vomiting after 4 and 6 days of treatment was significantly lower in the group receiving 250 mg of ginger four times a day compared to placebo RR (Borrelli F, 2005; 0.57 and 0.42; 70 and 26 women, 95% CI 0.34 to 0.95 and 0.18 to 0.98 respectively). **Low quality**

The number of retching during the first two days of treatment was significantly lower in the group of women treated with 125 mg of ginger four times a day for four days compared to the group of women treated with placebo (1 RCT, Willetts K, 2003; 120 women; the absolute results were not provided). **Low quality**

No significant differences were found in the number of vomiting episodes between the study groups of women treated with 125 mg of ginger four times a day for four days and the placebo group (1 RCT, Willetts K, 2003; 120 women; the absolute results were not provided). **Low quality**

The proportion of women with symptomatic improvement after seven days was significantly higher in the study group treated orally with 250 mg of ginger four times a day compared to placebo (1 RCT; Vutyavanich T, 2001; 70 women; RR 0.18, 95% CI 0.07 to 0.45). **Low quality**

No data on maternal mortality, admission rates, and hospital readmission were provided.

No significant differences were detected in the number of spontaneous abortions between the study groups treated orally with 250 mg of ginger four times a day and the group with placebo (1 RCT; Vutyavanich T, 2001; 70 women; the absolute results were not provided). **Low quality**

One RCT by Keating A (2002) identified no adverse effect associated with the treatment with ginger (26 women) and other RCT by Willetts K (2003) found that the most serious adverse effects were heartburn and reflux but no data were provided to enable comparisons between the groups.

Ginger versus pyridoxine (Vitamin B6)

An SR by Borrelli F (2005) and a subsequent RCT by Chittumma P (2007) comparing the effectiveness of ginger versus pyridoxine in the treatment of nausea and vomiting during pregnancy were identified. This review did not include a meta-analysis.

No significant differences were found in the average score on the intensity of nausea among the study group who took 500 mg of ginger for three days and a study group treated with 10 mg of pyridoxine three times a day for three days (1 RCT, Sripramote M (2003) 138 women, the absolute results were not provided). **Low quality**

No significant differences were found in the scores on the intensity of nausea relative to the start after 7, 14 and 21 days between a study group of women treated with 1.05 g of ginger on a daily basis and a study group treated orally with 75 mg of pyridoxine, both for three weeks (1 RCT, Smith C, 2004; 291 women; mean difference 0.2, 90% CI -0.3 to 0.8).

No significant differences were found in terms of the average score ofvomiting intensity in the group treated orally with 500 mg of ginger for three days and the study group treated with 10 mg of pyridoxine three times a day for three days(1 RCT; Sripramote M, 2003 15 / id; 138 women; the absolute results were not provided). **Low quality**

No significant differences were found in terms of the score on the intensity of vomiting and retching after 7, 14 and 21 days between the group treated with 1.05g of ginger on a daily basis and the group treated with 75 mg of pyridoxine on a daily basis, both for three weeks. (1 RCT by Smith C, 2004; mean difference 0.5 and 0.3; 90% CI 0 to 0.9 and 0 to 0.6, respectively). **Low quality**

No significant differences were found in the appearance of symptoms (including nausea and vomiting) between the study group treated daily with 1.05g of ginger and the group treated with 75 mg of pyridoxine, both for three weeks (1 RCT, Smith C, 2004; 291 women, the absolute results were not provided). **Low quality**

The difference between the perceptions of women in the general reduction of symptoms was not significant between the study group treated daily with 1.05 g of ginger and the group treated with 75 mg of pyridoxine, both for three weeks. (1 RCT, Smith C, 2004; 291 women; RR 0.97, 95% CI 0.77 to 1.21). **Low quality**

The mean scores on the intensity of nausea and vomiting measured by the Rhodes scale after four days of treatment were significantly lower in the group treated with 650 mg of ginger versus the group treated with 25 mg of pyridoxine three times a day (1 RCT; Chittumma P, 2007; 126 women; the absolute results were not provided). **Low quality**

No data on maternal mortality, admission rates, and hospital readmission were provided.

No significant differences were analysed regarding side effects such as retching, vomiting or postprandial heartburn, and no significant differences were found in terms of pregnancy outcomes between the study groups treated daily with 1.05 g of ginger and the study groups treated with 75 mg of pyridoxine, both for three weeks. However, significant differences were found regarding side effects like rashes in the group of women treated daily with 75 mg of pyridoxine compared to the group of women treated with 1.05 g of ginger on a daily basis, both for three weeks (1 RCT, Smith C, 2004; 291 women, the absolute results were not provided). **Low quality**

No significant differences were found in terms of drowsiness and dyspepsia between the study groups treated with 500 mg of oral ginger and the study group treated with 10 mg of pyridoxine, both for three days (1 RCT)

Pyridoxine

Pyridoxine versus placebo

Two SRs were identified: Jewell D (2008), Mazzotta P, (2000) which included two RCTs.

The scores on the intensity of nausea were lower in the group treated with pyridoxine compared to the group treated with placebo (1 SR; Mazzotta P, 2000, with two RCTs, 395 women; weighted mean difference -0.99, 95% CI -1.47 to -0.51). **Low quality**

The intensity of nausea according to the VAS scale was lower in the group treated with pyridoxine versus the group treated with placebo or untreated (1 SR, Jewell D, 2008, with two RCTs, 392 women; weighted mean difference 0.99 cm, 95% CI 0.51 cm to 1.47 cm). **Low quality**

No significant differences were found in the incidence of vomiting between the study group treated with pyridoxine and the study group untreated or treated with placebo. (1 SR, Jewell D, 2008, with two RCTs, RR 0.76, 95% CI 0.36 to 1.66). **Low quality**

No significant differences were found with regard to treatment failure between the group treated with pyridoxine and the group treated with placebo. Failure is defined as the failure in the resolution of symptoms or a significant improvement in clinical symptoms (1 SR; Mazzotta P, 2000, 3 RCTs, 949 women; RR 0.97, 95% CI 0.78 to 1.20). **Low quality**

No data on maternal mortality, admission rates, and hospital readmission were provided.

No significant differences were found in relation to side effects such as major foetal malformations among the study group treated with pyridoxine and the group treated with placebo (1 SR; Mazzotta P, 2000, 1369 women; RR 1.05, 95% CI 0.60 to 1.84). **Low quality**

Pyridoxine versus acupressure (see section 1.2)

Pyridoxine versus ginger (see section 3.2)

Acupuncture

Acupuncture versus placebo or no treatment

Two SRs by Jewell D (2008) and Helmreich RJ (2006) were identified. The first examined the effects of acupressure and acupuncture in the treatment of nausea or vomiting during early pregnancy, and identified two RCTs comparing acupuncture versus placebo or no treatment. The second SR examined the effects of acupressure, acupuncture, and electrical stimulation and identified two RCTs comparing acupuncture versus control for the treatment of nausea and vomiting in the early stages of pregnancy. Two RCTs were identified in both reviews by Smith C (2004) and Knight B (2001). The results are reported separately, since the first review combined the results of acupressure and acupuncture in the same analysis, and the second review included studies in women with hyperemesis gravidarum. However, both reviews provided information on similar results regarding the effects of acupuncture in women with nausea and vomiting in early pregnancy.

After a week of treatment, a greater improvement was identified in nausea for the group treated with traditional weekly acupuncture compared to the untreated group, both for four weeks (1 RCT, Smith C, 2004; 593 women; RR 0.93, 95% CI 0.88 to 0.99). **Low quality**

After two weeks of treatment, the improvement of nausea was significantly greater in the group treated with P6 acupuncture than in the untreated group, both treatments lasting for four weeks (1 RCT, Smith C, 2004; 593 women; the absolute results were not provided).

No significant differences were found in the proportion of women who reported nausea during pregnancy treated with multiple acupuncture and the group treated with placebo (1 RCT, Knight B, 2001, 55 women; the absolute results were not provided). **Low quality**

The appearance of dry heaves was significantly lower in the study group treated with P6 acupuncture weekly than in the group of women not treated with acupuncture, both treatments lasting for four weeks (1 RCT, Smith C, 2004; 593 women; the absolute results were not provided). **Low quality**

No data on maternal mortality, admission rates, and hospital readmission were provided.

No differences were found between the study groups treated with traditional acupuncture, P6 acupuncture, placebo and no treatment for four weeks in relation to adverse effects such as perinatal outcomes, congenital diseases, pregnancy complications or other neonatal outcomes (1 RCT, Smith C, 2004; 593 women; the absolute results were not provided). **Low quality**

Dietary interventions

No SRs or RCTs and no clinically important results from RCTs on the effects of dietary interventions other than the intake of ginger in the treatment of women with nausea and vomiting in the early stages of pregnancy were found.

Domperidone

No SRs or RCTs and no clinically important results from RCTs on the effects of domperidone in the treatment of women with nausea and vomiting in the early stages of pregnancy were found.

Metoclopramide

No SRs or RCTs and no clinically important results from RCTs on the effects of metoclopramide in the treatment of women with nausea and vomiting in the early stages of pregnancy were found.

Phenothiazines

Phenothiazines versus placebo

An SR (Jewell D, 2008) and a review focused on the adverse effects (Mazzotta P, 2000) were identified. The phenothiazines considered by the studies included in these reviews were mepyramine, promethazine and thiethylperazine.

No significant differences were found between the group of women treated with phenothiazines and the group treated with placebo in terms of the occurrence of nausea during pregnancy (1 SR, Jewell D, 2008, with two RCTs, 300 women; RR 0.28, 95% CI 0.06 to 1.29). **Very low quality**

No data on maternal mortality, admission rates, and hospital readmission were provided.

No significant differences in adverse effects and teratogenicity were found between the group of women treated with phenothiazines and the group of women treated with placebo (1 SR; Mazzotta P, 2000; 78,440 women; RR 1, 95% CI 0.8 to 118). **Very low quality**

The o ther review (Jewell D, 2008) gave no information on teratogenicity associated with phenothiazines. However, the adverse effects associated with different phenothiazines vary, making interpretation difficult on a synthesis analysis (1 SR; 161 women; the absolute results were not provided).

Phenothiazines versus antihistamines

A single RCT by Bsat FA (2003) was identified.

No significant differences were analysed in relation to the number of emetic episodes and the proportion of women who reported lack of improvement or worsening of symptoms after three days of treatment between the group of women treated with 25 mg of rectal prochlorperazine and the group treated orally with 25 mg of promethazine every 6 hours (1 RCT; Bsat FA, 2003; 174 women, the absolute results were not provided). **Low quality**

No data on maternal mortality, admission rates, and hospital readmission were provided.

Neonatal abnormalities as side effects were analysed in the group of women treated with 25 mg of rectal prochlorperazine every 12 hours when necessary and the group of women treated orally with 25 mg of promethazine every 6 hours when necessary. The neonatal abnormality detected in the group treated with prochlorperazine was a ventricular septal defect (1 RCT; Bsat FA, 2003; 174 women, the absolute results were not provided). **Low quality**

Summary of evidence

Acupressure	
Very low quality	Acupressure treatment significantly decreases the intensity of nausea symptoms and the duration of nausea and vomiting during early pregnancy. (Norheim AJ, 2001; Werntoft, 2001).
Very low quality	The adverse effects of acupressure treatment of nausea and vomiting during the initial stages of pregnancy are pain, stiffness and swelling of the hands (Helmreich RJ, 2006).
Very low quality	The treatment of nausea and vomiting during the initial stages of pregnancy with acupressure or pyridoxine shows no difference in relation to the intensity of nausea and vomiting. (Jamigorn M, 2007).

Antihistamines	
Low quality	Treatment with antihistamines significantly decreases the incidence of nausea during the early stages of pregnancy. (Jewell D, 2008)
Low quality	The failure of treatment with antihistamines is less than the treatment with placebo for nausea and vomiting during the early stages of pregnancy. (Mazzotta P, 2000).
Low quality	Drowsiness as adverse effect is significantly more frequent in the group treated with antihistamines (dimenhydrinate) versus the group treated with placebo. No significant differences were detected in relation to the occurrence of heartburn (Pongrojpaw D, 2007).
Low quality	The treatment of nausea and vomiting with antihistamines or phenothiazines shows no difference in relation to the incidence of nausea. (Jewell D, 2008).
Low quality	Treatment with antihistamine significantly reduces average daily episodes of vomiting per day after two days of treatment compared to treatment with ginger, showing no significant differences after 3 and 7 days of treatment. (Pongrojpaw D, 2007).
Ginger	
Low quality	Treatment with ginger produces a significant symptomatic improvement of nausea and vomiting during pregnancy after a week of treatment compared to treatment with placebo. (Vutyavanich T, 2001).
Low quality	Treatment with ginger significantly reduces the proportion of women who manifest vomiting after 4 and 6 days of treatment and the number of dry heaves during the first two days of treatment compared to treatment with placebo. No differences were found in relation to the number of emetic episodes. (Borrelli F, 2005; Willetts K, 2003).
Low quality	The most serious side effects derived from the treatment with ginger were heartburn and gastrointestinal reflux. Treatment with ginger showed no significant differences in side effects regarding the number of spontaneous abortions compared to the group with placebo (Vutyavanich T, 2001; Willetts K, 2003; Keating A, 2002).
Low quality	Treatment with ginger significantly reduces the intensity of nausea and vomiting (measured with the Rhodes scale) after four days of treatment compared to treatment with pyridoxine. (Chittumma P, 2007). No differences were found in the perception of women regarding the overall reduction of symptoms (Smith, 2004).
Low quality	Adverse events such as rashes after three weeks are significantly more frequent when using the treatment with pyridoxine compared to treatment with ginger. No differences were found concerning retching, postprandial vomiting, heartburn, drowsiness, or dyspepsia in that period (Smith C, 2004; Sripramote M, 2003).
Pyridoxine	
Low quality	Treatment with pyridoxine resulted in a significant decrease in the severity of nausea (measured by VAS) during gestation compared with the treatment with placebo. (Vutyavanich T, 2001).
Low quality	Adverse effects such as major foetal malformations resulting from the treatment with pyridoxine showed no significant difference compared to that of placebo. (Mazzotta P, 2000).

Low quality	The treatment of nausea and vomiting during the initial stages of pregnancy with pyridoxine or acupressure shows no difference in relation to the intensity of nausea and vomiting. (Jamigorn M, 2007).
Low quality	Treatment with ginger significantly reduces the intensity of nausea and vomiting (measured with the Rhodes scale) after four days of treatment compared to treatment with pyridoxine. (Chittumma P, 2007).
Acupuncture	
Low quality	Traditional acupuncture treatment produces a significant improvement in nausea (measured with VAS) during pregnancy compared to no treatment. (Smith C, 2004).
Low quality	Acupuncture treatment at P6 significantly reduces the appearance of dry heaves during pregnancy compared to no treatment. (Smith C, 2004).
Low quality	No differences were found between the treatment with traditional acupuncture, P6 acupuncture, or placebo for four weeks in relation to adverse effects such as perinatal outcomes, congenital diseases, pregnancy complications or other neonatal outcomes. (Smith C, 2004).
Phenothiazines	
Very low quality	Treatment with phenothiazines showed no significant differences in the occurrence of nausea during pregnancy compared with the treatment with placebo (Jewell D, 2008).
Very low quality	No differences were found between the treatment with phenothiazines and the treatment with the treatment with placebo in relation to the occurrence of adverse effects such as teratogenicity. (Mazzotta P, 2000).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality ofthe evidence. The quality of the evidence has decreased in most outcome variables evaluated for the treatment with acupressure, antihistamines, ginger, pyridoxine, acupuncture and phenothiazines due to limitations in the design of the studies (lack of randomisation) and / or imprecise results (partial or limited data about the results).
2. Balance between benefits and risks:
   a. Acupressure. Acupressure treatment has shown a clinical benefit for the treatment of nausea and vomiting during the early stages of pregnancy. The adverse effects of the use of this treatment are pain, stiffness, and swelling of the hands. However, the quality of the evidence supporting these benefits and risk is very low.
   b. Antihistamines. Treatment with antihistamines has shown a clinical benefit for the treatment of nausea during the early stages of pregnancy, although the use of this treatment has been associated with adverse effects such as drowsiness. The quality of the evidence supporting the benefits and risks of treatment with antihistamines is low.
   c. Ginger. Treatment with ginger has shown a clinical benefit for the treatment of nausea and vomiting during early stages of pregnancy after a week of treatment. The most serious side effects from the treatment with ginger are heartburn and

gastrointestinal reflux. The quality of the evidence supporting the benefits and risks of the treatment with ginger is low.

d. Pyridoxine. Treatment with pyridoxine has shown a clinical benefit for the treatment of nausea during the early stages of pregnancy, without having demonstrated a significantly greater number of adverse effects compared to placebo. However, the quality of the evidence supporting the benefits and risks of the treatment with pyridoxine is low.

e. Acupuncture. Traditional acupuncture treatment produces a significant improvement in nausea and retching during the early stages of pregnancy, without having demonstrated a significantly greater number of adverse effects compared to placebo. However, the quality of the evidence supporting the benefits and risks of the treatment with acupuncture is low.

f. Phenothiazines. Treatment with phenothiazines has shown no clinical benefits for the treatment of nausea during pregnancy nor a significantly greater number of adverse effects including teratogenicity compared to placebo. However, the quality of the evidence supporting the benefits and risks of the treatment with acupuncture is very low.

3. No studies examining the costs, use of resources or values and preferences of pregnant women were identified.

The following recommendations were formulated considering that pyridoxine is the only intervention that has shown benefits without showing side effects, unlike the rest, which have shown safety problems. Phenothiazines have not shown any benefit so a recommendation of this intervention is given as last therapeutic option. Although the studies analysed to answer this question included pregnant women treated with several active substances belonging to the group of antihistamines and phenothiazines, when making recommendations only those active ingredients sold in our country and which included this indication specified in the data sheet were considered. The low quality of the studies determined the strength of the recommendations.

Recommendations

Weak	We suggest administering of pyridoxine treatment for relief of nausea and vomiting during the early stages of pregnancy.
Weak	We suggest administering antihistamines (dimenhydrinate and meclizine), ginger and / or sessions of acupressure or acupuncture as therapeutic alternatives to pyridoxine for the relief of nausea and vomiting during the early stages of pregnancy.
Weak	We suggest using phenothiazines (thiethylperazine) as the last therapeutic option for the relief of nausea and vomiting during the early stages of pregnancy.

Managing heartburn

Antacids

Antacids versus placebo

A systematic review (Dowswell, 2008) published in 2008 that identified one RCT (Reisfield, 1971) evaluating the use of antacids for heartburn during pregnancy has been identified. The

RCT, which included 156 pregnant women with heartburn, compared magnesium hydroxide and aluminium hydroxide in combination with simethicone versus placebo. The assay method of randomisation was not clear.

An additional clinical trial with 50 women in which three interventions were compared during seven days has been identified (Kovacs, 1990):

- Magnesium hydroxide plus aluminium hydroxide plus oxethazaine (15 women).
- Magnesium hydroxide plus aluminium hydroxide without oxethazaine (17 women).
- Placebo (18 women).

The review (Dowswell, 2008) showed a higher proportion of women in the group of antacids (77/83, 93%) with a full or partial relief of heartburn compared to placebo (48/73, 66% RR: 1.41; 95% CI 1.18 to 1.68). **Low quality**

An RCT (Kovacs, 1990) showed that the antacid with or without anaesthetic was associated with a significant improvement in heartburn symptoms compared to placebo, although this improvement was at the edge of being significant (medium scale relief where heartburn symptoms 1 = mild to 5 = severe symptoms: 3.9 antacids with oxethazaine, 3.3 only with antacids and 2.9 with placebo; p = 0.05). **Low quality**

This same trial (Kovacs, 1990) showed that women treated with antacids required to a lesser extent the use of additional antacids than women in the placebo group (% of days in which participants used an antacid: 7% antacid with oxethazaine versus 13% only with antacid versus 29% with placebo; p = 0.0003). **Low quality**

The review by Dowswell, 2008 notes that there is limited information on the adverse effects associated with the preparations used. The trial included in the review (Reisfield, 1971) found that antacids were associated with a low rate of adverse effects (constipation, headache, cramps and dry mouth) compared with placebo (5/83 [6%] antacids versus 7/73 [10%] with placebo, significance not assessed). The other RCT evaluated (GT Kovacs, 1990) provided no information on adverse effects. **Low quality**

Antacids alone versus antacids with more acidity inhibitor drugs

A systematic review (Dowswell, 2008) published in 2008 that includes a trial with 30 women (Rayburn, 1999) which based antacids calcium antagonists plus ranitidine (H2 receptor antagonist) compared to antacid alone has been identified. After one week of treatment with antacids alone, women with four or more episodes of moderate to severe heartburn during the week (30 women) were randomised to continue with the treatment with antacids alone or with antacids plus ranitidine. The randomisationmethod was unclear.

The review found no significant difference between the antacid alone versus the antacid plus ranitidine in the intensity of the pain of heartburn after a week, although the score was lower in the group taking antacids plus ranitidine (mean difference in score (measured using the visual analog scale of 10 points, where 0 = no pain and 10 = incapacitating pain) -0.31, 95% CI -1.89 to +1.27). **Low quality**

The review found no significant difference between the antacid alone versus the antacid plus ranitidine in the intensity of the pain of heartburn after 2 weeks, although the score was lower in the group taking antacids plus ranitidine (mean difference in score (measured using the visual analogue scale of 10 points, where 0 = no pain and 10 = incapacitating pain) -2.13;. 95% CI -4.37 to +0.11). **Low quality**

The review showed that there is limited information on adverse effects associated with the preparations used. The trial identified by the review reported no adverse effects associated with ranitidine and that birth outcomes were favourable. No comparative data on adverse effects were collected. **Low quality**

A consensus document (Tytgat, 2003) recommends the use of H2 receptor antagonists such as ranitidine, combined with antacids in pregnant women if symptoms persist after the treatment with antacids alone. **Other clinical practice guidelines**

Acid inhibitor drugs

No systematic reviews or clinical trials comparing acidity inhibitor drugs versus placebo for heartburn in pregnant women have been identified.

A review combining acidity inhibitor drugs plus antacids versus antacids alone as discussed in the previous section, has been identified (Dowswell, 2008).

A meta-analysis (Gill, 2009) on the safety of histamine 2 receptor blockers (H2 receptor antagonists) was used. The data included congenital malformations, spontaneous abortions, premature birth and small for gestational age. The meta-analysis included four cohort studies, two prospective and two retrospective. The number of women included in the meta-analysis was of 2,398 women exposed and 119,892 unexposed. A random effects model was used to combine the results.

The meta-analysis (Gill, 2009) calculated an odds ratio of 1.14 for congenital malformations 95% CI 0.89, 1.45 for women exposed to H2 antagonists, based in 112/2398 (4.7%) women exposed and 5,699 / 119,892 (4.8%) for unexposed. **Low quality**

The odds ratio for preterm birth calculated from 2,421 women exposed and 119,072 unexposed was 1.17, 95% CI 0.94 to 1.47).

Based on 738 women exposed and 1,575 unexposed of two studies, the odds ratio for the incidence of spontaneous abortions exposed to H2 antagonists was 0.62 (95% CI 0.36 to 1.05).

The odds ratio for the incidence of small-for-gestational age calculated from 611 women exposed and 794 unexposed was 0.28 (95% CI 0.06 to 1.22).

Interventions aimed at modifying lifestyle (elevation of the head of the bed and changing dietary habits)

No systematic reviews, clinical trials, or cohort studies have been found on the elevation of the head of the bed, the reduction of caffeine or fat intake, the reduction in the size and frequency of meals for the treatment and prevention of heartburn in pregnant women.

Other clinical practice guidelines

A consensus document recommends that changes in lifestyle and diet should remain as the first line of treatment for heartburn in pregnant women (Tytgat GN, 2003). The measures include avoiding and reducing the intake of foods that cause reflux (such as fatty and spicy foods, tomatoes, products high in citric acid and carbonated beverages) and substances like caffeine. Avoiding non-steroidal anti-inflammatory drugs. The document also recommends other changes in lifestyles to reduce reflux and avoid lying down within three hours after eating. However, if heartburn is severe enough, medication should be taken after consulting a healthcare professional.

Summary of evidence

Antacids	
Low quality	Treatment with antacids relieved completely or partially heartburn in a higher percentage of women than placebo (Dowswell T, 2008).
Low quality	Antacids improve the symptoms of heartburn compared to placebo, although this improvement is not very significant (GT Kovacs, 1990).
Low quality	The use of antacids implies a less use of additional antacids versus placebo (GT Kovacs, 1990).
Low quality	Antacids were associated with a low rate of adverse effects (Dowswell T, 2008).
Low quality	There were no significant differences in the intensity of the pain of heartburn after a week between antacids and antacids plus ranitidine (Dowswell T, 2008).
Low quality	No significant differences were found between antacid alone versus antacid plus ranitidine in the intensity of pain of heartburn after two weeks (Dowswell T, 2008).
Low quality	No adverse effects associated with ranitidine were identified(Rayburn W, 1999).
Acid inhibitor drugs	
Low quality	There were no statistically significant differences in adverse events (birth defects, spontaneous abortions, premature births, and small size for gestational age) between women who took H2 receptor antagonists and those who did not.
Raising the head of the bed	
Very low quality	Changes in lifestyle and diet have been agreed as a treatment for heartburn in pregnant women.
Reducing caffeine intake	
Very low quality	Changes in lifestyle and diet have been agreed as a treatment for heartburn in pregnant women.
Reducing fat intake	

Very low quality	Changes in lifestyle and diet have been agreed as a treatment for heartburn in pregnant women.
Reducing the size and frequency of meals	
Very low quality	Changes in lifestyle and diet have been agreed as a treatment for heartburn in pregnant women.

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The quality of the evidence has decreased in most outcome variables evaluated for the treatment with antacids and acid inhibitor drugs due to limitations in the design of the study (lack of clarity in the method of randomisation) and / or imprecision of results (limited data or no statistical analysis between groups in one trial).
2. Balance between benefits and risks:
   a. Antacids. Treatment with antacids has shown a clinical benefit for the treatment of heartburn in pregnancy, without having demonstrated a significantly greater number of adverse effects compared to placebo. However, the quality of the evidence supporting the benefits and risks of the treatment with antacids is low, since the number of studies is low as well as their quality.
   b. Acid inhibitor drugs. The addition of acid inhibitor drugs to the antacids does not cause a significant improvement in the symptoms of pregnant women with heartburn. These drugs do not increase the risk of adverse effects. However, the quality of the evidence supporting the benefits and risks of the treatment with drugs that inhibit the acidity is low.
   c. Raising the head of the bed. Agreement was reached on the changes in lifestyle and diet as a treatment for heartburn in pregnant women, although the quality of the evidence supporting the benefits and risks of this treatment is very low.
   d. Reducing caffeine intake. Agreement was reached on the changes in lifestyle and diet as a treatment for heartburn in pregnant women, although the quality of the evidence supporting the benefits and risks of this treatment is very low.
   e. Reducing fat intake. Agreement was reached on the changes in lifestyle and diet as a treatment for heartburn in pregnant women, although the quality of evidence supporting the benefits and risks of this treatment is very low.
   f. Reducing the size and frequency of meals. Agreement was reached on the changes in lifestyle and diet as a treatment for heartburn in pregnant women, although the quality of evidence supporting the benefits and risks of this treatment is very low.
3. No studies examining the costs, use of resources or values and preferences of pregnant women were identified.

The following recommendations were formulated considering the balance between benefits and risks and the lack of studies comparing pharmacological interventions with modifications in the lifestyle of pregnant women.

Recommendations

√	Pregnant women with heartburn should be informed on changes in their lifestyle and their diet.
Weak	We suggest the use of antacids in pregnant women to relieve heartburn.
Weak	We suggest combining ranitidine (H2 receptor antagonist) with antacids if heartburn persists after a treatment with antacids alone.

Managing constipation

Increase fiber intake

Increase fiber intake versus no intervention

A Cochrane SR (Jewell, 2001) which assesses the increase of fiber intake in the treatment of constipation in pregnant women has been identified.

No further study on the update of the literature search has been identified (carried out in February 2012).

The SR (Jewell, 2001) included one RCT (Anderson, 1985) with 40 women in the third trimester of pregnancy divided into three groups comparing the ingestion of biscuit with cereal flakes ("corn-based biscuits") (10 g per day) or wheat bran (23 g per day) and a group of non-intervention (given the difficulty of obtaining a placebo similar to the interventions) for 2 weeks. The two treatment groups were analysedjointly as both correspond to the same type of intervention (natural fibers).

After two weeks of treatment a greater number of women assigned to the control group (10/13) did not show an increased frequency of defecation than in the intervention group (9/27), Peto OR 18 m; 95% CI 0.05 to 0.67 (Anderson, 1985). **Moderate quality**

No RCTs or SRs evaluating this comparison were found.

Increased fluid intake

No RCTs or SRs evaluating this comparison were found.

Use of osmotic laxatives

No RCTs or SRs evaluating this comparison were found.

Use of laxatives that increase the volume of faecal bolus

Use of laxatives that increase the volume of the faecal bolus versus placebo or no intervention

No RCTs or SRs evaluating this comparison were found.

Use of laxatives that increase the volume of the faecal bolus versus other treatments

No SRs or RCTs evaluating the use of laxatives that increase the volume of faecal bolus compared with the increase of fiber or liquid intake or the use of osmotic laxatives were found. Conversely, an SR (Jewell, 2001) that evaluates the comparison of intestinal motility with stimulant laxatives (see section Types of contraception during the postpartum period) was found.

Intestinal motility stimulant laxatives

Intestinal motility stimulant laxatives versus placebo or no intervention

No RCTs or SRs evaluating this comparison were found.

Intestinal motility stimulant laxatives versus other treatments

An SR (Jewell, 2001) evaluating the comparison with intestinal motility stimulant laxatives was found. No further study on the update of the literature search has been found (carried out in February 2012).

The SR by Jewell (2012) included one RCT (Greenhalf, 1973) comparing four oral treatment groups for constipation:

1. Senna 14 mg daily (Senokot).
2. Dioctyl sodium succinate 120 mg and 100 mg dihydroxyanthroquinone (Normax).
3. 10ml daily containing 60% of sterculia and 8% of frangula (standard Normacol).
4. 10ml daily containing 60% of sterculia (Normacol special)

Since groups 1 and 2 correspond to formulations of intestinal motility stimulant laxatives and groups 3 and 4 are formulations that share as mechanism of action an increase in faecal volume, the authors analysed together groups 1 and 2 on the one hand, and 3 and 4 on the other, comparing them.

Significant differences in favour of the laxative group forming faecal volume in relation to the effect on unresolved constipation were observed (140 women; Peto OR 0.30, 95% CI 0.14 to 0.61) (Greenhalf, 1973). **Moderate quality**

There were no significant differences between the groups regarding the acceptability of women in the use of laxatives (140 women; Peto OR 0.89, 95% CI 0.46 to 1.73) (Greenhalf, 1973). **Moderate quality**

Regarding adverse effects, if considered globally, the group of intestinal motility stimulant laxatives presented significantly more adverse effects (56/210) than the group of bulk-forming laxatives (32/210) (Peto OR 95% 2 08 [1.27, 3.41]). **Moderate quality**

Individual evaluation showed that abdominal pain is significantly more frequent in the group of motility stimulant laxatives than in the bulk-forming laxatives group (140 women; Peto OR 2.91 95% CI [1.39, 6 , 11]).

Diarrhoea was significantly more frequent in the group of motility stimulant laxatives than in the bulk-forming laxatives group (140 women; 95% Peto OR 2.90 [1.22, 6.91] IC).

Nausea showed no significant difference between groups (140 women; Peto OR 0.47 95% CI [0.13, 1.64]).

Summary of evidence

Increased fiber intake	
Moderate quality	Treatment with fiber supplement in the diet significantly increases stool frequency compared to no supplementation (Anderson, 1985). Potential adverse effects of supplementation with fibers were not assessed.

Administration of laxatives	
Moderate quality	Treatment with intestinal motility stimulant laxatives significantly increases the frequency of defecation compared to the faecal bulk-forming laxatives group (Anderson, 1985).
Moderate quality	In relation to the overall adverse effects, the group of women treated with intestinal motility stimulant laxatives showed a higher frequency of these. By analysing the type of adverse effect, it was found that the abdominal pain and diarrhoea were significantly more frequent in the group treated with intestinal motility stimulant laxatives than in the group treated with laxatives that increase faecal volume but no significant differences were observed between groups for nausea (Anderson, 1985).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The quality of the evidence has decreased in most outcome variables assessed due to limitations in the design of the studies (lack of placebos and incomplete data).
2. Balance between benefits and risks.
   a. A clinical benefit was observed when treating pregnant women with natural fiber supplement. Although the evidence available is still limited regarding the most appropriate type of supplement and there is no evidence regarding potential adverse effects, therefore this therapy is unlikely to generate significant damage.
   b. Administration of laxatives. The evidence so far comes from a single trial with moderate sample sizes and few outcome variables of interest (for example, it does not include outcome variables related to pregnancy such as presence of contractions or preterm labour). According to this evidence,bowel motility stimulant laxatives generate a higher proportion of women who solve their constipation problem compared to laxatives that increase faecal bolus volume though the latter have fewer adverse effects. It seems reasonable to prioritize the use of bulk-forming laxatives than motility stimulants given the lower frequency of adverse events, especially abdominal pain.
3. No studies examining the costs, use of resources or values and preferences of women were identified.

The following favourable recommendations were made considering that the effectiveness of the interventions in response to the treatment and the absence of unwanted effects contribute to the direction of the recommendation. Moreover, the existence of a limited number of studies, with a small number of patients and a moderate quality has determined the strength of the recommendation.

Recommendations

Weak	For pregnant women suffering from constipation we suggest increasing the intake of foods high in fiber to foster stool frequency.
Weak	Pregnant women suffering from constipation may consider the use of laxatives that increase faecal bolus volume as first-line laxatives intensify intestinal motility.

Managing varicose veins

Surgery

This therapeutic alternative is not addressed because it is usually postponed until after delivery.

Pharmacological treatment

Use of venous sclerotherapy versus placebo

No RCT evaluating the treatment with sclerotherapy drugs in varicose veins versus placebo in the symptomatic treatment of varicose veins during pregnancy has been identified.

Use of veno-active drugs (phlebotonics) versus placebo

An SR (Bamigboye, 2007) evaluating venoactive drugs in the symptomatic treatment of varicose veins in pregnant women has been identified.

No further study on the update of the literature search (conducted from September 2009 to February 2012) has been identified.

Phlebotonics are drugs, which enhance the venous tone (rutosides [troxerutine], hidrosmin, diosmin, calcium dobesilate, cromocarba, centella asiatica, disodium flavodate, grape seed extract, French maritime pine bark extract, and aminaftone) by different mechanisms.

The SR by Bamigboye (2007) included one single RCT (Bergstein, 1975) comparing O-Beta-hydroxyl ethyl rutoside (300 mg orally 3 times a day for 8 weeks) versus placebo in 69 pregnant women at 28 weeks of gestational age with visible varicose veins in the legs or the vulva and with symptoms.

The symptoms associated with varicose veins (night cramps, fatigue and paraesthesia) decreased significantly in the treatment group compared to the control group (69 women RR 1.89, 95% CI 1.11 to 3.22) (Bergstein, 1975).	**Moderate quality**
The presence of deep vein thrombosis showed no significant difference in the intervention group compared to the control group (69 women; RR 0.17, 95% CI 0.01 to 3.49) (Bergstein, 1975).	**Moderate quality**
Regarding adverse events, the RCT observed no significant increase in the treatment group compared to the placebo group (69 women, RR 0.86, 95% CI 0.13, 5.79) (Bergstein, 1975).	**Moderate quality**

Use of veno-active drugs (phlebotonics) versus the use of sclerosant drugs

No RCT evaluating the treatment with sclerosant drugs for varicose veins versus the use of phlebotonic drugs in the symptomatic treatment of varicose veins during pregnancy has been identified.

Non-pharmacological treatment

Use of elastic stockings or compression stockings versus placebo or no treatment

An SR (Bamigboye, 2007) evaluating the use of an external compression stocking in the symptomatic treatment of varicose veins in pregnant women has been identified. No further study on the update of the literature search (conducted from September 2009 to February 2012) has been found.

The SR by Bamigboye (2007) included one RCT (Jacobs, 1986) comparing compressive pneumatic stockings but the target population excluded pregnant women with varicose veins. There is another RCT evaluating external lower limbs compression stockings but in pregnant women without varicose veins (whose target is prevention not treatment) (Thaler, 2001).

The clinical practice guideline by NICE (NICE, 2008) identified a clinical trial on the effectiveness of compression stockings (class I or II) in preventing symptomatic varicose veins versus non-wearing compression stockings in 42 pregnant women with less than 12 weeks of gestation (Thaler, 2001). Although the compression stockings did not prevent the appearance of varicose veins (women not using stockings: 7/14 versus 5/12 class I stockings versus class II stockings 8/14; Fisher test = 0.94), a higher percentage of women using the stockings reported that their symptoms had improved (women using stockings 7/27 versus women who did not use them 0/15; RR 8.04, 95% CI 0.49 to 132.21).

Rest versus no rest

No RCT evaluating the treatment with rest versus no rest in the symptomatic treatment of varicose veins during pregnancy has been identified.

Use of reflexology techniques versus not using them or placebo

An SR (Bamigboye, 2007) evaluating the use of reflexology in the symptomatic treatment of varicose veins or oedema in pregnant women has been identified.

This review includes an RCT (Mollar T, 2003) evaluating two reflexology techniques versus no rest for the treatment of lower limb oedema but the inclusion criteria of the study did not establish that women are carriers of varicose veins and therefore stay outside the scope of this Guide.

Comparisons between different techniques of non-pharmacological treatment

No RCT evaluating the comparison between different non-pharmacological techniques for the treatment of varicose veins during pregnancy has been identified.

Summary of evidence

Moderate quality	Treating the symptoms caused by the presence of varicose veins in pregnant women decreases significantly with the use of rutoside after 8 weeks of treatment (Bergstein, 1975).
Moderate quality	No significant differences were observed in the presence of adverse effects or in the presence of deep venous thrombosis using this treatment as compared to placebo (Bergstein, 1975).

From evidence to recommendation

The strength and direction of the recommendation were established considering the following aspects:

1. Quality of the evidence. The quality of the evidence has decreased in most of the outcome variables assessed due to the design of the studies and / or imprecision of the results (few events or wide confidence intervals).
2. Balance between benefits and risks. A clinical benefit has been observed in the treatment of varicose veins with rutoside in pregnant women. There is still limited

evidence regarding the frequency of adverse events and complications given the small size of the sample and the low number of events in the only RCT included in the SR.

3. No studies examining the costs, use of resources or values and preferences of pregnant women were identified.

The following recommendation was made in favour of the intervention considering the favourable relative risk of the treatment in relation to the alleviation of symptoms, the low quality, and the small size of the sample of the single study found. On the other hand, the recommendation on the use of compression stockings has been taken from the clinical practice guideline by NICE.

Recommendations

Weak	We suggest providing information to women about that varicose veins are common during pregnancy, and that the use of compression stockings can help improve the symptoms, but does not ensure prevention.
Weak	We suggest administering rutoside (troxerutine) orally to those pregnant women with venous insufficiency to relieve their symptoms.

Managing haemorrhoids

Interventions for preventing haemorrhoids during pregnancy

Interventions for preventing haemorrhoids during pregnancy mainly include the treatment of constipation. See chapter "Interventions for the prevention and treatment of constipation during pregnancy."

Interventions for treating haemorrhoids during pregnancy

Rutosides for haemorrhoids during pregnancy

Rutosides versus placebo

An SR from the Cochrane Library (Quijano, 2005) assessing the risks, benefits and side effects of medical (non-surgical) conservative management of haemorrhoids in pregnant women and during the puerperium has been identified. No further study on the update of the literature search (carried out in February 2012) has been found.

The SR by Quijano (2005) included two RCTs (Wijayanegara, Titapant 1992 and 2001) with 150 pregnant women (between 14 and 33 weeks of gestational age) with haemorrhoids grades 1 to 3 (although Titapant (2001) excluded women with haemorrhoids grades 3 and 4). Both trials used as intervention oral hydroxyethylrutosides (troxerutine) in doses of 500 mg twice a day (Wijayanegara, 1992) and 600 mg a day (Titapant, 2001) for 4 weeks. The treatment was compared to placebo in both studies.

The combined analysis of the results of both studies in the placebo group showed a higher proportion of women who did not respond to the treatment (50/75) compared to the group of women treated with hydroxyethylrutosides (3/75) (150 women, Peto RR 0.07, 95% CI 0.03 to 0.20). **Moderate quality**

There were no statistically significant differences in relation to the adverse effects between the intervention group (4/75) and the control group (0/75) (150 women, Peto RR 4.99, 95% CI 0.60 to 41.49]) . **Low quality**

Both groups showed no significant differences in relation to foetal and perinatal deaths (intervention group (0/75) versus placebo (1/75) (150 women, Peto RR 0.34, 95% CI 0.01 to 8.15)). **Low quality**

Only one of the trials included in the review assessed the frequency of preterm birth and found no significant differences between the intervention group (1/48) and the control group (97 women, Peto RR 1.02, 95% CI 0.07 to 15.86) (Wijayanegara 1992) **Low quality**

There were no statistically significant differences in relation to the presence of congenital malformations among the intervention group (1/75) compared to the control group (0/75). The only woman who filed a malformation was included in the study at 33 weeks of gestational age (150 women, Peto RR 3.06, 95% CI 0.13 to 73.34]) (Quijano, 2005). **Low quality**

Rutosides versus other interventions

No RCTs or SRs evaluating this comparison were found.

Topical anaesthetics for the treatment of symptomatic or complicated haemorrhoids during pregnancy.

Topical anaesthetics versus placebo

No RCTs or SRs evaluating this comparison were found.

Topical anaesthetics versus other interventions

No RCTs or SRs evaluating this comparison were found.

Compounds with topical anaesthetics and corticosteroids for the treatment of symptomatic or complicated haemorrhoids during pregnancy.

Topical anaesthetics and corticosteroid compounds versus placebo

No RCTs or SRs evaluating this comparison were found.

Topical anaesthetics and corticosteroid compounds versus other interventions

No RCTs or SRs evaluating this comparison were found.

Compounds with corticosteroids for the treatment of symptomatic or complicated haemorrhoids during pregnancy.

Topical corticosteroid compounds versus placebo

No RCTs or SRs evaluating this comparison were found.

Topical corticosteroid compounds versus other interventions

No RCTs or SRs evaluating this comparison were found.

Sitz baths for the treatment of symptomatic or complicated haemorrhoids during pregnancy

Sitz baths for the treatment of symptomatic or complicated haemorrhoids versus placebo

No RCTs or SRs evaluating this comparison were found.

Sitz baths for the treatment of symptomatic or complicated haemorrhoids versus other interventions

No RCTs or SRs evaluating this comparison were found.

Summary of evidence

Moderate quality	The treatment of symptomatic haemorrhoids during pregnancy with rutosides significantly increases the improvement of symptoms after four weeks (Quijano, 2005).
Low quality	The treatment of symptomatic haemorrhoids during pregnancy with rutosides does not generate statistically significant differences in the frequency of adverse effects, foetal or perinatal deaths, preterm births or birth malformations when compared with placebo (Quijano, 2005).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The quality of the evidence has decreased in most outcome variables assessed for rutosides due to limitations in the risk of bias and the imprecision of results (few events or wide confidence intervals).
2. Balance between benefits and risks. Regarding rutosides, a clinical benefit has been observed with the treatment while the frequency of adverse events and possible damage showed no significant difference with the group with placebo. There is no evidence on the efficacy and safety of other therapeutic alternatives for the treatment of this disease during pregnancy.
3. No studies examining the costs, use of resources or values and preferences of the pregnant women were identified.

The following recommendation was made in favour regarding the effectiveness of the drug in response to the treatment and the absence of unwanted effects. The moderate and low quality of the available evidence has determined the strength of the recommendation.

Recommendation

Weak	We suggest the use of rutosides (troxerutine) orally for the treatment of symptomatic haemorrhoids grade 1 and 2 in pregnant women.

Managing low back pain

Preventive interventions for back pain in pregnant women

No RCTs or SRs evaluating preventive interventions for low back pain in pregnant women were identified.

Exercise added to usual prenatal care for the treatment of low back pain in pregnant women

(Non-aquatic) exercises versus no further treatment to prenatal care.

An SR (Pennick, 2008) which evaluates the non-aquatic exercise added to standard prenatal care for the treatment of low back pain during pregnancy has been identified.

No further study on the update of the literature search (carried out in February 2012) has been identified.

The SR by Pennick (2008) included two studies (235 participants) examining the effects of non-aquatic exercise in the treatment of low back pain during pregnancy (Suputtitada, 2002; Garshasbi, 2005). The interventions carried out in the studies were:

- Exercise while sitting with pelvic tilt (maintaining the position for 5 seconds and then relax for 5 seconds), 4 cycles of exercises every morning and evening; increase of 2 cycles per session from 2 to 4 weeks, up to 10 cycles per session, and then continue at this level for the next 4 weeks. The exercises should be done twice a day, five days a week for a total of 8 weeks. (Suputtitada, 2002).
- 15 moves in 60 minutes are to be performed: five minutes of slow walking, 5 minutes of extension movements, 10 minutes of general warm-up exercises, up to 15 minutes of anaerobic exercise, 20 minutes of specific exercise, after 5 minutes return to the initial position. Exercises are to be performed 3 times a week - under the supervision of a midwife - exercise intensity controlled by the frequency of maternal pulse - stopped, if the heart rate is higher than 140 / minute (Garshasbi, 2005).

Regarding the improvement of LBP one of the RCTs showed that the intensity of low back pain was significantly reduced in the group of women who exercised (measured with the Kebek questionnaire, range 0-100; 0 = no pain: $p = 0.006$), but no suitable numerical data supporting this statistic significance were provided(Garshasbi, 2005). The other RCT also showed greater relief of pain measured with a visual analog scale (VAS) (0-10, 0 = no pain) after eight weeks of exercise (standardised mean difference -5.34; 95% CI: -6.40 to -4.27) (Suputtitada, 2002).

One study evaluated the effect of stretching exercises in women with lumbar and pelvic pain, showing the results jointly (Martins, 2005). The study reported an **absence of pain** (measured by a visual analogue scale) in a significantly higher proportion in the group that exercised compared with the control group (69 women, RR 5.45, 95% CI 2.08, 14.30) .

The three RCTs evaluated **adverse effects** associated with exercise, but none of them reported events (Suputtitada, 2002; Garshasbi, 2005, Martins, 2005).

Aquatic exercise versus no further treatment to prenatal care

Two SRs (Pennick, 2008; Waller, 2009) evaluating aquatic exercise added to standard prenatal care for the treatment of low back pain during pregnancy have been identified.

No further study on the update of the literature search (carried out in February 2012) has been identified.

The SR by Pennick (2008) included a study (258 participants) analysing the effects of water gymnastics in the treatment of low back pain during pregnancy (Kihlstrand, 1999). The intervention carried out in the study was:

- 20 1-hour lessons per week of water gymnastics (adapted to pregnant women) and relaxa-

tion in the water (at 32-34 degrees). The first 10 sessions include exercises suitable for early pregnancy, and the last 10 sessions include suitable exercises for later pregnancy. The sessions lasted one hour divided into 30 minutes of exercise and 30 minutes of relaxation. The control group received only standard prenatal care. The women included were less than 19 weeks gestational age.

The SR by Waller (2009) included two studies (648 women) who analysed the effect of water gymnastics for pregnant women with back pain (Granath, 2006; Kihlstrand, 1999). The interventions carried out had already been analysed for the study by Kihlstrand; the study by Granath conducted comparisons between aquatic exercise and exercise on the floor.

With regard to pain relief, in an RCT (Kihlstrand, 1999) women who were in a water aerobics program reported significantly less intense pain one week after delivery, measured with a VAS (0-10; 0 = no pain) ($p = 0.034$).

In relation to absenteeism because of back pain in one RCT (Kihlstrand, 1999) 12.9% of women in the water gymnastics program (total of 982 days) and 21.7% of women in the group undergoing regular prenatal care (total of 1484 days) requested sick leave due to low back pain at some time during their pregnancy which shows a decrease in absenteeism, which was not significantly lower in the treatment group ($p = 0.09$).

No adverse effects related to the intervention (there were no differences in infections, maternal weight gain, gestational age at delivery, weight / height of the newborn or characteristics of delivery) were described.

Aquatic exercises versus additional non-water exercises to prenatal care

The SR by Waller (2009) included two studies (648 women) which analysed the effect of water gymnastics for pregnant women with back pain (Granath, 2006; Kihlstrand, 1999). The interventions carried out had already been analysed for the study by Kihlstrand and the study by Granath performed the following intervention:

– 45-minute sessions of active water gymnastics every week including strength training, flexibility and workout with 5 minutes of relaxation. The control group received gymnastic exercises on the floor of similar characteristics. The women who took part began these gymnastic exercises after 18 weeks of gestational age.

With regard to pain relief, in this RCT the women who took part in the water gymnastics program showed significantly less intense pain in the gymnastics program on the floor ($p = 0.04$), although details were not provided regarding the scale used to measure pain.

In relation to absenteeism because of back pain, no woman from the water gymnastics group required a sick leave permission due to back pain ($P = 0.03$).

No data on adverse effects related to the intervention were described.

Use of assistive devices for treating back pain during pregnancy

Two SRs (Pennick, 2008; Ho, 2008) evaluating the use of external devices for the treatment of low back pain during pregnancy have been identified.

No further study on the update of the literature search (carried out in February 2012) has been identified.

The RCTs included in the Cochrane SR (Pennick, 2008) compared the following treatment:

– The effectiveness of a pillow especially designed to support the abdomen of the pregnant woman (Ozzlo pillow) compared to a standard hospital pillow (Tontine pillow) in a crossover study design (crossover) where the order in the use of the pillow was randomised. The pillow was carried home and used for one week and then changed to the use of another type of pillow (Thomas, 1989). The study included 92 women who completed the two-week intervention.

The systematic review by Ho (2008) contained only three controlled studies including a group that received the use of lumbar support belts for pregnant women as intervention. The remaining studies included the belts in the two sections of the study (one study (Haughland, 2006) used lumbar support belts in a single section but only evaluated pelvic pain and not back pain, and therefore it was not taken into account). The interventions carried out were:

– Individualised physiotherapy, training, exercise and the use of a non-elastic support belt for women with posterior pelvic pain in women with pregnancies between 11 and 36 weeks of gestational (Noren, 1997).

– Use of a back support device (Carr, 2003).

Neither of these two studies (Noren, 1997; Carr, 2003) were randomised so their results for the realization of recommendations were not taken into consideration. The other randomised studies included in the review contained the use of back support belts in both sections within the study which made them unsuitable for the evaluation of these devices.

The impression described by women in relation to the prevention or improvement of low back pain using different pillows showed a benefit in favor of the Ozzlo pillow (92 women RR 1.84, 95% CI 1.32 to 2.55).

A statistically significant increase was also found in the use of the Ozzlo pillow in relation to the proportion of women who reported an improvement of insomnia (92 women, RR 1.62, 95% CI 1.23 to 2.13).

No adverse effects were reported with the use of either pillows.

Use of acupuncture for the treatment of back pain during pregnancy

Use of acupuncture for the treatment of back pain compared to standard treatment

Two SRs, one of them a Cochrane SR (Pennick, 2008; Ee, 2008) have been identified. Both reviews include the same RCTs (Elden, 2005; Kvorning, Wedenberg 2004 and 2000).

No further study on the update of the literature search (carried out in February 2012) has been identified.

The systematic review by Pennick (2008) included 318 pregnant women for this comparison (Elden, 2005 (n = 218), Kvorning, 2004 (n = 100)) in the third trimester of pregnancy. The following interventions were compared:

– Acupuncture treatment given by experienced acupuncturists twice a week for 6 weeks applied in 10 acupuncture points on sensitive areas and 7 points in overtime segmental areas (the needles are inserted to evoke De Qi and are left in place for 30 minutes stimulating that point every 10 minutes) (experimental group 1). The control group received regular care. The two groups also received general information about the disease and anatomy of the back and pelvis, tips on activities to do in daily life, were given a pelvic belt bra and a home exercise program conducted by a physiotherapist (Elden, 2005).

– Acupuncture treatment according to instructions following a protocol and periosteal stimulation. It began by stimulation of the LR3 and GV20 points and the local tendon points adding BL60, SI3 Y 1 of the lumbar and sacral bladder points (BL22-26) if necessary. De Qi stimulation was sought with needlespricked by increasing periods of time. The women received acupuncture twice a week in the first two weeks and then once weekly (no information on the total duration of treatment was given). The control group received no treatment (Kvorning, 2004).

The studies included showed considerable heterogeneity in the interventions and in the results measured as well as in the information provided by them, so it was not possible to perform a meta-analysis.

In relation to pain, the study by Elden showed that after the intervention, the group of women who received standard treatment (prenatal control only) reported greater pain when waking up in the morning and in the afternoon than the group receiving acupuncture, measured through the self-report with a visual analogue scale (222 women, in the morning a difference of medians reported was: 12; 95% CI 5.9 to 17.3, p <0.001 in the afternoon, the difference of medians reported was: 27; IC 95% from 13.3 to 29.5; p <0.001).

Kvorning showed that 60% of women in the group receiving acupuncture treatment had presented a complete reduction of pain intensity compared with 14% in the control group. It must be also highlighted that the control group received a large proportion of co-interventions that helped ease the pain: analgesic (5/35), physiotherapy (6/35) and sacro iliac support belts (15/35). In the group that received acupuncture only 4 women used sacro iliac support belts.

The studies included reported adverse effects. Elden et al reported no adverse effects in any of the three groups. Kvorning et al reported adverse effects in 38% of women in the acupuncture group (local pain and bruising, changes in heart rate and sweating, fatigue and nausea). In all cases the effects observed were minor. There were no effects on newborns or infants.

Using acupuncture for the treatment of low back pain compared to other treatments

Two SRs, one of them a Cochrane SR (Pennick, 2008; Ee, 2008) have been identified. Both revisions include the same three RCTs (Elden, 2005; Kvorning, Wedenberg 2004 and 2000).

No further study on the update of the literature search (carried out in February 2012) has been identified.

The systematic review by Pennick et al. included 316 pregnant women (Elden, 2005; n = 256, Wedenberg, 2000; n = 60 women before 32 weeks of gestational age), in which the following interventions were compared:

– Acupuncture treatment given by experienced acupuncturist physicians twice a week for 6 weeks given in 10 acupuncture points on sensitive areas and 7 points more in extra segmental areas (the needles are inserted to evoke De Qi and were left on the site for 30 minutes stimulating every 10 minutes) (experimental group 1). This treatment was compared to the performance of individual stabilization exercises modified for gestation during 6 hours for 6 weeks by two experienced physiotherapists (experimental group 2) (Elden 2005).

Acupuncture treatment three times a week for 2 weeks and then twice a week for two weeks (a total 10 30-minute sessions). Between 2 and 10 needles were used starting by the points of the fossa triangularis in the ear adding body or local points according to need; the needles were rotated gently 15 minutes after insertion until De Qi was reached. The other group received physiotherapy once

or twice a week for 6 to 8 weeks (10 50-minute sessions of group physiotherapy). Individualised treatments based on assessment together with the use of trochanteric belts for pelvic support, warm-up, massage and soft tissue mobilization if necessary were performed (Wedenberg, 2000).

In relation to pain, the studyby Elden showed a reduction in pain in the morning and in both groups without significant differences between them. It also described a significant difference in favour of the group treated with acupuncture regarding the reduction in pain intensity in the afternoon compared to the treatment with physiotherapy (difference of medians: -14; 95% CI -18 to -3 3; p = 0.0130).

The study by Wedenberg showed that both the women from the acupuncture group as those of the physiotherapy group reported less pain in the morning and evening, but the acupuncture group reported significantly less intense pain (P = 0.02 in the morning; P <0 01 in the afternoon).

In the group receiving physiotherapy, 12 women of the 30 included, did not complete the study, while in the group receiving acupuncture, none quitted. Therefore, caution needs to be taken when interpreting the results.

Regarding adverse effects, Elden did not describe any and Wedenberg showed small bruises at the puncture site in 2 women (7%) included in the acupuncture group.

Massage and physiotherapy for the treatment of low back pain during pregnancy

Massage and physiotherapy for the treatment of low back pain versus no treatment

A Cochrane SR (Pennick, 2008) has been identified. No further study on the update of the literature search (carried out in February 2012) has been identified.

The systematic review by Pennick et al. included 261 pregnant women for this comparison (Eden, 2005). The Eden study randomised three groups in which one received acupuncture, another physical therapy and another standard treatment. For this comparison, the relevant results are those from the last two groups.

The following interventions were compared:

- The treatment group performed individual stabilization exercises for gestation modified for 6 hours during 6 weeks by two experienced physiotherapists (experimental group 2).
- The control group received regular care. The two groups also received general information about the disease and anatomy of the back and pelvis, tips on activities to do in daily life, were given a pelvic support belt and home exercise program conducted by a physiotherapist (Elden, 2005).

In relation to pain, the study by Elden showed that after the intervention, the group of women who received standard treatment (prenatal control only) reported greater pain when waking up in the morning and in the afternoon than the group receiving physiotherapy measured through the self-report using a visual analogue scale of 100 (220 women, in the morning a difference of medians reportedwas: 9; 95% CI 1.7 to 12.8; P = 0.0312); in the afternoon a difference of medians observedwas: 13; 95% CI 2.7 to 17.5; P = 0.0245).

No adverse effects were reported.

Massage and physiotherapy for the treatment of low back pain compared to other treatment

The systematic review by Pennick et al. included 316 pregnant women for this comparison (Elden,

2005; n = 256; Wedenberg, 2000; n = 60 women before 32 weeks of gestation). The results of this comparison are described in Section 4.2.

Physical exercise for low back pain during pregnancy	
Moderate quality	The treatment of back pain with non-aquatic exercises shows a decline and disappearance of pain significantly lower in the group under treatment than in the group receiving standard treatment. No significant adverse effects were reported in those exercises within the studies included (Suputtitada, 2002; Garshasbi, 2005; Martins, 2005).
Moderate quality	The treatment of back pain with aquatic exercises shows a decrease in pain in the group under treatment compared to the group receiveing standard prenatal care (Kihlstrand, 1999).
Moderate quality	The treatment of back pain with aquatic exercises shows no difference regarding absenteeism or adverse effects in the group under treatment compared to the group receiving standard prenatal care (Kihlstrand, 1999).
Moderate quality	The treatment of back pain with aquatic exercises compared to floor exercises, has not shown a decrease in back pain and work absenteeism compared to non-aquatic exercises, showing no adverse effect (Granath, 2006).
Use of devices for low back pain during pregnancy	
Moderate quality	Using the Ozzlo pillow for the treatment of low back pain during pregnancy showed a significant improvement regading pain and insomnia when compared with the standard pillow (Thomas, 1989). No adverse event was recorded using either pillows (Thomas, 1989).
Use of acupuncture for back pain during pregnancy	
Moderate quality	The treatment with accupuncture compared to the standard treatment showed a significant improvement of LBP (Elden, 2005; Kvorning, 2004). Mild adverse events were observed with the use of acupuncture compared to the standard treatment (Elden 2005; Kvorning, 2004).
Low quality	The treatment with accupuncture compared to the treatment with physiotherapy shows a reduction in pain (Elden, 2005) and intensity (Wedenberg, 2000). Mild adverse events were observed with the use of acupuncture compared to the standard treatment (Elden, 2005; Wedenberg, 2000).
Massage and physiotherapy for the treatment of low back pain	
Moderate quality	The treatment with physiotherapy compared to the standard treatment showed significant improvement of back pain without significant adverse effects (Elden, 2005).

From evidence to recommendation

The strength and direction of the recommendation were established considering the following aspects:

1. Quality of the evidence. The quality of the evidence has decreased in most outcome variables assessed for exercise, use of devices, acupuncture and physiotherapy due to the risk of bias and / or imprecision of the results (few events or wide confidence intervals).
2. Balance between benefits and risks.

g. Exercise. A clinical benefit has been observed with the treatment of both aquatic and non-aquatic exercises with greater benefit of the aquatic ones with no adverse effects.

h. Device. The evidence so far comes from a single trial with a small sample and few outcome variables of interest. Under these conditions the evidence shows a benefit of using the Ozzlo pillow without identifiable adverse effects.

i. Acupuncture. There is limited moderate quality evidence showing any benefit on the efficacy and safety of the treatment with acupuncture for low back pain during pregnancy.

j. Physiotherapy. There is limited moderate quality evidence showing any benefit on the efficacy and safety of the treatment with physiotherapy for back pain during pregnancy.

3. Costs and use of resources. A cost study evaluating an intervention with self-help strategies in the management of low back pain during the puerperium has been considered (Bastiaenen, 2008). The study has shown that this strategy is cheaper than the standard, but is of limited application for the interventions evaluated in this guide.

4. No studies examining the values and preferences of women were identified.

The direction of the following recommendation is based on the identification of significant differences between the groups compared in the different interventions of interest and their strength in the quality of evidence and magnitude of the estimates of benefit and harm. The quality of the evidence determined the strength of the recommendation.

Recommendation

Weak	We suggest the performance of water exercises and other individualised exercise programs for pregnant women , as well as therapeutic massages to relieve low back pain during pregnancy.

5.5. Managing breech pregnancy from week 35

Key question:

- What interventions have shown a benefit to attempt a successful external cephalic version?
- What are the ideal conditions to perform a cephalic external version?
- What is the ideal time to attempt a cephalic external version?

Interventions to reverse a breech to cephalic presentation

Interventions to help external cephalic version

Tocolytic drugs

Two SRs (Cluver, 2012; Wilcox, 2010) evaluating the tocolytic drugs to help external cephalic version (ECV) in the breech presentation have been identified. A Cochrane SR has been selected (Cluver, 2012) as it was the most up to date.

The SR by Cluver (2012) included 13 trials (1548 women) comparing different tocolytic drugs: beta-stimulants (parenteral ritodrine, oral or parenteral salbutamol, parenteral terbutaline), calcium channel blockers (oral nifedipine) or nitric oxide donors (sublingual or parenteral nitroglycerin) to placebo.

A statistically significant increase was observed in the cephalic presentation at delivery and childbirth with the use of tocolytic drugs (beta-stimulants, calcium channel blockers, and nitric oxide donors) compared to placebo (8 studies, 993 women; RR 1.38, 95% CI 1.03 to 1.85) (Cluver, 2012). **Moderate quality**

A significant reduction was observed in the caesarean section rate with the use of tocolytic drugs compared to placebo (8 studies; 1,177 women; RR 0.82, 95% CI 0.71 to 0.94) (Cluver, 2012). **Moderate quality**

There were no significant differences in relation to the presentation of foetal bradycardia between the group treated with tocolytic drugs versus the group treated with placebo (3 studies, 467 women; RR 0.95, 95% CI 0.48 to 1.89) group (Cluver, 2012) . **Moderate quality**

Foetal acoustic stimulation

A Cochrane SR (Cluver, 2012) evaluating the vibroacoustic stimulation to facilitate the ECV in the breech presentation has been identified.

The SR included one single trial (26 women) comparing the vibroacoustic stimulation (in the midline of the spine of the foetus) with placebo.

A significant reduction in the risk of failure of the ECV was observed in the group with vibroacoustic stimulation compared to placebo (1 study, 23 women; RR 0.09, 95% CI 0.01 to 0.60) (Cluver 2012). **Low quality**

Regional analgesia

Two SRs (Cluver, 2012; Lavoide, 2010) evaluating regional analgesia to facilitate the ECV in breech presentation have been identified. The Cochrane SR has been selected (Cluver, 2012) as it is the one most up to date.

The SR by Cluver (2012) included six trials (554 women) comparing regional analgesia (spinal or epidural) with placebo. All studies except one applied tocolytic drugs in the two groups.

No statistically significant differences were observed in any of the outcomes of interest:

No statistically significant differences were observed in any of the outcomes of interest: **Low quality**

- Risk of cephalic presentation at delivery and childbirth (3 studies, 279 women; RR 1.63, 95% CI 0.75 to 3.53) (Cluver, 2012).
- Caesarean section rate (3 studies, 279 women; RR 0.74, 95% CI 0.40 to 1.37) (Cluver, 2012). **Low quality**
- Risk of foetal bradycardia (2 studies, 210 women; RR 1.48, 95% CI 0.62 to 3.57) (Cluver, 2012). **Moderate quality**

Transabdominal amnioinfusion

A Cochrane SR (Cluver, 2012) evaluating the transabdominal amnioinfusion to facilitate the ECV in breech presentation has been identified.

The SR by Cluver (2012) identified no RCTs that assess the transabdominal amnioinfusion to facilitate the ECV.

Systemic opioids

A Cochrane SR (Cluver, 2012) assessing systemic opioids to facilitate the ECV in breech presentation has been identified.

The SR did not identify any RCTs assessing systemic opioids compared to placebo to facilitate ECV, although one trial (95 women) comparing systemic opioids versus regional analgesia was found.

No statistically significant differences were observed in any of the outcomes of interest: **Low quality**

- Caesarean section (1 study, 95 women; RR 1.18, 95% CI 0.90 to 1.54) (Cluver, 2012).
- Presentation of foetal bradycardia (1 study, 94 women; RR 0.71, 95% CI 0.24 to 2.09) (Cluver, 2012). **Low quality**

Alternative interventions to ECV

Postural management

A Cochrane SR (Hofmeyr, 2000, updated in 2011) which assesses postural management for breech presentation has been identified.

The SR by Hofmeyr (2000) included six trials (417 women) assessing the position "Indian version," the knee-chest or supine position and raising the pelvis. Gestational age at inclusion was different between the studies.

No differences were observed in the risk of births with breech presentation in the group with postural management compared to the untreated group (6 trials; 417 women; RR 0.98; 95% CI from 0.84 to 1.15) (Hofmeyr, 2000). **Low quality**

No differences were observed in the caesarean section rate in the group with postural management compared to the untreated group (5 trials; 317 women; RR 1.10, 95% CI 0.89 to 1.37) (Hofmeyr, 2000). **Low quality**

No differences were observed in the risk of a low score on the Apgar score (less than seven) in the first minute in the group with postural management compared to the untreated group (3 trials, 237 women; RR 0.88; 95 0.50 to 1.55%) (Hofmeyr, 2000). **Low quality**

Moxibustion

Three SRs (Coyle, 2012; Li, 2009; van den Berg, 2008) evaluating the efficacy and safety of moxibustion on changing the presentation of the foetus on breech presentation have been identified. The Cochrane SR has been selected (Coyle, 2012) as it is the most up to date.

The SR by Coyle (2012) identified eight trials (1346 women) comparing moxibustion (moxibustion alone or in combination with postural techniques or acupuncture) versus a control group (no treatment, postural techniques or acupuncture). Moxibustion was applied to the acupoint BL67 for 20 minutes (in most tests); once or twice a day or twice a week; during a period of 4 days to 2 weeks (Coyle, 2012).

No differences were observed in the risk of non-cephalic presentation at childbirth in the group treated with moxibustion compared to the untreated group (3 trials, 594 women; RR 0.90, 95% CI 0.67 to 1.19) (Coyle, 2012). **Low quality**

No differences were observed in the risk of needing ECV (breech presentation at end of the trial) in the group treated with moxibustion compared to the untreated group (2 trials; 472 women; RR 0.67; 95% CI 0.34 to 1.32) (Coyle, 2012). **Low quality**

No differences were observed in the caesarean section rate in the group treated with moxibustion compared to the untreated group (2 trials; 472 women; RR 1.05; 95% CI 0.87 to 1.26) (Coyle, 2012). **Moderate quality**

The women in the group treated with moxibustion reported adverse events related to the treatment, including unpleasant odour, nausea and abdominal pain of contractions (1 trial, 122 women; RR 48.33, 95% CI 3.01 to 774.86) (Coyle, 2012). **Low quality**

Ideal conditions for the external cephalic version

Clinical factors

An SR (Kok, 2008) identifying clinical factors that may predict the success of an attempted external cephalic version (ECV) has been identified. The SR by Kok (2008) included 53 studies (36 cohort studies, 7 case-control studies, and 10 randomised clinical trials) and 10,149 women. In most of the included studies (n = 33; 81%) tocolytic drugs were administered prior to ECV.

The following clinical predictors were identified associated to the success of ECV:

- Multiparity (15 studies; OR 2.5; 95% CI 2.3 to 2.8).

- Without collocation in the breech presentation (7 studies; OR 9.4, 95% CI 6.3 to 14).
- Relaxed uterus (3 studies; OR 18, 95% CI 12 to 29).
- Palpable foetal head (2 studies; OR 6.3, 95% CI 4.3 to 9.2).
- Weight of the mother under 65 kg (7 studies; OR 1.8, 95% CI 1.2 to 2.6).

The gestational age (10 studies; OR 4.2, 95% CI 0.20 to 88) and fundal height showed no significant effect on the ECV.

Ultrasound factors

An SR (Kok, 2009) identifying ultrasound factors that can predict the success of an attempt of ECV has been identified. The SR by Kok (2009) included 37 studies (31 cohort studies, 3 case-control studies, and 3 randomised clinical trials) and 7,709 women. In most of the studies included (n = 27; 73%) tocolytic drugs were administered prior to ECV.

The following ultrasound predictors were identified associated to the success of ECV:

- Posterior location of the placenta (27 studies; OR 1.9; 95% CI 1.5 to 2.4).
- Complete breech position, defined as the buttocks down, with the legs bent at the knees and the feet close to the buttocks (20 studies; OR 2.3; 95% CI 1.9 to 2.8).
- Amniotic fluid index>10 (13 studies; OR 1.8, 95% CI 1.5 to 2.1).

The estimation of foetal weight and the position of the foetal spine (anterior, lateral or posterior) showed no significant effect on the ECV.

Ideal time for the external version

External cephalic version at term

A Cochrane SR [Hofmeyr 1996, updated in 2011] evaluating the effects of external cephalic version (ECV) at term on the measures of pregnancy outcome has been identified.

The SR by Hofmeyr 1996 included seven RCTs (1245 women) comparing ECV at term (with or without tocolysis) compared to not attempting ECV in women with breech presentation.

A statistically significant and clinically relevant reduction of cephalic births was observed when ECV at term (7 RCTs, 1245 women; RR 0.46, 95% CI 0.31 to 0.66) was attempted (Hofmeyr, 1996).	**Low quality**
A statistically significant reduction in caesarean section rates was observed when ECV at term (7 RCTs, 1245 women; RR 0.63, 95% CI 0.44 to 0.90) was attempted (Hofmeyr, 1996).	**Low quality**
No significant differences were observed in the incidence of perinatal death (6 RCTs, 1053 women; RR 0.34, 95% CI 0.05 to 2.12) (Hofmeyr, 1996).	**Low quality**

ECV before term

A Cochrane SR (Hutton, 2006) evaluating the effectiveness of the conduct of beginning ECV before term (before 37 weeks of gestation) for breech presentation has been identified.

The SR by Hutton (2006) included three trials (514 women) comparing different interventions:

- ECV conducted and completed before term (from 32 weeks of gestation) versus no ECV.
- ECV started before term (33 weeks) and up to 40 weeks of gestation and could be repeated until delivery versus no ECV.
- ECV started before term (34 to 36 weeks of gestation) versus ECV started after the term (37 to 38 weeks of gestation).

ECV before term versus no ECV

No differences were observed in the rate of non-cephalic presentation at childbirth between the group with ECV before term compared to the group that did not undergo ECV (1 RCT, 102 women; RR 1.04, 95% CI 0.64 to 1.69) (Hutton, 2006).	**Low quality**
No differences were observed in the caesarean section rate between the two groups (1 RCT; 102 women; RR 1.82; 95% CI 0.57 to 5.84), nor in the rate of stillbirth or neonatal mortality less than 7 days (1 RCT, 102 women; RR 1.04, 95% CI 0.64 to 1.69) (Hutton, 2006)	**Low quality**

ECV started before term versus no ECV

The ECV group had a significantly lower rate of non-cephalic presentation at childbirth (44%) compared to the group without ECV (74%) (1 study; 179 women; RR 0.59, 95% CI 0.45 to 0.77) (Hutton, 2006).	**Low quality**
No differences were observed in the rate of caesarean sections (1 study, 179 women; RR 0.62, 95% CI 0.27 to 1.43) (Hutton, 2006).	**Low quality**
No differences were observed in the rate of stillbirth or neonatal mortality less than 7 days between the two groups (1 study, 179 women; RR 0.34, 95% CI 0.01 to 8.16) (Hutton, 2006).	**Low quality**

ECV started before term versus ECV started after term

No differences were observed in the rate of non-cephalic presentation at childbirth between the group with ECV started before term versus the group with ECV started after term (1 study, 233 women; RR 0.86, 95% CI 0.70 to 1.05) (Hutton, 2006).	**Low quality**
No differences were observed in the caesarean section rate between the two groups (1 study; 233 women; RR 0.90, 95% CI 0.76 to 1.08), nor in the rate of stillbirth or neonatal mortality less than 7 days (1 study, 233 women; RR 0.33, 95% CI 0.01 to 8.10) (Hutton, 2006).	**Low quality**

Summary of evidence

Interventions to reverse a breech to cephalic presentation	
Moderate quality	The administration of tocolytic drugs before the ECV increases the incidence of newborns with cephalic presentation and decreases the caesarean section rate without presenting foetal bradycardia compared to placebo (Cluver, 2012).

Low quality	Foetal acoustic stimulation for ECV decreases the risk of failure of the ECV (Cluver, 2012).
Low / moderate quality	The ECV under regional analgesia (spinal or epidural) does not increase the cephalic presentation, decreases the rate of caesareansection, or presents more foetal bradycardia compared to placebo (Cluver, 2012).
There are no randomised controlled trials to determine the efficacy and safety of amnioinfusion to improve the success of ECV (Cluver, 2012).	
Low quality	The administration of systemic opioids for ECV does not reduce the risk of caesarean section and presents more foetal bradycardia compared to regional analgesia (Cluver, 2012).
Low quality	The postural management (as an alternative to ECV) does not decrease the risk of non-cephalic presentation at childbirth, caesarean section or a low score on the Apgar score compared to undergoing no treatment (Hofmeyr, 2000).
Low / moderate quality	Moxibustion (as an alternative to ECV) does not decrease the risk of non-cephalic presentation at childbirth, of needing ECV or caesarean section compared to undergoing no treatment. The treatment with moxibustion presented several adverse events such as unpleasant odour, nausea and abdominal pain of contractions (Coyle, 2012).
Ideal conditions for external cephalic version	
Very low quality	The following clinical factors have been associated with the success of ECV: multiparity, non-collocation of the foetus in breech presentation, relaxed uterus, palpable foetal head, weight of the mother under 65 kg (Kok, 2008).
Very low quality	The following ultrasound factors have been associated to the success of ECV: posterior location of the placenta, complete breech position, and amniotic liquid index >10 (Kok, 2009).
Ideal time for the external cephalic version	
Low quality	ECV at term is associated with a significant reduction of births with breech presentation and caesarean sections. No significant effect on perinatal mortality was observed (Hofmeyr, 1996).
Low quality	Although the ECV started before term (33 weeks) compared to non-attempt of ECV has been associated with a significant decrease in the rate of non-cephalic presentation at birth, it has not shown any benefit in other outcomes, nor compared to ECV performed at term (Hutton, 2006).

From evidence to recommendation

For the recommendation on the interventions to reverse a breech to cephalic presentation, the strength and direction of the recommendation were established considering the following aspects:

1. Quality of the evidence. The quality of evidence has decreased due to methodological limitations of the studies as well the heterogeneity and / or inaccurate results.
2. Balance between benefits and risks. Tocolytic drugs appear effective in promoting ECV although there are limited data on its safety. There is limited evidence on the efficacy and safety of other interventions to promote ECV (foetal acoustic stimulation, regional analgesia, amnioinfusion, or systemic opioids). There is limited evidence on postural management or moxibustion as alternatives to ECV.
3. No studies examining the costs, use of resources or values and preferences of pregnant women were identified.

The direction of the recommendation on tocolytic drugs was established considering that these drugs appear effective in promoting ECV although there are limited data on their safety. The existence of doubts about the balance between the wanted outcomes (cephalic presentation and decreased caesarean section) and the unwanted ones (adverse events) of tocolytic drugs to promote ECV determined the strength of the recommendation.

In the case of the recommendation on the ideal time for the ECV, the strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The quality of the evidence has decreased due to limitations in the design of the studies, the heterogeneity, and the inaccuracy of the results.
2. Balance between benefits and risks. ECV at term reduces the number of childbirths with breech presentation and caesarean sections, although there is not enough evidence to evaluate any risk of ECV at term. There is limited evidence to assess whether ECV before term has any benefit compared to ECV at term.
3. No studies examining the costs, use of resources or values and preferences of pregnant women were identified.

The development group made a recommendation in favour of ECV at term because it has shown to be effective in reducing the number of childbirths in cephalic presentation and caesarean sections. On the other hand, a recommendation against ECV before term has been made because it has shown better results when compared to the procedure performed at term, and the results compared to non-completion of the procedure are not sufficiently consistent. The recommendation has a weak force in both cases due to the limitations identified in the literature and the lack of consistent data on possible complications related to the procedure.

Recommendations

Weak	We suggest administering ECV to those pregnant women with the baby in breech presentation at term gestation (37 weeks) and no contraindications to the procedure in order to reduce breech presentations and caesarean deliveries for this presentation.
Weak	We suggest the administration of tocolytic drugs prior to attempt ECV in those pregnant women with singleton breech presentation who have accepted the realization of ECV.
Weak	We suggest not performing an attempting an ECV before term (37 weeks) to those pregnant women with the baby in breech presentation.
√	The following conditions which have shown to have a bearing on the success of external cephalic version should be taken into account: multiparity, no fitting of the baby in breech presentation, relaxed uterus, palpable foetal head, weight of mother under 65 kg and subsequent ecographic criteria of posterior placental location, complete breech position and amniotic fluid index> 10.

5.6. Preparation for childbirth

Key question:

- How effective is conducting education programs for preparing birth?

Effectiveness of birth preparation programs

A Cochrane SR evaluating the impact of participation in a program of perinatal education in the acquisition of knowledge, the level of anxiety and sense of control before childbirth, pain during childbirth, breastfeeding, attention span to the newborn, and other psychosocial factors was identified (Gagnon 2007).

The RS included 9 RCTs (for a total of 2,284 women) evaluating different perinatal education programs (individual or group) during pregnancy which included information on pregnancy, childbirth and parenthood, excluding studies aimed at promoting specific aspects (lactation, how to improve mood, smoking). The programs evaluated in the nine RCTs included in the SR were very different from each other. Their quality was limited; they included small samples (10 to 318 participants) and measuring the outcomes of interest was also very heterogeneous, making it difficult to extract firm conclusions about the effectiveness of these programs.

This SR did not find consistent results, due to the limitations discussed (Gagnon, 2007). Three of the included RCTs showed that participation in a perinatal education program for the preparation of childbirth improved the knowledge gained. One RCT showed improved knowledge of 1.62 points on a scale of 20 points (n = 48; DM 1.62, 95% CI 0.45 to 2.75) (Corwin, 1999), while another showed that participants in the program were twice as likely as controls to acquire knowledge (n = 223; RR 2.22, 95% CI 1.27 to 3.90) (Klerman, 2001). **Low quality**

In this same study, participation in a perinatal education program for the preparation of childbirth improved the perception of being able to master the acquired knowledge as well as changes in behaviour (n = 223; RR 1.40, 95% CI 1.05 to 2.09) (Klerman, 2001).

Another study showed that labour was shorter in women who had participated in an education program (n = 200; DM -1.10 h; 95% CI -1.64 to -0.56) (Mehdizadeh, 2005).

These variable results made the authors of the SR conclude that the benefit of perinatal education programs to prepare for childbirth are still unknown, so more research is necessary to determine the effectiveness of these programs, taking into account the resources assigned to this type of prenatal care, despite the popularity and acceptance these programs have.

On the other hand, another review of the literature emphasizes that the perinatal education for childbirth preparation remains an essential component of healthcare during the prenatal period, but should promote the implementation of evidence-based practices. Fostering the informed participation of pregnant women and their partners in their own pregnancy, childbirth and puerperium, is likely to achieve greater satisfaction and better results (Bailey, 2008). **Expert opinion**

This review describes both the essential aspects to be addressed in perinatal education programs for preparation to childbirth, as well as different program modes that have appeared (although centred in an American context).

Essential contents of perinatal education for childbirth preparation (adapted from Bailey, 2008).

Aspect	Description and information
Labour and normal delivery	Anatomy and physiology of pregnancy and childbirth, stages of labour and common experiences.
Pain management: medical and non-medical methods	Use of relaxation and breathing techniques, hydrotherapy, continuous support during labour, analgesia, and local anaesthesia.
Possible medical interventions during labour and delivery	Intravenous fluids, foetal monitoring, induction techniques, episiotomy, assisted vaginal delivery, caesarean section.
Delivery room or place in which childbirth will take place	Visit to the delivery room, aspects to consider whilst in the delivery room, description of stay in the delivery room and healthcare professionals involved.
Labour work and delivery	Signs of labour work.
Warning Signs	Symptoms of preterm labour, premature rupture of membranes, foetal distress, bleeding or haemorrhage.
Breastfeeding	Benefits, postures, checking the correct implementation of breastfeeding, signs of satiation, support and breastfeeding accessories.
Newborn care	Basic feeding, bathing, hygiene, rest and sleep, warning signs.
Care during the puerperium	Recovery time, perineal hygiene, signs and symptoms of postpartum depression.

Most common perinatal education programs for childbirth preparation (adapted from Bailey 2008).

Name and description	Modality
Lamaze (1960) Preparing couples for unmedicated childbirth, aiming to promote and support normal birth through perinatal education.	(six 2-hour sessions, two 3-hour sessions, one 7-hour session) one individual 3-hour class
Bradley method (1965) Conceives birth as a natural process and promotes avoiding analgesia for pain and medical intervention during normal childbirth and the puerperium.	12 classes per week that begin in the fifth month of pregnancy
Mongan method (Hypnobirthing, 1989) Promotes education for a relaxed natural childbirth, enhanced by hypnosis techniques. The method argues that in the absence of fear and tension, severe pain does not have to be important during labour.	Five 2.5 hour classes
Birthing From Within (1998) It emphasizes on cultivating an attitude of mindfulness, in which consciousness of birth is taken, doing their best at all times.	12 hours of classes (six 2-hour classes and four 3-hour classes, or an intensive weekend)
Birth Works (1994) Promotes a philosophy that develops the self-confidence of women, the confidence, and faith in the innate ability to give birth.	Ten 2-hour classes
Calm Birth (2005) Based on meditation and mind-body medicine.	Purchase a CD

Other clinical practice guidelines

In our environment, there are some education programs for preparation at birth. In the case of Catalonia, for example, the program aims to comprehensively promote the development of three fundamental dimensions in mothers and their partners (General Directorate of Public Health, 2009): i) the attitudes and emotions related to each phase of the birth process; ii) behavioural aspects that competently address the process of pregnancy, childbirth and puerperium; iii) knowledge of the birth process and implications at different stages. This proposal is aimed at giving an opportunity to program participants to share experiences, answer questions, feel part of a group that shares similar interests and expectations, contrasting their own experiences with others, getting a wider and more sensitised vision, or reflect on their own reactions to new situations.

The program consists of eight sessions on the following topics:

- Introduction.
- The pregnancy and the changes it entails.

- Pregnancy and welfare.
- The process of childbirth.
- Situations which define the progress of labour.
- Puerperium.
- Breastfeeding.
- Assistance to the newborn.

Each session consists of objectives, the implementation of activities and strategies related to the topic of the session and teaching materials and audio-visual resources are made available. During each session,participants also work on the development of body awareness and psychophysical training, straining exercises, massage, breathing and relaxation.

Summary of evidence

Low quality	The literature available does not allow firm conclusions about the effectiveness of prenatal education programs for the preparation of childbirth (Gagnon, 2007). Several studies with small samples have evaluated different types of programs which have suggested that his participation will contribute to a better understanding and improvement of self-perception regarding the ability to apply the acquired knowledge (Corwin, 1999; Klerman, 2001), and may contribute to a shorter duration of labour (Mehdizadeh, 2005).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The programs evaluated in the nine RCTs included in the SR were very different between each other, their quality was limited, they included small samples (10 to 318 participants), and measuring the outcomes of interest was also very heterogeneous. The results come from very small studies with limitations in the description of baseline values and the magnitude of change, which is sometimes not very relevant.
2. Balance between benefits and risks. In the studies evaluated in the Cochrane SR by Gagnon (2007), no possible damages arising from the participation in a perinatal education program were evaluated, but it is unlikely that participation in an activity of this style can affect an undesired effect.
3. No studies examining the costs and use of resources of pregnant women were identified.
4. Values and preferences of patients. A SR of 13 qualitative studies described the aspects of perinatal education programs that were most helpful to the participants and which could offer better training about childbirth and the puerperium. Overall, the results of the studies considered showed the preference of women for small groups within a learning environment in which to exchange views between the participants and the teacher is promoted, and where information tailored to individual circumstances can de discussed.

The direction and strength of the following recommendation were established considering

that the literature has shown very limited results from the evaluation of various perinatal education programs, although some studies have shown positive results to promote the knowledge and skills of the participants. On the other hand, it is not expected that participation in these programs can provoke any harm to participants. Likewise, the literature about the preferences of users and their partners in these programs has highlighted the positive perception of these programs, as an area of learning to acquire the skills and information needed to adapt to new circumstances.

√	All pregnant women and their partners should be offered the opportunity to participate in a program of preparation for the birth in order to acquire knowledge and pregnancy-related skills, childbirth, care of the postpartum period, the newborn and during the breastfeeding period.

5.7. Managing pregnancy from week 41

Key question:

- What is the most appropriate obstetric management of pregnancy from week 41?

Effective interventions for the management of pregnancy from weeks 41 and 42

Four SRs (Gülmezoglu, 2006; Caughey, 2009; Wennerholm, 2009; Hussain, 2011) evaluating the induction of labour versus expectant management according to the weeks of gestation have been identified.

The Cochrane SR (Gülmezoglu, 2006) and the SR by Caughey (2009) included women from weeks 37 to 38 and up to 42 weeks of gestation. Instead, the SRs by Wennerholm (2009) and Hussain (2011) included women with a gestation of 41 weeks or more.

The SRs by Wennerholm (2009) and Gülmezoglu (2012) have been selected for being the most up to date SRs. They also include a study population (41 or more weeks of gestation) and the results of the outcomes (in relation to the mother and the newborn) which are best suited for the key question asked.

The SR by Wennerholm (2009) included 13 RCTs comparing elective induction of labourwork at 41 or more weeks of gestation versus watchful waiting in 6,617 women. Nine trials included women with 41+ 0 weeks of gestation and four trials included women with 42+0 weeks of gestation. The Cochrane SR by Gülmezoglu (2012) included 14 RCTs with the same comparison as discussed above, with 4 RCTs involving women at 41 weeks of gestation and 11 RCTs with women over 41 weeks of gestation.

Although the SR by Wennerholm (2009) showed no significant differences in perinatal mortality between the group with elective induction and the one with watchful waiting (11 RCTs; 1 / 3,119 cases in elective induction versus 8 / 3,097 cases of watchful waiting; RR 0.33, 95% CI 0.10 to 1.09). The update of the Cochrane SR showed a statistically significant reduction of perinatal mortalityin favour of elective induction of labour at 41 weeks of gestation (14 RCTs; 1 / 3,315 cases with elective induction versus 11 / 3,282 cases with watchful waiting; RR 0.31, 95% CI 0.11 to 0.88) (Gülmezoglu, 2012). This result would mean that compared to a watchful waiting behaviour, perinatal death can be avoided with elective induction of labour after 41 weeks every 410 pregnancies (95% CI 322 to 1.492). The SR by Hussain (2011) showed the same results. **Low quality**

Both SRs excluded clinical trials or cases of perinatal deaths (one in the group with elective induction and two in the group with watchful waiting in the review by Wennerholm, 2009) in which the child had a severe congenital malformation.

Elective induction of labour and delivery was significantly associated with a lower risk of infants with meconium aspiration syndrome compared to watchful waiting (7 RCTs, 14 / 1,114 cases with elective induction versus 33 / 1,107 cases with watchful waiting; RR 0.43, 95% CI 0.23 to .79) (Wennerholm, 2009). **Low quality**

Elective induction of labour and delivery was significantly associated with a lower risk of caesarean section compared to watchful waiting (13 RCTs; 658 / 3,318 cases with elective induction compared to 750 / 3,299 cases with watchful waiting; RR 0.87; 95 % 0.80 to 0.96) (Wennerholm, 2009). The Cochrane SR showed similar results (12 RCTs; 591 / 3,004 cases with elective induction versus 649 / 2,990 cases with watchful waiting; RR 0.91, 95% CI 0.82 to 1.00) (Gülmezoglu, 2012). **Moderate quality**

The Cochrane SR (Gülmezoglu, 2012) showed a significantly reduced risk of macrosomia associated with elective induction of labour when the pregnancy exceeds 41 weeks versus watchful waiting (5 RCTs, 250 / 2,309 events in the induction group versus 341 / 2,608 events in the watchful waiting group; RR 0.85, 95% CI 0.73 to 0.99). **Moderate quality**

The SR by Wennerholm (2009) narratively described some outcomes related to maternal complications. The SR found no significant differences between elective induction of labour and watchful waiting in the rate of maternal complications such as postpartum haemorrhage, perineal trauma or endiometritis. **Moderate quality**

Summary of evidence

Low quality	Elective induction of labour at 41 or more weeks of gestation reduces the risk of perinatal mortality compared to watchful waiting (Hussain, 2011; Gülmezoglu 2012).
Low quality	Elective induction of labour at 41 or more weeks of gestation decreases the risk of meconium aspiration syndrome compared to watchful waiting (Wennerholm, 2009).
Moderate quality	Elective induction of labour at 41 or more weeks of gestation reduces the risk of macrosomia compared to watchful waiting (Hussain, 2011; Gülmezoglu, 2012).

From evidence to recommendation

The strength and direction of the recommendation were established considering the following aspects:

1. Quality of the evidence. The quality of the evidence has decreased due to the risk of bias of the studies and their imprecise results (very few events).
2. Balance between benefits and risks. Elective induction of labour at 41 or more weeks of gestation reduces the risk of perinatal mortality, as well as the meconium aspiration syndrome, without increasing the risk of caesarean section. The meconium aspiration syndrome is an indicator that provides little information about foetal distress (Wennerholm, 2009; Hussain, 2011; Gülmezoglu, 2012).
3. No studies examining the costs and use of resources of pregnant women were identified.
4. Values and preferences of pregnant women. A study included in the SR by Wennerholm (2009) evaluated maternal satisfaction according to the intervention (Heimstad, 2007). Women with 41 or more weeks of gestation preferred induction of labour versus prenatal monitoring (74% versus 38% of women, respectively, said they would prefer the same treatment in a subsequent pregnancy).

The direction and strength of the following recommendation was established based on the fact that studies on this question are consistent in their findings and the intervention of the studies

(elective induction) is unlikely to present additional risks versus the comparison intervention (watchful waiting). Moreover, no alternative to the management of pregnancy from 41 or more weeks of gestation being clearly superior to any other has been observed. Furthermore, different SRs on the intervention presented conflicting results regarding the critical outcomes (Gülmezoglu, 2012; Caughey, 2009; Wennerholm, 2009; Hussain, 2011). Given this scenario, it would be important to consider the values and preferences of pregnant women as well as the cost-effectiveness of the interventions as determining factors on the strength of the recommendation.

Recommendation

Weak	We suggest offering to pregnant women the chance to induce labour at the time deemed most appropriate from the week before reaching weeks 41 and 42 of gestation, after reporting on the benefits and risks of induction.

6. Care during puerperium

6.1. Hospital care during puerperium

Key question:

- What checks and care are most suitable for the newborn during hospitalisation?
- What checks and care are most suitable for the mother during hospitalisation?
- Which specialist is most suitable for the control of hospital care during puerperium?
- What are the benefits of non-separation and mother-infant rooming-in during the hospital puerperium period for maternal and neonatal health? What are the benefits of bedding-in in mother's bed during the hospital puerperium period for maternal and neonatal health?

Controls and postnatal newborn care during hospital stay

The Committee on Standards of the Spanish Society of Neonatology has developed recommendations based on the scientific literature for the care of the healthy newborn at birth and hospital puerperium aimed at avoiding an excessive use of interventionism and prioritizes care leading to early detection of complications or risk situations (Sánchez Luna, 2009).

On the other hand, although some guide says there is no evidence in the literature to support the number and content of the physical examinations to be performed to the newborn, other authors have suggested that a single revision of the newborn within 24 hours of birth would be enough (Green et al., 2008). In any case, the content of the physical examination of the newborn is based on expert opinion and good clinical judgment, supplemented with different screening tests (Demott et al., 2006).

Physical examination of the newborn

A narrative review of the literature (Green, 2008) concludes that in healthy newborns a single physical examination within the first 24 hours of life would be enough, from the results of an RCT (Townsend, 2004). This RCT, compared the scanning by a trained midwife versus a paediatrician with expertise. In the group, which had been explored by a midwife, it was checked whether the fact of repeating the examination at home 10 days after delivery had any benefits. It also analysed the impact of this intervention on maternal satisfaction as well as the number of complications identified in the first 24 hours and those that resulted in referrals to specialised care.

The RCT showed no difference in the number of cases referred to specialist care for problems properly identified during scanning depending on whether the exploration was performed by a midwife or a paediatrician (826 participants; 5.9% versus 4.6%; OR 1.2, 95% CI 0.66 to 2.26). There were no differences in the number of incorrect referrals (826 participants, 1.2% versus 0.95%; OR 1.2, 95% CI 0.32 to 4.49).

Moderate quality

The satisfaction of mothers with the care received during the physical exploration of the newborn was high, since 85% of mothers said they were satisfied or very satisfied, although significantly more mothers whose babies were attended by a midwife expressed their satisfaction (85% versus 78%; OR 0.54, 95% CI 0.39 to 0.75).

The health professionals from both groups were recorded during the exploration performed to newborns and an independent committee evaluated the process. The conclusion of these authors was that both paediatricians and midwives had been trained appropriately, and therefore could carry out the physical examination properly. On the other hand, repeating the exploration at home did not provide any benefits to the cases referred to specialised care when any complication was detected.

Good clinical practice

The CPG by NICE (Demott, 2006) suggested that the physical examination includes the following practices:

- Evaluation of the maternal and family perinatal history
- Evaluation of previous estimates of birth weight and head circumference
- Verification that the baby has made a urination or a bowel movement, meconium, and otherwise record for subsequent monitoring
- Observation of general condition of the child (including skin colour, breathing, activity and posture)
- Evaluation of mood of the parents and observation of the interaction between mother and baby
- Evaluation of mood of the parents and observation of the interaction between mother and baby
- Evaluation of the exposed body parts of the baby: scalp, head and fontanelle, face, nose, lips, palate, ears, neck and head and facial symmetry with an ophthalmoscope
- Examination of the neck and clavicles, limbs, hands, feet, assessing proportions and asymmetries
- Evaluation of the cardiovascular system (heart rate, rhythm and femoral pulse, heart murmur, and laterality defects of the heart)
- Evaluation of effort and breathing rate
- Observation of the abdomen (colour, shape, exploring possible organomegaly) and examination of the umbilical cord
- Observation of genitals and anus (check undescended testicles in boys and hymen permeability in girls)
- Evaluation of the back skin and bone structure of the spine
- Observation of skin colour and texture, birthmarks or rashes
- Evaluation of muscle tone, behaviour, movements and posture, checking reflexes in case of doubt
- Checking of the symmetry of the limbs and skin folds, perform Barlow and Ortolani manoeuvres on a flat and firm surface
- Check crying
- Evaluation of specific potential risks in the baby's home, alerting the relevant health professional in those cases where there is suspicion of the possibility of inadequate care
- Review of the baby's eyes (size, position, detection of detachment) and red reflex test

Identification of the newborn

Good clinical practice

The correct identification of the newborn ensures safety for the baby and his/her family and facilitates the coordination of the healthcare personnel. On the other hand, a secure identification system avoids separation of the mother and her baby, preventing confusion among newborns. Identifying and opening a medical history ensures that any care provided is recorded and shown on the health history (Sánchez Luna, 2009).

The footprint or foot printing is not sufficient to identify the newborn by the difficulty in obtaining it and the difficulty of identifying continuously the pair mother-baby. Bracelet systems or umbilical cord with a code improve identification (Sánchez Luna, 2009).

Umbilical cord care

Low quality

Since the umbilical cord after birth represents a way of colonization, which can lead to an infection, section is very important to be performed with sterile material and a safe sealing system must be used. However, there is uncertainty about whether cord care with antiseptic or antibiotic solutions provides a benefit to the fact of keeping it dry and clean since birth.

A Cochrane SR (Zupan, 2004) that included 21 RCTs involving 8,959 newborns did not show that the use of antiseptic solutions (alcohol, chlorhexidine, triple dye) provided an advantage over the fact of keeping the umbilical cord clean and dry.

Although antiseptics showed a decreased colonization of the cord, and mothers who used these products showed less concern about it, antiseptic solutions did not reduce the risk of infection (4 RCTs, 2,831 participants; RR 0.53, 95% CI 0.25 to 1.13) and also delayed the fall of the cord (4 RCTs, 2,354 participants; DM 3.51 days more with alcohol, 95% CI - 0.41 to 7.43).

Good clinical practice

Given these results, the document of the Committee on Standards of the Spanish Society of Neonatology recommends monitoring hygiene measures like hand washing, the use of clean gauze to cover the cord and frequent change as well as regular change of the diaper. These practices are preferable to the use of antiseptic solutions as 70 degrees alcohol or chlorhexidine at 4% (Demott, 2006).

Prophylaxis of neonatal ophthalmia

Moderate quality

Since the newborn has a limited storage of vitamin K, especially in those who perform exclusive breastfeeding or who are premature, the risk of bleeding by the deficiency of this vitamin increases during the first six months of life.

A Cochrane SR (Puckett, 2000) identified two RCTs comparing intramuscular administration of 1 mg of vitamin K after birth versus placebo. The studies showed a reduced risk of bleeding between the first and seventh day of life (1 RCT, 3,338 participants, RR 0.73, 95% CI 0.56 to 0.96), and an improvement in the biochemical parameters of coagulation status.

Good clinical practice

Parents must be informed about the administration of vitamin K (MSPS, 2010). If they do not want vitamin K to be administered intramuscularly, an oral regimen should be offered (2 mg of oral vitamin K at birth, followed, in total breastfed or partly, of oral 1 mg weekly until the 12th week) stressing the importance of compliance with this guideline.

Prophylaxis of neonatal ophthalmia

Moderate quality

During the first two weeks of life, conjunctivitis may occur in the newborn manifested between the second and fifth day of life, which could complicate without proper treatment. Infection occurs through vertical transmission from mother to child by a sexually transmitted disease (gonorrhoea and C. trachomatis mainly) that is sometimes asymptomatic, so the need for a universal prophylaxis after birth should be performed. This could be avoided if the adequate screening for sexually transmitted diseases is carried out during pregnancy (Sánchez Luna, 2009).

Should a screening and treatment of sexually transmitted diseases not have been carried out during delivery, a prophylaxis of neonatal conjunctivitis can be performed with antibiotic or antiseptic solutions administered after delivery. One RCT comparing this treatment with placebo, showed a lower proportion of newborns with conjunctivitis after two months of life in those who had received a solution of silver nitrate at 1% (630 participants; HR 0.61; 95% CI from 0.39 to 0.97) or erythromycin at 0.5% (HR 0.69, 95% CI 0.44 to 1.07) (Bell, 1993). The most commonly eye drops used for this purpose are tetracycline at 1% or erythromycin at 0.5% (Sánchez Luna, 2009).

The topical application of silver nitrate solution at 1%, erythromycin ointment at 0.5%, tetracycline ointment at 1%, or povidone iodine at 2.5% are considered equally effective (MSPS, 2010).

Good clinical practice

The National Strategy for Sexual and Reproductive Health (MSPS, 2010) in its Guide on Care from Birth highlights the importance of the carrying out of some of these practices (administration of vitamin K or eye drops), as well as not separating the mother from the newborn, and therefore proposes to respect the time of skin contact with his / her mother until at least 2 hours after having been born.

Summary of evidence

Moderate quality	A single scan within 24 hours of the baby's life has proved sufficient to identify complications and proper referral to specialist care. The results of the examination showed no difference on whether an adequately trained midwife or paediatricians performed it (Townsend, 2004; Oreen, 2008).
Other clinical practice guidelines	The identification of the newborn and opening a medical history ensures that any care provided is recorded and shown on the health history and facilitates identification of the couple mother – baby (Sánchez Luna, 2009).
Moderate quality	The use of alcohol or other antiseptic solutions does not provide an advantage to the fact of keeping the umbilical cord clean and dry (Zupan, 2004; Demott, 2006; Sánchez Luna, 2009).
Moderate quality	The administration of vitamin K after birth is an effective way to prevent bleeding caused by a deficiency of this vitamin (Puckett, 2000; Sánchez Luna, 2009).
Moderate quality	The administration following delivery of antibiotic drops or ointment in newborns has shown to be a suitable strategy for prophylaxis of neonatal conjunctivitis (Bell, 1993; Sánchez Luna, 2009). Topical administration of silver nitrate solution at 1%, erythromycin ointment at 0.5%, tetracycline ointment at 1%, or povidone iodine at 2.5% are considered equally effective (MSPS, 2010).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. In the case of studies on the use of antiseptics for umbilical cord care, studies with methodological limitations, presenting heterogeneous and inaccurate results because of the limited size of the sample of some of them have been evaluated. Studies on the administration of prophylactic vitamin K are suitably designed but the results show some imprecision due to the limited size of the sample. This case would apply to the study which has evaluated the administration of an antibiotic solution for the prevention of neonatal conjunctivitis and the need for a physical examination of the newborn.
2. Balance between benefits and risks. All the procedures assessed in this section are intended to prioritize the care aimed at early detection of complications or risks.
3. Costs and use of resources. The RCT on the exploration of the baby's condition showed a slight saving between 2 and 4.5 £ per baby with the scanning carried out by a trained midwife.
4. Values and preferences of patients. Mothers of babies who underwent a physical examination by a trained midwife were more satisfied than mothers in the regular care group, though satisfaction with the care received was high in both groups (85%).

Recommendations

Strong	A single physical examination of the newborn in the first 24 hours of birth should be carried out in order to identify complications that may require specialised care.
√	The baby should be identified correctly from the time of umbilical cord ligation and possible separation of the mother and newborn should be avoided. Before carrying out any physical separation between the mother and the baby, a system of identification should be placed with the personal information of both, which should be visible throughout the hospital stay.
Strong	The umbilical cord should be cleaned with soap and water, dried afterwards and covered with clean dressings that must be changed frequently, and the diaper should be changed after bowel movements or urinations by the baby, in order to keep the cord dry and clean. This care should be performed until the umbilical cord falls following the aseptic and hygiene hand washing measures. This care should start only when the contact between the mother and her newborn is finished.
Strong	After birth, babies should be administered an intramuscular dose of 1 mg of vitamin K to prevent haemorrhage caused by a deficiency of this vitamin.
√	When parents do not accept the intramuscular administration of vitamin K, an oral regimen of 2 mg at birth should be administered, followed in partially or total breastfed babies by a weekly dose of 1 mg until the 12th week of life.
Strong	The administration of a topical antibiotic is recommended in the newborn after birth to reduce the risk of neonatal conjunctivitis.
√	Erythromycin ointment at 0.5% or tetracycline ointment at 1%, in a single-format should be used to increase the safety of the procedure.

√	The newborn should not be separated from his / her mother only for administering vitamin K or antibiotic eye drops, respecting the time of skin contact with his / her mother for this procedure.

Controls and care of the mother during the hospital puerperium

The Uptodate information resource contains a current review on scientific literature that summarizes the basic care for the mother during hospital puerperium (Berens, 2011).

In this review of the literature, the importance of promoting the necessary support during the hospital puerperium to ensure that a sense of confidence and competence about motherhood is established, and thus promote the bond between the mother and the baby is highlighted. In this process, the father should be involved to participate in the care of the newborn.

Other clinical practice guidelines

Evaluation and monitoring of the mother

The body temperature, blood pressure, heart rate, and respiratory rate of the mother should be monitored regularly. The possibility of uterine inertia, excessive bleeding, or signs of internal bleeding, bladder distention, or dyspnoea or pleuritic pain as a warning sign of a pulmonary embolism must also be assessed.

When an episiotomy has been performed during childbirth, signs of oedema, the presence of pain or purulent secretions, or dehiscence of the suture zone should be observed. In these women a special perineal care should be performed, ensuring proper hygiene in the area.

It is important to control the onset of fever in the puerperium, defined as a temperature above 38°C except for the first 24 hours after childbirth. In case of fever, an examination should be performed to identify the source of a possible urinary tract infection, surgical wound, mastitis, endometritis, septic pelvic thrombophlebitis, an adverse reaction to a drug or complications from anaesthesia.

Laboratory tests

Routine monitoring of haemoglobin levels and leukocyte count after childbirth have not shown to provide greater value to determine the risk of complications (Nicol, 1997; Hartmann, 2000; Petersen, 2002; Partlow, 2004) and should only be requested in those cases where signs of bleeding or anaemia, or infection are observed.

Prevention of venous thromboembolism

The risk of venous thromboembolism increases considerably after childbirth and remains high during the first two weeks, so thromboembolic prophylaxis is indicated in women who have been identified at high risk during pregnancy.

Vaccination

The hospital puerperium period is the time to immunise women with those vaccines that may not have been administered during pregnancy (see Key Question on vaccination during pregnancy). Anti-D immunoglobulin should be administered to those RhD negative mothers with an RhD positive baby.

Pain

Pain and fatigue are two of the symptoms that most afflict women after childbirth (Declercq, 2008). To achieve relief from pain derived from uterine involution, short-acting NSAIDs such as ibuprofen 600 mg showed a greater benefit than paracetamol or opioids (Deussen, 2011). Furthermore, paracetamol in doses not exceeding 4000 mg a day has shown postpartum perineal pain relief (Chou, 2010). The pain subsides spontaneously at the end of the first week after childbirth.

Voiding difficulty and urinary retention

Urine retention after childbirth is common and occurs when a spontaneous voiding is not achieved six hours after delivery. Treatment with oral analgesia is recommended, as well as encouraging women to try to go to the bathroom when they are relaxed or taking a bath of hot water (Yip, 2004).

Summary of evidence

Other clinical practice guidelines	Hospital puerperium should foster the bond between the mother and the baby with the involvement of the father in the process. Special attention should be given to the status of the mother, and to the appearance of fever or any other clinical signs that may indicate a complication. Regular testing or procedures in women in which no warning signs are identified should be avoided (Berens, 2011).

From evidence to recommendation

The strength and direction of the recommendation were established considering the following aspects:

1. Quality of the evidence. The instructions provided in this section were made from a guide, which develops recommendations based on good clinical practice.
2. Balance between benefits and risks. All the procedures assessed in this section are intended to prioritize care aimed at early detection of complications or risk situations.
3. No studies examining the costs and use of resources or the values and preferences of postpartum women were identified.

The direction and strength of the following recommendation was made considering that all the procedures assessed are intended to prioritize care aimed at the early detection of complications or risk situations.

Recommendation

√	The checks and care provided to the mother during the hospital puerperium period are aimed at identifying signs that may warn of possible complications, providing care to facilitate recovery of the birth process and promoting self-care and baby care, especially regarding food and hygiene, as well as promoting the bond between the mother and the baby.

Qualified healthcare professionals to control hospital puerperium

A Cochrane SR (Hatem et al., 2008) comparing the results of implementing a model of care led by midwives compared to models led by medical specialists such as obstetricians and family physicians has been identified. In the model tested, the midwife is who coordinates the entire process and provides care to pregnant women during the whole process of pregnancy, as well as being in contact with specialist care physicians if required.

The SR evaluated this care model at any time during the pregnancy, childbirth and puerperium and discussed a number of specific outcomes for the puerperium period and the duration of hospital stay, incidence of postpartum depression, the onset of breastfeeding, maintaining breastfeeding after 3 months, the prolonged presence of perianal pain, pain during sexual intercourse, urinary or faecal incontinence, back pain or perceived control of the mother during childbirth and the puerperium.

The SR included 11 RCTs with 12,276 women in various health systems in high-income countries (Australia, Canada, New Zealand, and the UK). The continuity of healthcare, defined as the percentage of women attended by a known health professional during the process, varied widely between the studies but it was much higher among the models led by midwives than by other professionals (from 63 to 98% from 0.3 to 21%). The studies compared the model of midwifery versus a mixed model in seven RCTs (where the planning and delivery of care is shared between different health professionals), and to a medical model in three RCTs. The latter study compared it to a model of regular care. Most studies in the SR included women without risk of complications or minor complications during pregnancy. In four RCTs, the evaluation focused on hospital care during childbirth and the puerperium.

In all studies the model led by midwives contemplated routine visits to obstetricians and family physicians, with varying frequency of visits. The number of visits was decided depending on the risk of pregnant women in 1 study, between one and three visits for all women in six RCTs, or when complications were identified in 2 studies.

This SR showed that compared with the attention given by health professionals in a medical specialty, the model of care led by midwives affected a limited number of outcomes related to the puerperium. **Moderate quality**

The babies of mothers treated in a model led by midwives had a shorter hospital stay (2 RCTs, 259 participants, DM - 2 days, 95% CI -2.15 to -1.85), a difference which was statistically significant. The authors of the SR stated that these results should be taken with caution, as the data in the original studies did not respond to a normal distribution.

A trial showed a higher percentage of women who initiated breastfeeding among mothers who had received the care of midwives (405 participants, RR 1.35, 95% CI 1.03 to 1.76).

Although the results failed to show a significant difference, the babies cared for in a model led by midwives were referred to a lesser extent to specialised care or an intensive care unit (10 RCTs, 11,782 participants, RR 0.92, CI 95% 0.81 to 1.05), and a lower percentage of mothers showed postpartum depressive symptoms (1 RCT, 1,213 participants; RR 1.94, 95% CI 0.18 to 21.32). **Moderate quality**

The subgroup analysis of the studies that included women without risk of complications showed no significant differences when compared to the outcomes discussed above. **Moderate quality**

The SR did not identify any RCTs to evaluate the impact of this model of care on the maintenance of breastfeeding, prolonged perineal pain, incontinence, or back pain. **Moderate quality**

Summary of evidence

Moderate quality	A model of care in which the midwife coordinates and provides care to women, establishing a contact with healthcare professionals when required, has shown some benefits for mothers and their babies (as a shorter hospital stay or a greater initiation of breastfeeding) without major adverse events (Hatem et al., 2008).

From evidence to recommendation

The strength and direction of the recommendation were established considering the following aspects:

1. Quality of the evidence. Although no study has a high risk of bias, the quality of the evidence has decreased considering the possibility that the studies that have contributed to some of the analyses presented biased results (due to an asymmetry of the data which did not correspond to a normal distribution of the sample), thus affecting a problem of accuracy with the estimation of the result. In the case of other variables such as referral of babies to specialised care or the percentage of mothers with postpartum depression, the quality of the evidence has decreased due to vagueness, because the results suggested a significant effect of the intervention, such as its absence.
2. Balance between benefits and risks. The RCTs from the SR evaluated showed no significant adverse events. It is however stated that the results of these studies should be applied to a context in which both pregnancy and childbirth develop without obstetric or medical complications. However, this assessment is beyond the scope of this CPG.
3. Costs and use of resources. Three of the RCTs included in the SR by Hatem (2008), provided financial data derived from the implementation of models led by midwives conditioned by the healthcare system and the time in which the studies were developed, but in general they showed costs which were similar between the model carried out by midwives and the one coordinated by professional healthcare specialists. One RCT showed that the cost of postnatal care was $745 in the model performed by midwives compared to $833 in the second model. In another study, the average cost per delivery and puerperium was higher in the standard care group ($A 3,475) than in the model carried out by midwives ($A 3,324). In a recent British RCT it was observed that the costs were significantly lower in the group following the model by midwives (£397) than the control group (£444; $p < 0.01$).
4. Values and preferences of postpartum women. The SR by Hatem (2008) collected data on the satisfaction of mothers with different care models evaluated from nine RCTs, which showed a great variability and inconsistency in the definition of this outcome and its measurement. Overall mothers who received care in programs led by midwives emphasized satisfaction with the information, the recommendations and details received, the way of being given explanations and the behaviour of the healthcare professionals, as well as other aspects directly related to the delivery.

The direction and strength of the following recommendation was made considering that the models led by midwives have shown a similar effect to other models led by healthcare

professionals, without complications and with a favourable outcome. Moreover, the costs of this models also appear to be similar. No major complications are expected to arise in those cases without risk and the perception of the mothers is broadly positive.

Recommendation

Strong	Hospital care and postnatal care for mothers and their babies should be coordinated and delivered by a midwife, identifying those cases that may require additional or specialised care

Benefits of non-separation and co-sleeping during the hospital puerperium period

An SR (Moore et al., 2012) evaluating the effect of early skin-to-skin contact (before 24 h postpartum) between mother and the healthy newborn on maternal variables, newborn and breastfeeding has been identified.

An RCT (Ball et al., 2006) evaluating the location of the newborn at bedtime during the hospital puerperium period has also been included.

Skin-to-skin mother-infant contact versus standard contact

The Cochrane SR by Moore (2012) included 34 RCTs with 2,177 mother-child dyads. Most studies (30) included only healthy term newborns, while the remaining included healthy late preterm newborns (34 to 37 complete weeks of gestation).

The intervention evaluated in the SR compared with the usual mother-child contact, including placing the infant wrapped in the arms of his / her mother, in open cots or below radial heaters in the same room with the mother or elsewhere. There were significant differences between studies both at the time of initiating skin-to-skin contact and its duration. There were also differences in the degree of separation that was applied to the group compared.

Physiological stability of the newborn

Low quality

One RCT (Bergman, 2004) that included 35 preterm newborns compared skin-to-skin contact to late contact with the use of an incubator next to the mother. The study measured the physiological stability of the newborn by the SCRIP score, a measure of cardio-respiratory stability in preterm babies that evaluates the heart and respiratory rate as well as the oxygen saturation with a score between 0 and 18.

Higher SCRIP scores were observed within 6 hours after birth in newborns who maintained a skin-to-skin contact with their mothers (1 RCT, 31 newborns, DM 2.88, 95% CI 0.53 to 5.23). In a subgroup of newborns weighing less than 18.00 grams, there was also a trend toward a greater stabilization in the group that maintained skin-to-skin contact, although without statistical significance (1 RCT, 13 newborns, DM 4.92, 95% CI -1.67 to 11.51).

Breastfeeding

Those participants who made skin-to-skin contact showed better results on several variables regarding breastfeeding. It was more frequent that mothers who maintained skin-to-skin contact with their babies kept breastfeeding until 4 months after childbirth (13 RCTs, 702 participants, RR 1.27, 95% CI 1.06 to 1.53). **Moderate quality**

A trend was observed for a longer duration of breastfeeding in mother-baby couples with skin-to-skin contact although without statistical significance (7 RCTs, 324 couples; DM 42.55 days; 95% CI -1.69 to 86.79). **Low quality**

When performing a sensitivity analysis excluding an SR responsible for the statistical heterogeneity (performed in a different population), the results reached statistical significance (6 RCTs, 264 couples; DM 63.73 days; 95% CI 37.96 to 89.50).

Three to six months after birth, there were more participants who maintained exclusive breastfeeding in the group in which skin-to-skin contact was performed (3 RCTs, 149 participants, RR 1.97, 95% CI 1.37 to 2.83). **Low quality**

The Document on Care from Birth of the National Strategy for Sexual and Reproductive Health (MSPS, 2010) states that with a skin-to-skin contact between 50 and 110 minutes, the probability that the newborn makes a feed spontaneously is eight times higher than that of a shorter contact time, according to the results from a series of 651 cases in newborns (Gómez Papi, 1998). **Other clinical practice guidelines**

Breast problems: painful breast engorgement

Two RCTs (Bystrova, 2003; Shiau, 1997) evaluated painful breast engorgement measured by a validated scale (Hill, 1994) or by the perception of tension or breast hardness of mothers. **Low quality**

Painful breast engorgement three days after childbirth was lower in women who had performed skin-to-skin contact (MD -0.41, 95% CI -0.76 to -0.06).

Location of the newborn during the nights of the hospital puerperium stay: cot in the same room versus cot by the bed and versus in the same bed.

One RCT analysed different degrees of mother-newborn contact during hospital stay after delivery. 64 mother-newborn couples were included and randomised to different locations of the newborn: a cot in the same room, a cot attached to the bed of the mother (sidecar type) and in the mother's bed provided with rails to prevent falls (Ball, 2006).

Breastfeeding attempts and successful attempts.

The mother-newborn pairs who slept in the same bed made more attempts to breastfeed during the night and more successful attempts than the couples in which the newborn slept in a separate cot (attempts to breastfeed per hour: DM 1.87; 95 % CI 0.63 to 3.11; successful attempts per hour: DM 0.90; 95% CI 0.19 to 1.61). **Low quality**

The mother-newborn pairs in which the newborn slept in a cot by the mother's bed, made more attempts to breastfeed and more successful attempts than couples in which the newborn slept in a separate cot (attempts to breastfeed: DM 1.57, 95% CI 0.58 to 2.57; successful attempts: DM 0.96; 95% CI 0.18 to 1.73).

here were no differences in the number of attempts to breastfeed or the number of successful attempts (attempts to breastfeed:DM 0.30; 95% CI -1.12 to 1.72; p =

0.64 successful attempts: DM -0 06, 95% CI -0.95 to 0.83 p = 0.93) between pairs who slept in the same bed or in a cot attached.

Sleep Duration

There were no statistically significant differences in sleep duration of mothers or newborns between the different modes. **Low quality**

Maternal satisfaction

The satisfaction scores of women whose babies were in a separate cot were below average. Instead, the scores of women who slept in the same bed with the baby, had scores above average. However, these differences were not statistically significant. **Low quality**

Safety

None of the newborns experienced adverse events during the study. There was a higher frequency of events with potential respiratory risk when sleeping in the same bed as compared to sleeping in a separate cot (DM 0.11, events in one hour from 0.01 to 0.21). However, there were no differences in the frequency of events with potential risk of falling (DM 0.02, events in one hour -0.01 to 0.06). **Low quality**

There were no differences in the frequency of events with potential respiratory risk or falls between sleeping in a cot attached or in a separate cot (respiratory risk: DM 0.02 (-0.03 to 0.07), risk of falling: DM 0.02 (-0.12 to 0.06). There were also no differences in the frequency of risk events between sleeping in the same bed or in a cot attached. There were no differences either between sleeping in the same bed or in a cot attached (respiratory risk: DM 0.09 (-0.01 to 0.19), risk of falling: DM 0,002 (-0.05 to 0.51).

Summary of evidence

Moderate quality	Skin-to-skin contact between the mother and the newborn. The available evidence (an SR with 34 RCTs and 2,177 participants) suggests that skin-to-skin contact between the mother and the newborn 24hours after birth has a mutually beneficial effect.
Low quality	Skin-to-skin contact compared to regular contact is associated with increased cardiorespiratory stability in healthy late preterm newborns (34 to 37 weeks of completed gestation).
Moderate quality	Those mothers who perform skin-to-skin contact with their newborn are more likely to maintain breastfeeding between 1 and 4 months after delivery than those mothers performing regular contact.
Low quality	Those mothers who have a skin-to-skin contact with their newborn maintain breastfeeding for longer (64 days on average) than those who do not perform skin-to-skin contact.
Low quality	Those mothers who perform skin-to-skin contact with their baby are more likely to maintain exclusive breastfeeding for 3 to 6 months after delivery than those performing regular contact.

Low quality	Those women performing skin-to-skin contact with their newborn have lower levels of self-reported painful breast engorgement than those not performing it.
Low quality	Location of the newborn during the nights of hospital puerperium stay: separate cot, cot by the bed, in the same bed. The available evidence (one RCT with 64 participants) suggests that further attempts to breastfeed during the night (both successful and unsuccessful) occur when newborns sleep in the same bed as the mother or in a cot attached (sidecar type) than when placed in a separate cot. No differences were found between newborns located in the same bed or in a cot attached in terms of the frequency of attempts to breastfeed.
Low quality	No differences were found in the sleep duration of the mother or the baby depending on whether the baby slept in the same bed, in a cot attached or in a separate cot.
Low quality	No statistically significant differences were found regarding the satisfaction scores of mothers between the different locations of the newborn.
Low quality	There is a higher frequency of events with potential respiratory risk when the newborn sleeps in the same bed as compared to when sleeping in a separate cot. No differences were found in the frequency of events with potential risk of falling when sleeping in the same bed as opposed to sleeping in separate beds.
Low quality	No differences were found in the frequency of events with potential respiratory risk or fall when comparing sleeping on a cot attached to sleeping in a separate cot or comparing sleeping in the same bed to sleeping in a cot attached.

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The main causes that limit confidence in the results are, first, the methodological limitations of some studies. Although blinding such interventions is impossible to achieve, it is possible to perform a blinded assessment of the outcomes. This process was performed in very few studies. Furthermore, the authors of the SR suspected of the existence of publication bias as they observed greater effects of the intervention in smaller studies. Other aspects that limit the quality of the evidence are the significant variability in the results between the different studies and the lack of precision in some results.
2. Balance between benefits and risks. The SR did not assess the risks associated with the intervention (early mother-newborn skin-to-skin contact). The RCT evaluating the different locations of the newborn during the nights in the hospital puerperium stay did not observe the occurrence of any adverse events. However, a higher frequency of events with potential respiratory risk was identified when the newborn was located in the same bed as the mother compared to when he/she was located in a separate cot. No differences were found in the frequency of events with potential risk of falling.
3. Costs and use of resources. No studies assessing the costs of these interventions were identified. A priori, facilitating early mother-newborn skin-to-skin contact does not seem to have a significant cost associated. In relation to the location of the baby during hospital stay, it should be assessed if there are facilities available as well as enough space in hospital rooms and the associated cost.

4. No studies evaluating the values and preferences of patients were found . Only the included RCT evaluated maternal satisfaction regarding the different locations of the newborn, with no statistically significant difference.

The direction and strength of the following recommendations were formulated considering that the interventions that facilitate skin-to-skin contact between the mother and the newborn within the first 24 hours of postpartum have a positive effect on the maintenance of breastfeeding, in reducing painful breast engorgement and enhancing cardiopulmonary stability in late preterm newborns. However, it is unclear when to start the skin-to-skin contact, how, and for how long. Moreover, the Working Group has decided to add a recommendation stating that at least during the first two hours of life a healthcare professional can monitor the skin-to-skin contact to promptly detect possible complications in the newborn. This monitoring should in no way be detrimental to perform skin-to-skin contact immediately after birth. Facilitating that the mother and her baby sleep in the same bed or in a cot by the bed of the mother during the nights of hospital puerperium stay, enables feeding attempts. However, sleeping in the same bed generates more events with respiratory potential risk to the newborn than sleeping in a cot attached or in a separate cot. Regarding the skin-to-skin contact intervention, the apparent absence of risks as well as the also apparent low cost associated, will make the recommendation be considered strong. In relation to the location of the baby during hospital stay, the low quality of the evidence and the lack of cost studies also determine the strength of the recommendations as weak.

Recommendations

Strong	Healthy babies should be placed immediately after birth, on the abdomen or breast of their mother and skin-to-skin contact should be maintained.
√	During the first two hours of life,skin-to-skin contact should be supervised by a health professional in order to identify any potential complications in the babies.
Weak	We suggest that mothers with healthy newborns, during the nights of hospital stay during the puerperium, ask to have the newborn asleep in a cradle attached (sidecar type) to the mother's bed.

6.2. Discharge and advice on care during the puerperium

Key questions:

- What are the benefits and safety of early discharge?
- What is the appropriate information and recommended care provided at the time of hospital discharge? What are the warning signs related to the mother and the newborn, which must be provided at discharge?

Benefits of early discharge

A systematic review (SR) evaluating the safety, impact, and effectiveness of early discharge in healthy women who had normal deliveries with healthy children was found. It assessed the health and maternal well-being, satisfaction with postnatal care, the costs of health care, and its impact on families. It also compared early discharge to standard care, offered in the units where the clinical trials were conducted.

The SR included 10 randomised clinical trials (RCTs) or quasi-randomised (qRCTs) (4,489 women), six of which recruited and randomised women during pregnancy, usually during the weeks 30 to 38 of gestation (Boulvain, 2004; Carty, 1990 ; Gagnon, 1997; Waldenström, 1987; Winterburn, 2000; Yanover, 1976) and the remaining four, just after childbirth (Brooten, 1994; Hellman, 1962; Sainz Bueno, 2005; Smith-Hanrahan, 1995). The follow-up periods of the various studies ranged from three weeks to six months after childbirth.

The definition of 'early discharge' differed in the different studies, depending on where it was carried out. In five of the 10 studies, usually the discharge of normal birth was given after 48 hours postpartum (Gagnon, 1997; Sainz Bueno, 2005; Waldenström, 1987; Winterburn, 2000; Yanover, 1976). In these studies, 'early discharge' was defined as that given between 6 and 48 hours after delivery. In the study by Smith-Hanrahan et al., hospital discharge was usually given at 60 hours postpartum, and 'early discharge' was defined as that given before this period (Smith-Hanrahan, 1995). In the remaining four studies, the discharge was usually given four days or more after birth, and 'early discharge' was defined as that given between 12 to less than 72 hours postpartum (Boulvain, 2004; Brooten, 1994; Carty, 1990; Hellman, 1962). One study included women who had an unscheduled caesarean section (at the risk of complications) (Brooten, 1994). The results presented below exclude this study, since the guide does not include such pregnancies.

In the son / daughter

No significant differences were found in the risk of hospital readmission between three and eight weeks postpartum in the children of mothers who were given early discharge, compared to mothers who received regular care (6 RCTs, 3313 women, RR 1.74, 95% CI 0.88 to 3.45) (Sainz Bueno, 2005; Boulvain, 2004; Smith-Hanraban, 1995; Waldenström, 1987; Yanober, 1976; Hellman, 1962).	**Very low quality**
Likewise, the women who took an early discharge, did not report significantly more problems in feeding their children than the women who received regular care (two RCTs, 2405 women, RR 0.89; 95% CI 0.43 to 1.86) (Boulvain, 2004; Hellman, 1962).	**Very low quality**

In the mother

Regarding the risk of hospital readmission between three and six weeks postpartum, no significant differences were found between women who were given an early discharge compared to women who were given regular care (7 RCTs, 3,387 women, RR 1.29, 95% CI 0.29 to 2.80) (Boulvain, 2004; Carty, 1990; Hellman, 1962; Sainz Bueno, 2005; Smith Hanrahan, 1995; Waldenström, 1987; Yanober 1976).	**Very low quality**
The proportion of women likely to develop depression one month after childbirth was not significantly higher among women who were given an early discharge compared to women who received regular care (2 RCTs, 889 women, RR 0.56; 95% CI 0.21 to 1.51).	**Very low quality**
As for breastfeeding in the first eight weeks after delivery, no significant differences were found between the groups (early discharge versus regular care) (8 RCTs, 3,895 women, RR 0.90; 95% CI 0.76 to 1.06 (Boulvain, 2004; Carty, 1990; Gagnon, 1997; Hellman, 1962; Sainz Bueno, 2005; Smith-Hanrahan, 1995; Walderström 1987; Winterburn, 2000).	**Very low quality**
The proportion of women who did not breastfeed their children six months after childbirth, was not significantly different between the comparison groups (early discharge versus regular care) (3 RCTs, 973 women, RR 0.92; 95 % 0.80 to 1.05) (Sainz Bueno, 2005; Boulvain, 2004; Waldenstörm, 1987).	**Very low quality**

The authors of the SR (Brown S, 2009) report it was not able to perform a restricted hospital readmissions analysis between 7 and 28 days after childbirth, because the studies did not give enough information to facilitate the analysis. No study included the duration of the hospitalisation of the children, or the period immediately after childbirth and before hospital discharge. Only two used validated measurement tools with known sensitivity and specificity to identify a probable maternal depression. Boulvain et al. used the Edinburgh Postnatal Depression scale (Boulvain, 2004) and Sainz Bueno used the hospital anxiety and depression scale (Sainz Bueno, 2005).

In the assessment on breastfeeding, the results include women who had not started it or had stopped at the moment of follow-up. Five of the studies did not provide details on information about how breastfeeding had been analysed (Boulvain, 2004; Hellman, 1962; Sainz Bueno, 2005; Smith-Hanrahan, 1995; Waldenström, 1987).

The following table shows the accepted criteria for early discharge to mothers and babies, collected in the document on care since birth from the National Strategy for Sexual and Reproductive Health (MSPS, 2010):

Early discharge criteria	
In the mother	In the newborn
Term pregnancy without conditions which require postpartum monitoring (hypertension, preeclampsia, gestational diabetes, Rh isoimmunisation). Vaginal delivery. Walking ability. Maternal HBsAg is known. Syphilis serology has been performed. Immediate puerperium without complications and incidents (diuresis, oral tolerance, temperature, blood pressure, no bleeding ...). Good recovery from episiotomy, if any. Absence of family, social or environmental risk (teenage mother, mental illness, lack of family support, inability of the mother in providing care to the child). Living close to (up to 20 km) referral hospital and being able to go to hospital.	Born at term. Appropriate weight for gestational age. Adequate oral feeding. Normal on clinical examination and vital signs. Absence of illness requiring hospitalisation. Ability to maintain temperature. Urination and bowel movement (meconium). No significant jaundice. Blood group, Rh and direct Coombs is known if the mother is the group O +. Extraction performed for congenital hypothyroidism. Vaccination against hepatitis B performed, as appropriate.

Summary of evidence

Very poor quality	Regarding hospital readmissions of healthy children and mothers who did not present a risk of pregnancy complications or who had no complications during childbirth, early hospital discharge showed a non-significant increased risk of readmission compared to regular care. The risk of depression (probability) showed a non-significant decrease in the group of mothers who were given early discharge compared to the group who received regular care. Likewise, a non-significant decreased risk of not breastfeeding and informing about feeding problems in the early discharge group compared to the group who received regular care was observed.

From evidence to recommendation

The strength and direction of the recommendation were established considering the following aspects:

1. Quality of the evidence. The Cochrane SR evaluating early hospital discharge compared to regular postnatal care only included few studies and with methodological limitations that hindered the detection of significant differences. One of the main limitations encountered was the heterogeneity of the definitions of 'early discharge' ranging from less than 24 hours after delivery to less than 72 hours. Several studies had a low number of participants, with the possibility of favourably including women who had no preferences over postpartum hospital stay or those who preferred shorter hospital stays. The exclusions subsequent to randomisation in the early discharge group, in studies that reported it, were relatively high (24% to 44% of women), similar to the amount of follow-up losses (30.75 to 51.4%).

2. 2. Balance between benefits and risks. In the studies found, no significant differences were observed in the diverse outcomes analysed between the groups. Favourable trends were observed in the group of early discharge for all maternal and neonatal outcomes studied, except for hospital readmissions where regular care was preferred (Brown, 2010). In all RCTs included in the Cochrane review, early discharge was accompanied by some level of support given by nurses or midwives. However, in practice this may not be the same. It is unclear the impact of this support on the safety and acceptability of early discharge programs (Brown, 2010).

3. 3. Costs and use of resources. In the analysis of the costs associated with early discharge policies compared to regular care, it is important to consider not only the hospital costs, but also those related to the support provided to the mother and her son in primary care (follow-up visits, phone calls ...) as well as those directly related to the woman and her family. An SR (Brown, 2010) identified two studies evaluating the cost of early hospital discharge versus regular care (Sainz Bueno, 2005; Boulvain, 2004). In both studies, the cost of hospitalisation was lower in the early discharge group compared to regular care. In the Spanish study, the average cost of hospitalisation in the early discharge group was $382 compared to $647 in the regular care group (Sainz Bueno, 2005). In the study by Boulvain et al., the cost of hospitalisation was 5,218 Swiss francs for the early discharge group compared to 6,772 Swiss francs for the regular care group (Boulvain, 2004). When the community cost of after-care hospital discharge is combined with the cost of maternal and neonatal readmissions, Sainz Bueno et al. stated that the costs were lower in the early discharge group compared to the regular care group ($125 versus $154, respectively) (Sainz Bueno, 2005). On the contrary, the study carried out by Boulvain et al., found that these combined costs were higher in the early discharge group compared to the regular care group (932 Swiss francs versus 481 Swiss francs respectively). This finding was mainly justified by the community after-discharge costs, which were higher in the group of early discharge (528 Swiss francs, SD = 267 versus. 234 Swiss francs, SD = 273, respectively). As for non-medical costs, Boulvain et al. compared during the first six weeks after birth, the travel costs, the childcare for siblings, and those related to the loss of income due to absence from work of either the mother or the father. They found no significant differences in these non-medical and indirect costs between groups. Finally they highlighted that the total average cost was significantly lower for the early discharge group (7,798 Swiss francs, SD = 6.419) compared to regular care group (9,019 Swiss francs, SD = 4.345) (Boulvain, 2004).

4. 4. Values and preferences of postpartum women. An SR assessed the satisfaction with postnatal care in which women were given early discharge compared to those receiving regular care (Brown, 2010), finding no significant differences between groups (3 RCTs, 841 women, RR 0,60, 95% CI 0.36 to 1.00) (Sainz Bueno, 2005; Boulvain, 2004, Waldenstörm, 1987). However, there is a great heterogeneity among the results. There are different models of postnatal care, but few take into account the preferences of the mothers and their families.In 2006, Ellegert et al. published a study of cost minimisation evaluating different models of postnatal care (early discharge, regular care, preferences of the parents) (Ellegert, 2006). They incorporated a model that took into account the preferences of the parents in the choice of postnatal care they wanted. This model included three options of care: hospital maternal unit, family room, and / or early discharge program. The family room was a place where the whole family could be the time they wanted, had a midwife who offered support and assistance during the day and a nurse was on duty overnight.Thus, women with low risk complication pregnancies and who had had healthy children, along with their

families, decided which of these different options they preferred for their postnatal care. The authors reported that this model based on the preferences of the parents was the one, which recorded lower costs. It was also stated that it was difficult to measure the satisfaction and preferences of women who had their first child, since they could not get to evaluate something different and unknown from what they had experienced so far. Ellegert et al. state that postnatal care should be safe from the medical standpoint and should incorporate the parents in the decision making process. They conclude that a postpartum care option that allows to develop and apply the parents' own care tools may be one of the most beneficial options for all (Ellbert, 2006).

The direction and strength of the following recommendation were established considering the likelihood of a lower cost of early discharge, since other factors (benefit / risk balance, values and preferences of patients), according to the evidence found, have not been key to establish it. The quality of the evidence is very low, especially given the difficulty of analysing the results due to the different definitions used for early discharge, the few studies found and the methodological limitations thereof. There is no clear balance between the benefits and risks of the intervention and there is variability in terms of the values and preferences of women, so the recommendation was made as weak.

Recommendation

Weak	We suggest providing hospital discharge within 48 hours to those women whose babies were born at term without complications, when provided a proper monitoring can be ensured.

Appropriate information and warning signs at hospital discharge

A Cochrane SR (Bryanton, 2010) evaluating the effectiveness of formal training activities on postnatal education for parents regarding the general health of babies and the relationship between parents and newborns has been identified.

This SR evaluated studies on any type of structured educational intervention aimed at training the parents on issues related to the health of the babies or the relationship between parents and newborns, performed in the first two months of the baby's life, organized in groups or individually conducted by an educator. The training activities could deal with many topics such as newborn care, food, elements aimed at preventing risks such as the baby position in the cot, or aspects related to the baby's behaviour such as crying or sleep. The workshops were aimed at mothers, fathers or both. Those activities aimed to provide training on breastfeeding or prevent postpartum depression were excluded, as well as those aimed at families with their baby admitted to an intensive care unit.The SR evaluated the impact of these formal training activities in the baby's development, its behaviour, the acquisition of knowledge and the perception of ability and confidence of the parents. The SR included 25 RCTs, of which 15 contained information related to the outcomes of interest in which 2,868 mothers and 613 fathers had taken part. From these studies, four evaluated courses on sleeping habits, thirteen on the behaviour of newborns, four for general information about the health and care of the newborn, three on issues related to the safety of babies, and one specifically aimed at improving the involvement and skills of the parents.

Additionally a recent narrative review aimed at highlighting the main aspects that should be discussed with the parents before they leave the hospital after birth has been identified (Block, 2012). This report also includes major warning signs regarding the baby. The warning signs related to the mother have been compiled from the Up-to-date literature resource (Berens, 2011).

Low quality

The studies from the SR by Bryanton (2010) assessed outcomes of very different interests related to the growth and development of the newborn associated with crying and sleep, elements aimed at preventing risks or the acquisition of knowledge and competences for its care, making it difficult to analyse the data. However, the results shown in different studies were very limited.

The result of two RCTs showed how participation in a workshop on sleeping habits contributed to a gain of approximately 29 minutes of sleep a night for 24 hours (95% CI 18.53 to 39.73). On the other hand, two other RCTs showed that participation in a workshop improved maternal knowledge about the behaviour of the babies four weeks after childbirth with a gain of 2.8 points on a scale of 10 points (95% 1.78 to 3.91). Instead, studies evaluating training activities on health after delivery, showed no significant effect on the outcomes of interest in the SR. Likewise, the only study evaluating an activity aimed at improving the training and involvement of the parents in the newborn showed very modest results with little clinical relevance and no long-term effect.

Those studies evaluating activities on preventive aspects of care to babies showed an improvement in the safe transport of babies in the vehicles after discharge (1 RCT; OR 59.18, 95% CI 2.95 to 187.72) or a better awareness of their bath temperature (1 RCT; OR 2.56, 95% CI 1.83 to 3.59).

Information about care of the baby at discharge

Other clinical practice guidelines

Furthermore, a recent narrative review has compiled the most important aspects to discuss with the parents on the care for their babies, structured by areas of interest (Block, 2012):

Position in the cot and bed sharing

Recommended puttingthe baby to sleep on its back, warning to avoid putting the baby face down since it greatly increases the risk of sudden infant death (Ponsonby, 1993; Mitchell, 1997; Thompson, 2006).

Once the parents and the newborn are at home, co-sleeping should be avoided, especially during the first weeks of life, as it increases the risk of sudden infant death (Vennemann, 2012). Avoid leaving blankets or pillows in the cot.

The use of the pacifier is controversial. Its use reduces the risk of sudden infant death (Hauck, 2005; Nelson, 2012), and on the other hand it has not shown to favour the maintenance of breastfeeding (Jaffar, 2011).

Breastfeeding

Establish breastfeeding gradually increasing feeds progressively so that the breast can adapt. Report colostrum and evolution into breast milk in the first days after childbirth. Report on the characteristics of the milk after each feeding, its duration and frequency, and advice on the appropriate spaces and environments for breastfeeding. Inform on the possibility of the baby spitting up.

Provide advice on the care of the breasts and nipples while breastfeeding lasts. Offer advice on how to prepare feeding bottles.

Development and condition of the baby

Report on the baby's growth during the first 12 weeks of life, which may lead to more demands for food.

Report on the regularity of the baby's bowel movements. Normally it can be two in the first two days but more often as the baby's feeding increases and thus the possibility of making a deposition after each feed. Warn that hard stools or with less than 48 hours are often caused by constipation and may be cause for consultation with the paediatrician.

Report on fontanelles, their features and offer advice on the care of the scalp in the first weeks of life.

Provide advice on the care of the umbilical cord until it falls.

Offer advice on the baby's everyday bath reporting on issues related to water temperature and hygiene products. Report on the skin of babies in the first weeks and its care. Report on the possibility that the skin has a yellowish colour in the first weeks.

Report on the possibility that the baby stops breathing for short periods followed by rapid breathing in the first weeks because of the process of lung maturation.

Information about care of the mother at discharge

Other clinical practice guidelines

Likewise, before discharge, the mother should be informed on a range of issues relevant to her home care (Directorate General of Public Health, 2003):

- Information on the warning signs.
- Hygiene and wound care in those mothers who have been practiced an episiotomy or caesarean section, establishing a care plan.
- Breast care and information about breastfeeding, trying to observe the woman in one of the feeds to discuss and amend incorrect positions.
- Advice on a balanced and varied diet to foster the recovery of the mother.
- Advice on progressive physical activity, daily walks, to promote the recovery of the mother's muscle tone as well as the activity in everyday life.
- Advice on sleeping habits and taking breaks
- Advice on sexuality and contraception
- Set up a visits plan to allow the follow-up of care

Information about warning signs

In a review of the literature (Berens, 2011) the key warning signs of possible complications of the mother that may require consultation with a health professional are highlighted as follows:

- Appearance of lochia with a foul odour, heavy bleeding or haemorrhage
- Fever
- A worsening or new experience of perianal or uterine pain
- Sharp pain (headaches, chest or abdominal)
- Dysuria (painful, incomplete or difficult urination)
- Problems with breasts (redness, pain, heat)
- Pain or swelling in the legs
- Mood which affects the relationship with the baby, the rest of the people or does not allow to perform a normal activity

Other clinical practice guidelines

On the other hand, the following have been highlighted as major warning signs related to the baby (Block, 2012):

- Fever
- Presence of red stools or with blood traces
- Hard stools or with less frequency after 48 hours of life
- Tanned or yellowish skin after the first few weeks of life
- The baby stops breathing for periods of more than 20 seconds
- Excessive spitting up or vomiting

It is necessary to emphasize to parents to contact healthcare professionals if they have any questions. On the other hand, it is useful to provide printed materials such as brochures or leaflets containing all this information which they can consult at home (Berens, 2011).

Summary of evidence

Low quality	There is not enough information available to assess the impact of formal educational interventions after childbirth on the health of babies or the knowledge and skills of parents. The different interventions and outcomes of interest assessed in the literature and the modest results observed do not allow highlighting any workshop format that can be of any benefit (Bryanton, 2010). Such interventions have only shown in studies with a small sample, a modest improvement in the duration of night sleep or the knowledge of the behaviour of the newborn.

It is necessary to inform the parents on a number of issues related to the care, health, and development of the baby before discharge. This information should also highlight which are the main warning signs in both the mother and the baby that may require consultation with a health professional. Providing brochures, which collect all this information, promotes the resolution of doubts after discharge

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The studies in the SR by Bryanton (2010) did not provide sufficient detail to assess their risk of bias. The multitude of interventions and outcomes assessed did not allow to know for sure if there is some form of intervention that stands out from the rest, or what results can provide any benefit. Finally, the limited size of most of the studies, affects the inaccuracy of the results.
2. Balance between benefits and risks. None of the RCTs by Bryanton (2010) assessed the possibility that adverse events or complicationsmay arise from taking part in a training workshop.
3. Costs and use of resources. The studies from the SR by Bryanton (2010) did not assess the costs of implementing these training workshops.
4. No studies examining the values and preferences of pregnant women in relation to this question were found.

The direction and strength of the following recommendations were formulated considering that the results in the literature are insufficient to recommend the establishment of formal educational interventions after delivery to improve the knowledge of parents about the health of their babies, as well as their skills and competencies, as is derived from the SR by Bryanton (2010). For this reason, a recommendation aimed at providing the information necessary for the mothers during hospitalisation is formulated. Weak recommendations arising from the absence of information to support this practice were made.

Recommendations

Weak	We suggest encouraging parents to take part in educational activities after birth, specifically targeting at their own training on issues related to health, development and relationship with their babies.
√	During hospitalisation after birth, health professionals should take advantage of routine contacts with mothers and their partners to offer useful information on baby care and warning signs in the mother or baby. Mothers and their partners should be encouraged to take this time to answer questions and express any concerns related to the care of their babies.
√	Prior to discharge, the mothers and their partners should be provided with informational materials that offer them answers to possible doubts about infant care.

6.3. Monitoring visits during the puerperium in primary care

Key Questions:

- What are the appropriate checks during the puerperium in primary care, and at what time and place should these be made? Who is the ideal professional to assist during the puerperium in primary care?

Controls and skilled professionals during the puerperium in primary care

Care model during the puerperium at discharge

The Strategy for Sexual and Reproductive Health sets out targets to provide quality healthcare in reproductive health with continuity at all levels of the National Health System (MSPS, 2011).

Among its recommendations are promoting the coordination of different assistance services and levels of care to ensure equity in the access to health care for women, and to incorporate the recommendations of the Strategy itself to the maternal and child care services portfolio. The unification of clinical practice in the care provided to the reproductive process is proposed by incorporating and adapting protocols and clinical practice guidelines, as well as the coordination between the professionals who care for pregnant women or postpartum women and their families (nurses, midwives, family medicine, emergencies, obstetrics, nursing assistants) and between the hospital and the primary or specialty care.

The CPG on care after childbirth by NICE (Demott, 2006) identified three great RCTs designed to assess care strategies, with large differences between them, in addition to the model of regular care after childbirth in the British health system (MacArthur, 2002 2003; Morrell 2000a, 2000b; Reid, 2002). Overall, the RCTs showed no remarkable health benefits for the mothers, but a benefit was observed in their emotional state and their satisfaction with the care received was better than in the model of regular care.

In an RCT 36 primary care centres in a region of the United Kingdom were randomised (2,064 participants) to an intervention in which the care was led by midwives without consultations with primary care physicians in a program that lasted three months. The midwives planned a series of visits in the homes of the women based on the assessment of the needs of women according to the EPDS scale.Four months after, the emotional and physical status of women was evaluated according to the subscales that measure these domains on the EPDS scale and SF36 respectively, in addition to assessing the satisfaction of women with the care received (MacArthur, 2002, 2003).

Two RCTs evaluated the impact of support programs after childbirth (Morrell 2000a, 2000b; Reid, 2002). One RCT evaluated the cost—effectiveness of a support program in which 623 mothers were randomised to a group that received postpartum regular care, or an additional intervention in which a midwife offered individualised support to mothers in a program with a maximum of 10 3—hour visits to their homes during the first month pregnancy. The RCT evaluated the impact of the program on the physical wellbeing of women (SF36), their risk of postpartum depression (EPDS), or the rate of breastfeeding, satisfaction with the care and the costs of participation in the program. In another RCT 1,004 Scottish women were randomised to an intervention in which they were offered participation in a weekly support group after childbirth or another group based on support from a help manual with information on the puerperium stage

(Reid, 2002). The intervention began four weeks after childbirth and was compared to the regular care model, evaluating its impact on the risk of postpartum depression (EPDS scale) or the state of emotional and physical wellbeing (SF36), and social support (SSQ6).

Moderate quality

The RCT by MacArthur (2002) (2,064 participants) did not show that taking part in a program of visits performed by the midwife up to 3 months after childbirth had an impact on the physical condition of women (difference in the physical component of SF36 : —1.17, 95% CI —2.52 to 0.19; P = 0.089). However, the emotional component scores of SF36 and the EPDS scale were better after 4 and 12 months in women who had participated in the intervention (regression coefficient after 4 months: 3.03, 95% CI 1.53 4.52; after 12 months: 2.74, 95% CI 1.48 to 4.00; P <0.00002), and were also less likely to show indicative postpartum depression scores (> 13) according to the EPDS scale (95% CI 0.43 to 0.76 OR 0.57).

The support program from the RCT by Morell (2000), did not improve the physical and emotional state of the participants compared with the results of mothers who received regular care after six weeks of follow-up (623 participants; difference in the SF36 - 1.76, 95% CI - 4.7 to 1.4; difference in the EPDS scale 0.7, 95% CI - 0.2 to 1.6). No significant differences were observed in the number of mothers breastfeeding their babies (RR 1.05, 95% CI 0.99 to 1.11 90% versus 85%). The results after six months of follow-up were similar. In another RCT evaluating an intervention support, participation in support groups or the use of a help manual showed no benefit in the physical, emotional or social wellbeing of the mother after three and six months of follow-up (Reid, 2002). In addition, poor adhesion to the support program (only 18% of women participated in this activity) limited the possibility to observe any effect of this intervention.

Moderate quality

Although the satisfaction with the care received in the RCT by MacArthur (2002), did not differ significantly between the two models compared, women who received additional care from midwives evaluated care better than expected at higher rates than those who received regular care (2,064 participants; OR 1.35, 95% CI 1.08 to 1.70). Women especially appreciated being able to discuss with midwives on their symptoms and being able to do it without difficulty. Although no numerical data were provided, the RCT by Morrell (2000) also reported that women who participated in the support program had a high level of satisfaction with the home visits carried out by the midwife.

Other clinical practice guidelines

There are within our scope care protocols that incorporate relevant aspects of puerperium care (Directorate General of Public Health, 2003; Breastfeeding Committee from the Hospital 12 de Octubre, 2011). These documents propose clinical pathways that include coordinating visits with health professionals involved in the monitoring of the woman and her baby in the puerperium period. These guidelines are developed, as in other similar clinical practice guidelines (Demott, 2006), based on clinical judgment, the professional skills required to perform the different visits and the scientific basis for maintaining and promoting the health of mothers and their babies.

The main considerations on the proposed care model for puerperium care after hospital discharge are compiled in a model that integrates home visits with a puerperium control visit which incorporates elements similar to those within the trial by MacArthur (2002), (Directorate General of Public Health, 2003).

Good clinical practice

Monitoring during the puerperium of mothers and babies who have undergone a process of pregnancy and childbirth without complications should be a continuation of the care provided in hospital. Scheduling home visits will be aimed at advising and providing the necessary assistance for both the woman and the newborn. The ability to perform this monitoring should be discussed in the last prenatal visits and be offered again at the time of discharge.

The puerperium home visits will be conducted in coordination between the care levels within primary care and the hospital ensuring the agility of transmission of relevant information between these groups involved. In the last home visit, the mother will be appointed for a visit to primary care to perform a postpartum control.

Those women who do not receive a puerperium home visit should establish a plan of visits to primary care in order to make an overall assessment of their health and receive advice on issues that may be considered necessary.

Criteria are established to assess the prioritisation of visits depending on the needs of each woman. The biological criteria are aimed at identifying the specific needs of first-time mothers, multiparous, who have given birth to twins or those who have had a premature or caesarean section delivery. On the other hand, a number of criteria are identified to assess psychosocial situations that determine the need for additional or special care (teenage mothers, with dependencies, unfavourable economic or social situation, with insufficient control during pregnancy, or who have suffered a stillbirth, and other cases affecting the normal evolution of adaptation to motherhood). The specific needs of mothers who have received an early discharge should also be taken into account.

Other clinical practice guidelines

This model proposes the creation of up to three home visits that start within the first 24 to 48 hours after discharge and are consecutively scheduled depending on the assessment made at the previous visit.

The Document on Care from Birth of the National Strategy for Sexual and Reproductive Health (MSPS, 2010) highlights the importance of establishing the first contact after discharge. The document recommends that from the maternity home the visit of the primary care matron is scheduled, or, if this service does not exist, set up an appointment with the corresponding primary care centre for the third or fourth day of life.

Puerperium control visit

Good clinical practice

The model of care at childbirth and the puerperium mentioned in the previous paragraph (Directorate General of Public Health, 2003) proposes scheduling a puerperiumcontrol visit around 40 days after childbirth, which would take place in the primary care centre, or in hospital in those cases where a more comprehensive control is required or in which any disease or condition exist that deserve a more detailed assessment.

The issues proposed to be addressed in this visit are:

- Asses the health of women and newborns.
- Assess breastfeeding.
- Assess the pelvic floor.
- Inform and train about contraception
- Assess the social and family environment.

Other clinical practice guidelines

Other documents insist on the importance of assessing the emotional state of women (Demott, 2006). The need to explore during each visit after delivery the emotional status of women, their family and social support. Likewise, coping strategies developed to address situations of daily life are emphasised. Women and their partners or relatives should be encouraged to inform healthcare professionals about any emotional change or change of mood.

This paper proposes that 10 to 14 days after childbirth it should be explored if the woman has resolved any symptoms associated with postpartum depression (crying, anxiety, and low mood) and assess the possibility of a postpartum depression if these symptoms have not disappeared.

In the puerperium control visit the health professional who performs the check must ensure that all aspects related to the physical, emotional and social well-being of women are explored.

Other clinical practice guidelines

The American College of Obstetricians and Gynaecologists (ACOG, 2007) recommends in its CPG on care after childbirth to perform a control visit between 4 and 6 weeks after childbirth, though it could be conducted previously if problems or medical or obstetric complications may arise. The visit for a mother who has had a caesarean section delivery should be performed between 7 and 14 days after delivery. It also proposes the following content for this visit.

Evaluation, exploration and controls	Information and advice
Reviewing developments since discharge. Physical examination (weight, blood pressure, abdomen, breasts). Vaccine review. Uterine involution. Wound healing. Contraception and sexuality. Breastfeeding. Adaptation to motherhood. Emotional state.	Breastfeeding. Eating habits. Postpartum depression. Link, union and adaptation with the baby Family planning. Health promotion measures

Adapted from ACOG (2007)

Summary of evidence

Other clinical practice guidelines	According to the Strategy for Sexual and Reproductive Health, the healthcare provided to women in reproductive care should ensure the continuity of the care at all levels of the Spanish NHS. The healthcare devices and levels of care should be coordinated to ensure access to care, which incorporates the recommendations from clinical practice guidelines and integrates the care provided by the professionals assisting women and their families between the different care services (MSPSI, 2011).
Moderate quality	The RCTs, which have evaluated extent programs from further care to regular care in primary care, have not shown a benefit in the physical status of mothers. However, women receiving continuity in their healthcare are more satisfied with their puerperium experience (MacArthur, 2002, 2003; Morrell, 2000a, 2000b; Reid 2002).
Moderate quality	An intervention based on the extension of puerperium care through the identification of physical and emotional health problems of mothers by a midwife, has shown an improvement in the emotional well-being of women, with greater satisfaction among the women who received care and with a favourable cost-effectiveness balance (MacArthur, 2002, 2003).
Moderate quality	Support activities after childbirth such as discussion groups, help manuals, or home visits have shown no benefit for the welfare of mothers and seem to be cost effective (Morrell, 2000a, 2000b; Reid, 2002).
Other clinical practice guidelines	Follow-up during the puerperium for mothers and babies should be a continuation of the care received at the hospital, and should be plannedin the last prenatal visits. In the case of making home visits, these will be aimed at advising and providing the necessary assistance for both the woman and the newborn, and should be planned in coordination with the different care systems. Women who do not receive home visits should establish a visit schedule to make an overall assessment of their health and that of the baby and receive the necessary advice.
Other clinical practice guidelines	A puerperium control visit should be carried out 40 days after childbirth in the primary care centre, or hospital in those cases that require a more exhaustive control. In this visit, all those aspects related to the physical, emotional and social well-being of women and newborns should be explored (Directorate General of Public Health, 2003; Demott, 2006).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The RCTs evaluated have a suitable design without major limitations in design or implementation. The quality of the evidence has decreased due to the differences between the diverse evaluated interventions that could affect the consistency of the results.
2. Balance between benefits and risks. The RCTs evaluated in this clinical question do not show complications arising from the interventions evaluated.
3. Costs and use of resources. The puerperium care extension program from the RCT by

MacArthur conducted a cost effectiveness analysis of the intervention for the British health system. The authors stated that the costs of the intervention were lower than in regular care, although the analysis of the results made it impossible to assess this with certainty. The authors described a range of costs in different primary care centres in which the intervention cost ranged between 305 and 650 £. In the home support program from the RCT by Morrell (2000) after six weeks of follow-up, the costs for the system were higher in the intervention group than in the group receiving regular care (635 versus 456 £; p = 0.001), results which remained after 6 months (815 versus 639 £; p = 0.001).

4. Values and preferences of pregnant women. The participation of women in the extended care program from the RCT by MacArthur (2002) showed greater satisfaction than expected with the care received, appreciating aspects such as the ability to communicate and the easiness to do so. Those women who participated in the support program from the RCT by Morrell (2000) also reported a high level of satisfaction with the home visits of the midwife.

The direction and strength of the following recommendations were formulated considering that the availability of some RCTs have shown greater satisfaction of women when the continuity of the care is ensured and the care model is aimed at assessing the physical and emotional health problems of women. The recommendations from other protocols and clinical practice guidelines have been incorporated. Although few studies have evaluated different care models and these have not shown a clear impact on the physical health of mothers and newborns, it is considered that the benefits provided by a model that ensures a continuity of care exceeds in any circumstances the unwanted effects of this model.

Recommendations

Strong	Ensuring continuity of care for women and babies after hospital discharge should be provided by using a model of care where the midwife coordinates the actions of the various professionals involved in the care for mothers, newborns and their families.
√	Prior to discharge the first appointment with the midwife or the Primary Care Centre should be set for the third or fourth day of life of the newborn.
√	A minimum of two visits in the first 40 days after hospital discharge should be offered, the first between 24 to 48 hours after discharge, and another one at the end of the quarantine.
√	Women should be offered the possibility of conducting home visits after discharge according to their circumstances and the evolution and characteristics of their pregnancy and childbirth. These visits are aimed at providing advice and assistance on care for women and newborns.
√	Those women who do not wish to receive home visits, should be offered the possibility to attend visits to a primary care centre or hospital for an overall assessment of their health and that of the newborn and to receive the necessary advice.
√	During each puerperium visit, the emotional status of women, their family and social support and coping strategies developed to address situations of daily life, should be explored. Likewise any emotional or attitude change should be assessed with them and their partners.

6.4. Managing common problems in the puerperium

Key Questions:

- What is the benefit of the treatments for perineal pain?
- What is the benefit of the treatments for post-dural puncture headache?
- What is the benefit of the treatments for low back pain post-dural puncture?
- What is the benefit of the treatments for constipation?
- What is the benefit of the rehabilitation of the pelvic floor muscles during the puerperium?

Treatments for perineal pain

Oral paracetamol / acetaminophen

A Cochrane SR (Chou, 2010) evaluating the efficacy of a single systemic administration of paracetamol (acetaminophen) used for the relief of acute postpartum perineal pain has been identified.

The SR by Chou (2010) included 10 trials (2,307 women) evaluating two different doses of paracetamol: five studies evaluated 500 mg to 650 mg of acetaminophen; six studies evaluated 1,000 mg of paracetamol. One study compared two doses of paracetamol (1000 mg and 650 mg) and placebo (Chou, 2010).

It was observed that women had significantly more pain relief with paracetamol compared to placebo (10 studies, 1279 women; RR 2.14, 95% CI 1.59 to 2.89). Both doses of 500 to 650 mg and 1000 mg were effective to provide more pain relief than placebo (Chou, 2010). **Low quality**

In addition, significantly fewer women needed further treatment for pain relief with paracetamol compared to placebo (8 studies; 1,132 women; RR 0.34, 95% CI 0.21 to 0.55) (Chou, 2010). **Low quality**

The studies included comparing paracetamol 500 to 650 mg versus placebo did not assess the incidence of adverse events in the mother or the newborn, and therefore no information is available about them (Chou, 2010).

The studies included using higher doses of acetaminophen (1000 mg) reported adverse events in the mother. No significant differences regarding nausea, drowsiness, stools or gastric discomfort were identified (Chou, 2010). **Low quality**

Rectal analgesia

A Cochrane SR (Hedayati, 2003) evaluating the effectiveness of analgesic rectal suppositories for pain from perineal trauma following childbirth has been identified.

The SR by Hedayati (2003) included three studies (249 women). Two of the three trials included compared diclofenac with placebo and the third study compared indomethacin with placebo (Hedayati, 2003).

Up to 24 hours after childbirth, no differences were found in the presence of pain (mild, moderate or severe) among women who received NSAID suppositories (nonsteroidal anti-inflammatory drugs) compared to placebo (2 studies, 150 women; RR 0.37, 95% CI 0.10 to 1.38), although the two individual studies reported relative risks favouring the group which underwent treatment (Hedayati, 2003). This could be explained by the limited number of events in both trials and the high heterogeneity between them (I2: 91%). **Low quality**

In the first 24 hours after childbirth, women in the group treated with diclofenac suppositories required less additional analgesia compared to placebo (1 study group; 89 women; RR 0.31, 95% CI 0.17 to 0.54). This effect was also observed after 48 hours postpartum (1 study, 89 women; RR 0.63, 95% CI 0.45 to 0.89). Although no differences remained 72 hours after childbirth (Hedayati, 2003). There is no data on the outcome of interest on the use of indomethacin suppositories. **Moderate quality**

The three trials reported that women experienced no adverse events with the use of analgesics rectal suppositories or placebo (the SR contains no quantitative results) (Hedayati, 2003). **Low quality**

Topically applied anaesthetics

A Cochrane SR (Hedayati, 2005) evaluating the effects of topical anaesthetics to relieve post-partum perineal pain during hospitalisation and after discharge has been identified.

The SR by Hedayati (2005), included eight studies (976 women), on a research up to 2007, comparing topically applied anaesthetics (lignocaine, cinchocaine and a preparation for topical hydrocortisone acetate at 1% and HCl pramoxine at 1%) to placebo, no treatment or other treatments (Hedayati, 2005).

Up to 24 hours after childbirth, no study showed statistically significant differences in pain between the group under treatment and the control group (placebo or no treatment) (3 studies; 236 women, MD -0.24, 95% CI -0.52 to 0.03) (Hedayati, 2005). **Low quality**

Two trials assessed additional analgesia administered for perineal pain. One trial found that less additional analgesia was required with epifoam (combination of hydrocortisone acetate and pramoxine hydrochloride) when compared to placebo (1 trial, 97 women; RR 0.58, 95% CI 0.40 to 0.84). However, lignocaine / lidocaine showed no difference regarding the use of additional analgesia (Hedayati, 2005). **Low quality**

In the studies no adverse events were formally measured, however, some studies reported no side effects severe enough to discontinue the treatment (Hedayati, 2005). **Low quality**

Local cooling

A Cochrane SR (East, 2012) evaluating the effectiveness and the adverse effects of localized cooling treatments (ice packs, cold gel pads, cold bath) compared to no treatment, other treatments with cold and without cold; applied to the perineum after prolonged perineal trauma during childbirth has been identified.

The SR by East (2012) included three trials comparing a cooling treatment (ice pack) versus no treatment (248 women) and two trials comparing a cooling treatment (cold gel pads) versus no treatment (284 women).

The SR also included other comparisons, two cooling treatments (ice packs versus cold gel pads) or cooling treatment versus other interventions (pulsed electromagnetic energy, witch hazel pads, pramoxine / hydrocortisone, oral paracetamol, gel packs and compression) East (2012).

Ice pack

Between 24 and 72 hours after childbirth, the women treated with ice packs had significantly fewer self-reported moderate or severe pain compared to those participants without treatment (1 study, 208 women; RR 0.61, 95% CI 0.41 to 0.91). Although these differences were not observed in terms of pain score in a smaller study (1 study, 71 women; DM -0.53, 95% CI -1.45 to 0.39; pain scale: 0 [no pain] 10 [maximum pain]) (East, 2012). **Low quality**

Between 3 and 14 days after childbirth, there were no statistically significant differences in self-reported moderate to severe pain or in terms of pain scores between the groups (East, 2012). **Moderate quality**

There were no reports on adverse events related to the ice packs (East, 2012).

Cold gel pads

Between 24 and 72 hours after delivery, no differences were observed in self-reported moderate to severe pain between the group treated with cold gel pads compared to the group without treatment (1 study, 209 women; RR 0.73, 95% CI 0.51 to 1.06). (East, 2012) Although differences were found regarding pain scores in a smaller study (1 study; 75 women; DM -1.39 95% CI 2.36 to 0.42). **Moderate quality**

Between 3 and 14 days after childbirth, no differences were observed in self-reported moderate to severe pain between the group treated with cold gel pads compared to the group without treatment (1 study, 209 women; RR 2.81, 95% CI 0.12 to 68.13). (East, 2012) Although differences were found regarding pain scores in a smaller study (1 study; 75 women; DM -1.39 95% CI 2.36 to 0.42). **Moderate quality**

There were no reports on adverse events related to cold gel pads (East, 2012).

Therapeutic ultrasound

A Cochrane SR (Hay Smith, 2000) evaluating the effects of therapeutic ultrasound for treating acute perineal pain, persistent perineal pain and / or dyspareunia after childbirth has been identified.

The SR by Hay Smith (2000) included four studies (659 women): two studies comparing ultrasound with placebo for the treatment of acute perineal pain, a study comparing ultrasound with placebo for persistent perineal pain and dyspareunia and two studies comparing ultrasound with pulsed electromagnetic energy for the relief of acute perineal pain (Hay Smith, 2000).

The number of women who showed no improvement after treatment was lower in women who had been treated with ultrasound compared to placebo (2 studies, 339 women; OR 0.37, 95% CI 0.19 to 0.69) (Hay Smith, 2000). **Low quality**

Although, no other outcome reached significance (pain from the last 24 hours to 10 days or pain from one week to three months), no differences were observed in persistent perineal pain among women treated with ultrasound compared to the group treated with placebo (Hay Smith, 2000). **Moderate quality**

None of the studies included in the SR evaluated directly the safety of therapeutic ultrasound or reported on the adverse events of the treatment (Hay Smith, 2000).

Summary of evidence

Intervention	
Low quality	Oral paracetamol is more effective than placebo in relieving the postpartum perineal pain. Women treated with both doses of paracetamol (500 mg to 650 mg - 1,000 mg) were more likely to report adequate pain relief and less likely to receive additional analgesia than women assigned to placebo. There is little information on the adverse effects reported by women receiving paracetamol for perineal pain. None of the studies reported adverse effects of paracetamol in the newborn (Chou, 2010).
Low quality	Rectal analgesia appears to be effective in reducing short-term moderate pain from perineal trauma after childbirth (within the first 24 hours) and leads to a lower use of additional analgesia until 48 hours after delivery when compared to placebo. No adverse events were reported on the use of rectal analgesia (Hedayati, 2003).
Low quality	Topically applied anaesthetics do not relieve the pain that occurs after childbirth. The use of additional analgesia for perineal pain decreases with epifoam compared to placebo. No adverse events of topically applied anaesthetics were formally assessed (Hedayati, 2005).
Moderate quality	Ice packs reduce moderate to severe self-reported perineal pain compared to no treatment within 24 to 72 hours after childbirth. The cold gel pads reduce perineal pain between 24 to 72 hours and 3 to 14 days after childbirth. There were no reports on adverse events of localized cooling treatments (East, 2012).
Moderate quality	Ultrasound treatment improved acute perineal pain after the treatment compared to placebo. No differences were observed in persistent perineal pain. No studies were reported on adverse events regarding the treatment (Hay Smith, 2000).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The quality of evidence decreased regarding the use of oral paracetamol, rectal analgesia and the use of topically applied anaesthetics for the treatment of postpartum perineal pain mainly due to issues related to the use by studies of different methods of pain measurement or the small number of events.
2. Balance between benefits and risks. Oral paracetamol (500 mg to 650 mg - 1,000 mg) is effective as an analgesic for the treatment of perineal pain after childbirth. Although the evidence is limited, there appears to be no significant increase in adverse events. Rectal analgesia can relieve the pain experienced by women because of perineal trauma and intensity of any pain within the first 24 hours after childbirth and resort less to additional analgesia within the first 48 hours. However, the effect on pain relief and the use of analgesia in the long-term is unknown. The acceptability of the rectal route of administration should be considered. There is currently limited evidence on the efficacy and safety of topically applied anaesthetics to treatperineal pain after childbirth. There is also limited evidence on the efficacy and safety of the treatment with localized cold (ice packs and cold gel pads) to relieve perineal pain after childbirth. There is currently limited evidence on the efficacy and safety of ultrasound to relieve perineal pain after childbirth.
3. No studies examining the costs and the use of resources or the values and preferences of pregnant women were identified.

The direction of the following recommendations was formulated considering that oral paracetamol is more effective than placebo in relieving the postpartum perineal pain. Rectal analgesia with NSAIDs appears to be effective in reducing short-term moderate pain from perineal trauma after childbirth (within the first 24 hours) and leads to a lower use of additional analgesia until 48 hours after childbirth when compared to placebo. The benefit-risk balance of topically applied anaesthetics localized cold therapy and therapeutic ultrasound is uncertain. Moreover, the quality of moderate to low evidence of the studies included determined the strength of the recommendations.

Recommendations

Weak	We suggest administering a dose of oral paracetamol (of 500-1000 mg every 8 to 12 hours) for perineal pain after childbirth.
Weak	We suggest administering rectal diclofenac analgesia for perineal pain during the first 48 hours after childbirth.
Weak	We suggest not treating perineal pain after childbirth with topical anaesthetics
Weak	We suggest using localized cooling treatment (ice pack and cold gel pads) as second line treatment for perineal pain after childbirth.

Treatments for post-puncture headache

Pharmacological treatment

A Cochrane SR (Basurto, 2011) evaluating the efficacy and safety of drugs for treating post-dural puncture headache (PDPH) has been identified.

The SR by Basurto (2011) included seven trials (200 participants). Six compared different drugs to placebo: oral and intravenous caffeine, oral gabapentin, intramuscular adrenocorticotropic hormone (ACTH), subcutaneous sumatriptan or oral theophylline. No trials compared the treatments of interest to conventional analgesics or NSAIDs. One study compared intravenous hydrocortisone to the conventional treatment (bed rest, hydration, paracetamol and pethidine) (Basurto, 2011).

The participants who took part in the trials were mostly women (≥140 / 159) and mainly women after childbirth with a dural puncture due to a regional anaesthesia (≥118 / 140). Three trials included men (≥19 / 159) (Basurto, 2011).

Intravenous caffeine showed a significant decrease in the proportion of participants with persistent PDPH compared to placebo one to two hours after surgery (1 study, 41 participants; RR 0.29; 95% CI 0.13 to 0.64) (Basurto, 2011).	**Very low quality**
Oral gabapentin showed a significant decrease in terms of pain scores compared to placebo, with differences in the first day (1 study, 20 participants; DM -1.60, 95% CI -1.92 to -1.28), second day (DM -2.60, 95% CI -2.87 to -2.33) and third day (MD -2.90, 95% CI -3.10 to -2.70), although the effect was not maintained after the fourth day of the intervention (Basurto, 2011).	**Low quality**
Oral theophylline showed a significant lower average of the sum of pain scores compared to placebo (1 study, 11 participants; DM -12.00, 95% CI -17.19 to -6.81)	**Low quality**

The intramuscular ACTH, oral caffeine and subcutaneous sumatriptan showed no difference in reducing pain scores compared to placebo during follow-up. **Very low quality**

The studies reported no clinically significant adverse events regarding the drugs evaluated (ACTH, oral caffeine, gabapentin or theophylline) (Basurto, 2011). **Very low quality**

Epidural blood patch

A Cochrane SR (Boonmak, 2010) evaluating the efficacy and safety of the epidural blood patch for the prevention and treatment of PDPH has been identified.

The SR by Boonmak 2010 included nine trials (379 participants). Six studies evaluated the epidural blood patch for the prevention of PDPH and three evaluated the epidural blood patch for the treatment of PDPH (two compared it to a conservative treatment and one with a sham procedure) (Boonmak 2010).

The participants from five trials were obstetric women. The remaining trials included women who had PDPH (the SR did not specify the gender of participants) (Boonmak, 2010).

The therapeutic epidural blood patch significantly reduced the presence of PDPH compared to the conservative treatment (1 study, 40 participants; OR 0.18, 95% CI 0.04 to 0.76). This difference was also observed when comparing the therapeutic epidural blood patch and a sham procedure (1 study, 12 participants; OR 0.04, CI 95% 0.00 to 0.39) (Boonmak, 2010). **Low quality**

The therapeutic epidural blood patch significantly reduced the presence of PDPH compared to the conservative treatment (1 study, 40 participants; OR 0.18, 95% CI 0.04 to 0.76). This difference was also observed when comparing the therapeutic epidural blood patch and a sham procedure (1 study, 12 participants; OR 0.04, CI 95% 0.00 to 0.39) (Boonmak, 2010). **Low quality**

The therapeutic epidural blood patch significantly decreased the intensity of headache compared to the conservative treatment (1 study, 32 participants; DM -7.10, 95% CI -7.69 to -6.51) (Boonmak, 2010). **Low quality**

Regarding adverse events, a greater number of women with the therapeutic epidural blood patch presented lumbar pain compared to placebo (1 study, 12 participants; OR 23.17, 95% CI 2.57 to 208.60) (Boonmak, 2010). **Low quality**

Summary of evidence

Intervention	
Very low quality	Intravenous caffeine reduces the number of participants with PDPH after one to two hours compared to placebo. The treatment with oral gabapentin versus placebo reported better scores in the visual analogue scale after one, two, and three days. The treatment with oral theophylline shows a lower average of the sum of pain compared to placebo. The intramuscular ACTH, oral caffeine, and subcutaneous sumatriptan showed no clinically relevant effects. There are no clinically significant adverse events related to the tested drugs (Basurto, 2011).
Low quality	The therapeutic epidural blood patch reduces the PDPH, intense PDPH, and headache intensity compared to a sham procedure. The PDPH is reduced when compared to a conservative treatment. However, the epidural blood patch produces more lumbar back pain than a sham procedure (Boonmak, 2010).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The studies available in the review by Basurto (2011) had a high risk of bias, with inaccurate results and sometimes showed limitations in the applicability of the results.
2. Balance between benefits and risks. There is limited evidence within a heterogeneous population and with a short-term assessment of the benefit and safety of the pharmacological treatment for PDPH. There is limited evidence within a heterogeneous population with a short-term assessment of the benefit and safety of the therapeutic epidural blood patch for the treatment of PDPH.
3. No studies examining the costs and use of resources or values and preferences of pregnant women were identified.

The direction of the following recommendations was formulated considering that intravenous caffeine has shown to be effective for treating PDPH as it reduces the number of participants with persistent PDPH. Gabapentin and theophylline also show a decrease in pain intensity scores compared to placebo. The intramuscular ACTH, oral caffeine, and subcutaneous sumatriptan showed no clinically relevant effects. The therapeutic epidural blood patch reduces PDPH, intense PDPH and intense headache intensity compared to a sham procedure. PDPH also reduces as compared with a conservative treatment. However, the epidural blood patch produces more back pain than a sham procedure. There is limited evidence within a heterogeneous population and with a short-term assessment of the benefit and safety of pharmacological treatments and the epidural blood patch for PDPH, which determined the strength of recommendations.

Recommendations

√	Women with persistent headache after epidural analgesia should be referred to the appropriate anaesthesiology service for proper assessment and treatment.
Weak	We suggest not administering intramuscular adrenocorticotropic hormone (ACTH), oral caffeine or subcutaneous sumatriptan for the treatment of post-LP headache.
Weak	We suggest not administering an epidural blood patch for the treatment of post-LP headache as first-line treatment.

Treatments for low back pain

Some randomised controlled trials (Howell et al., 2002; Orlikowski, 2006) and prospective cohort studies (Breen, 1994; Macarthur, 1995; Russell, 1996; Macarthur, 1997; Thompson, 2002) show no relationship between epidural analgesia during labour and back pain after childbirth (Demott, 2006; Charlier, 2012).

No studies evaluating the effectiveness of the interventions for post-dural puncture backache after childbirth have been identified.

Recommendation

√	Women with low back pain after childbirth should receive the same therapeutic treatments as the general population.

Treatments for constipation

The NICE CPG (Demott, 2006) establishes its recommendations on the management of constipation during the puerperium from the results of a Cochrane SR on interventions to treat constipation during pregnancy (Jewell, 2001).

This SR and its results are described in the question on the management of constipation during pregnancy of this CPG. The SR included one RCT conducted on 40 women comparing the intake of natural fibers (cereal flakes cookies or wheat bran) during two weeks versus not taking any food with fiber. **Moderate quality**

Women who had taken natural fibers for two weeks showed a greater increase in defecation frequency than women who had not taken any fibers (10/13 versus 9/27; OR 0.18, 95% CI 0.05 to 0.67).

This same review identified one RCT evaluating the use of intestinal motility stimulant laxatives. In this RCT 140 women received daily laxatives with the following compositions: Senna extract (Senokot 14 mg), 120 mg of a combination of dioctyl sodium sulfo succinate and 100 mg of dihydroxyanthraquinone (Normax), 10 ml with extract sterculia at 60% and frangula at 8% (Normacol standard) or 10 ml at 60% of sterculia extract alone (Normacol special). The groups compared were those treated with intestinal motility stimulant laxatives (Senokot and combination) and the two laxatives containing the sterculia extract. **Moderate quality**

The study showed that intestinal motility stimulant laxatives increased the frequency of defecation to a greater extent than sterculia extract laxatives (140 women; OR 0.30, 95% CI 0.14 to 0.61), without any differences observed in the acceptability of the treatment. Intestinal motility stimulant laxatives caused more undesired effects than the bulk-forming laxatives (56/210 versus 32/210; OR 2.08, 95% CI 1.27 to 3.41), mainly as abdominal pain, diarrhoea or nausea.

In light of these results the NICE CPG states that women who suffer from constipation during the puerperium should increase the intake of fiber and fluids, and if that does not solve the problem take a motility stimulant laxative (Demott, 2006).

An SR on the literature included in the Clinical Evidence on constipation in adults (Muller-Lissner, 2010) also highlights the high-fiber diet and osmotic laxatives (macrogol (polyethylene glycol)) as two beneficial treatments for the resolution of constipation. **Moderate quality**

When compared with a diet low in fiber or a diet without fiber, a diet high in fiber diet showed an increased frequency of defecation after three weeks. In an RCT carried out in 59 women who consulted their physician for constipation, these three types of diet were compared (Hongisto, 2006). The women in the group following a high-fiber diet showed a higher frequency of defecation after three weeks (mean difference in the frequency of defecation 0.3 per day, 95% CI 0.1 to 0.5).

The women in the group following a high-fiber diet reported a higher proportion of abdominal distension than women in the other groups during the first week of the diet (DM on symptoms, 2.1; 95% CI 1.1 to 3.0) but these symptoms disappeared later.

A trial carried out in 117 women with chronic constipation compared a diet high in fiber compared to the same diet with plenty of fluid intake (Anti, 1998). The latter caused a significant increase in the frequency of bowel movement (increase from the beginning of the trial in the weekly frequency: 2.4 times more (1.8 to 2.4) compared to 1.3 (2.0 to 3.3); p <0.001) and reduced the need for laxatives.

Moderate quality

One RCT carried out in 151 women with a frequency of 2 bowel movements per week, showed that the use of osmotic laxatives (macrogol (polyethylene glycol)) increased the frequency of bowel movement versus placebo (mean 4.5 versus 2.7 stools; p <0.001) (DiPalma, 2000). The results were virtually the same in an RCT that included 55 participants with a constipation level similar to the previous study. Osmotic laxatives taken twice daily significantly increased the frequency of bowel movements compared to placebo (mean 4.8 versus 2.8 stools; p <0.002) (Corazziari, 1996). A final RCT with crossover design carried out in 34 women who took a daily dose of macrogol also increased the frequency of bowel movements compared to placebo (weekly frequency: 13.56 versus 5.53) (Baldonedo, 1991).

Summary of evidence

Moderate quality	Diets high in fiber have shown a favourable effect on the resolution of constipation (Jewell, 2001; Muller-Lissner, 2010), which can be enhanced with an abundant fluid intake (Anti, 1998; Muller-Lissner, 2010).
Moderate quality	Intestinal motility stimulant laxatives and osmotic laxatives have shown a favourable effect on the resolution of constipation (Jewell, 2001; Muller-Lissner, 2010).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The quality of evidence has decreased due to limitations in the design of the studies considered. Although none of the evaluated studies has been performed in women during the puerperium, the consistency of the results across the studies in pregnant women and adult population does not provide arguments to believe that the results are not applicable to the target population for this guide.
2. Balance between benefits and risks. The studies evaluated in this clinical question have shown how an increase in gastrointestinal symptoms is associated with the interventions assessed when compared with placebo or no treatment, but in no case were there any serious consequences registered.
3. No studies examining the costs and use of resources or values and preferences of pregnant women were identified.

The direction of the following recommendations was formulated considering that the interventions evaluated in this section have shown a benefit in resolving constipation with some adverse events that are not serious and do not exceed their benefits. The strength of the recommendations was determined by the consistent results in different populations of interest.

Recommendations

Strong	Women with constipation in the puerperium period should be offered advice to reinforce the intake of natural fiber and fluids in their diet.
Strong	An osmotic or intestinal motility stimulant should be administered to women in whom constipation persists despite an increased intake of natural fibers and liquid laxative.

Benefits of the pelvic floor musclesrehabilitation

Training pelvic floor muscles to prevent incontinence

Good clinical practice

The birth preparation program described in the section on Pregnancy within this Guide (General Directorate of Public Health, 2009), includes from the second session (entitled 'The pregnancy and the changes it implies') to start practicing pelvic floor exercises to reduce the risk of urinary incontinence in the future. The following three exercises are recommended:

Selective contraction of the pelvic floor muscles.

Starting position: the woman sits up straight in a chair or mat, with both legs straight or in "tailor sit." She is instructed to:

1. Contract inward and upward only the pelvic floor muscles, preventing the contraction of the abdominal, abductors and buttocks. Maintain the contraction for 4 to 5 seconds.

2. Relax for 8 or 10 seconds.

3. Do 10 consecutive contractions.

Breathe freely without apnoea.

During the day, two or three repetitions of 10 contractions at different positions should be performed.

The document, which sets up this birth preparation program, emphasizes that to ensure the proper performance of the exercise, the woman should do a vaginal muscular touch before starting the training session. If this were not possible, in principle, it would be enough to assess the central fibrous core. This assessment involves placing the finger on the core and if a strong outward pressure is perceived when making the contraction, then it is a "reverse crunch" which adversely affects the pelvic floor. Consequently, pelvic floor exercises should not be performed until the correct compression and execution of the movement is proven through a touch.

Perineal and abdominal contraction

Make an abdominal inspiration followed by a prolonged expiration, while maintaining the contraction of the abdomen and the perineum for 3 seconds.

Recognising the bony pelvis and its mobility

With the help of a model reproducing the pelvis and through the exploration and pelvis of a pregnant woman, the idea is to help pregnant women to recognize the space that her child must go through at birth. The model of the pelvis will be displayed, the bones that form it and its mobility will be explained.

Training of pelvic floor muscles to treat incontinence

Two SRs evaluating the efficacy and safety of non-surgical treatments to treat urinary and / or faecal incontinence have been identified (Hay-Smith, 2008; Imamura, 2010). The Cochrane SR has been selected as it specifically includes the population and the intervention of interest (Hay-Smith, 2008).

The SR by Hay-Smith (2008) included 16 trials (6,181 women) evaluating a program on pelvic floor muscle training (PFMT) to improve the function of the pelvic floor muscles and the external anal sphincter, or both (Hay-Smith, 2008).

PFMT was defined as a program of repeated voluntary contractions of the pelvic floor muscles taught and supervised by a healthcare professional. All types of PFMT programs were considered, including the use of variations in the purpose and timing of the PFMT (for example, PFMT for strengthening, PFMT for urge suppression), ways to teach PFMT, types of contractions (rapid or sustained) and the number of contractions (Hay-Smith, 2008).

Those women following a PFMT after childbirth were about 20% less likely to have urinary incontinence compared with controls after 12 months (3 studies; RR 0.79; CI 95% 0.70 to 0.90) (Hay-Smith, 2008).	**Moderate quality**
Those women following a PFMT after childbirth were about 50% less likely to inform on faecal incontinence 12 months after childbirth (2 studies; RR 0.52, 95% CI 0.31 to 0.87) (Hay Smith, 2008).	**Moderate quality**
None of the women in the PFMT group reported adverse events (1 study) (Hay-Smith, 2008).	**Moderate quality**

Summary of evidence

Good clinical practice	During preparation for childbirth women should start practicing pelvic floor exercises to reduce the risk of urinary incontinence in the future, instructing them on how to perform selective contraction exercises of the pelvic floor muscles, perineal and abdominal contraction, and recognition of the bony pelvis and mobility (Directorate General of Public Health, 2009).
Moderate quality	Women with postnatal urinary incontinence after childbirth who performed PFMT were less likely than women who received no treatment or received usual postnatal care to report urinary incontinence 12 months after childbirth (RR 0.79, 95% CI 0.70 to 0.90). Faecal incontinence was also reduced after 12 months of childbirth: women who performed PFMT had about half the likelihood of reporting faecal incontinence (RR 0.52, 95% CI 0.31 to 0.87). No adverse events due to PFMT were observed (Hay-Smith, 2008).

From evidence to recommendation

The strength and direction of the recommendation were established considering the following aspects:

1. Quality of the evidence. The available studies show inconsistent results without having been able to identify the reasons for those losses.
2. Balance between benefits and risks. Consistent with the results of other SRs on the PFMT for the treatment of urinary incontinence in women (Hay-Smith, 2006; Imamura, 2010), it seems that PFMT is an effective treatment for urinary and faecal incontinence in women after childbirth. Although there is insufficient evidence about the effects and long-term safety.
3. No studies examining the costs and use of resources or values and preferences of pregnant women were identified.

The direction of the following recommendations was formulated considering that PFMT is an effective treatment for urinary and faecal incontinence in women after childbirth. The strength of the recommendations was determined by the quality of the evidence from studies as moderate and the balance between the benefits and risks of PFMT is favourable in the short-term.

Recommendations

Weak	We suggest that women starting the practice of pelvic floor exercises whilst preparing for childbirth to reduce the risk of urinary incontinence after delivery.
Weak	We suggest carring out a training program of pelvic floor muscles in women with urinary or faecal incontinence after childbirth.

6.5. Contraception during the puerperium

Key Questions:

- At what point can a contraceptive treatment after delivery be started?
- What special considerations should be made after delivery by type of birth control?

Starting contraception

A clinical practice guideline by the British RCOG (Royal College of Obstetricians and Gynaecologists) (FSRHC, 2009) and two systematic reviews of observational studies that evaluated the recovery of fertility after childbirth (Jackson, 2011) and a second one on the effectiveness of lactational amenorrhea as a contraceptive method were identified (van der Wijden, 2003).

The British RCOG guide (FSRHC, 2009) considered that during the first 21 days after childbirth no type of contraceptive method is required. Women who remain amenorrheic and who perform exclusive breastfeeding can avoid using contraception until 6 months after childbirth.

If a hormonal contraceptive treatment is begun after the 21 days after childbirth, pregnancy should be ruled out. Once the contraceptive therapy has been started, abstinence or using an additional method of contraception during the first 7 days, or during the first two days in the case of progestogen-only contraceptives should be recommended.

A systematic review showed the results of four observational studies that evaluated the period between childbirth, the first menstruation and ovulation in non-lactating women (Jackson, 2011). Those studies in which women received treatment to suppress lactation were excluded. The studies evaluated the date of the first menstruation through questionnaires and the first ovulation by the hormone progesterone determination or body temperature. The first menstruation occurred, on average, between 45 and 64 days and the first ovulation between 45 and 94 days after childbirth. Up to 71% of menstruations were preceded by ovulation and up to 60% were potentially fertile. **Low quality**

A Cochrane SR (van der Wijden 2003) included two case-control studies and ten uncontrolled studies that evaluated the effectiveness of lactational amenorrhea as a contraception method. **Low quality**

The pregnancy rate after 6 months in amenorrheic women with exclusive breastfeeding showed a range between 0.88% and 1.2%, depending on the definition used in the original study. The definitions were intended to rule out bleeding before 56 days after childbirth; any bleeding after childbirth separated at least 10 to 14 days from the immediate postpartum bleeding and the perception of women returning to menstruation.

The National Strategy for Sexual and Reproductive Health (MSPSI, 2011) considers the puerperium as a period in which to promote the health of women and attend to their own physical and emotional changes in that moment, providing advice, and the necessary care for their welfare.

In this sense, this period can promote a broader view of the experience of sexuality that does not focus on the coital activity. It is important that health professionals foster the creation of privacy spaces where women and their partners can address their experiences regarding sexuality, provide adequate contraceptive advice, and clarify any misconceptions about sex after pregnancy.

Types of contraception during the puerperium

No specific literature search has been carried out for this section. A narrative summary is conducted from the series by the Faculty of Sexual and Reproductive Health Care in the British RCOG (Royal College of Obstetricians and Gynaecologists). For a proper evaluation of the quality of the evidence, specific questions for each of the types of contraceptives considered appropriate in this situation should be formulated.

On the other hand, the "Medical eligibility criteria for the use of contraceptives" by the WHO provides a series of recommendations for medical eligibility criteria, different types of birth control (WHO, 2011). Although the main contraindications contained in this document are included in this section, it is advisable to inquire to tailor the decision in accordance with the characteristics and background of each woman.

Combined hormonal contraceptives (CHC)

Since the parameters of coagulation and fibrinolysis are normalized approximately 3 weeks after childbirth, combined hormonal contraceptives can be started after 3 weeks in women who do not breastfeed, provided there are no formal contraindications to the treatment.

The "Medical eligibility criteria for the use of contraceptives" according to the WHO (WHO, 2011), discouraged women who do not breastfeed their babies the use of CHCs before 21 days after childbirth, extending the period to 42 days after childbirth for women with a risk factor for venous thromboembolism. In lactating women, the use of CHCs until 6 months after childbirth should be discouraged.

The use of combined hormonal contraceptives in breastfeeding women is not contemplated in the product data sheet although the British RCOG guideline details that they can be used between 6 weeks after childbirth and up to 6 months in lactating women it should only be consider if other methods cannot be used.

Progestogen oral contraceptives

Other clinical practice guidelines

Progestogen oral contraceptives can be used any time after childbirth in both women breastfeeding and those who do not. If this type of contraceptive method is started from day 21 after childbirth, women should be advised to use extra contraception for at least 48 hours, preferably within the first 7 days.

The "Medical eligibility criteria for contraceptive use" by the WHO (WHO, 2011) indicate that lactating women may only use this method when six weeks have elapsed after childbirth, and it states no restrictions for mothers who do not breastfeed.

Injectable progestogen contraceptives

Other clinical practice guidelines

Injectables are contraindicated in "Medical eligibility criteria for contraceptive use" according to the WHO (WHO, 2011) for women who are breastfeeding for at least 6 months after childbirth, and breastfeeding women are advised not to delay the start of the method beyond 42 days after childbirth.

In women who do not perform breastfeeding, the use of medroxyprogesterone injectable contraceptives should be started during the first 5 days after childbirth. Although the use of medroxyprogesterone injectable contraceptives in breastfee-

ding women is not covered in the product data sheet, it can be started from day 21 and 6 weeks after childbirth in the case of risk of pregnancy. No other contraceptive methods can be used. The risk of bleeding, especially in the immediate postpartum period should be warned.

Progestogen contraceptive implants

Other clinical practice guidelines

The "Medical eligibility criteria for the use of contraceptives" by the WHO (WHO, 2011) indicate that lactating women can use this method after 6 weeks postpartum and in women who do not breastfeed at any time after childbirth.

Although implantable progestin contraceptives are not associated with increased bleeding, it should be noted that any case should be reported to exclude other causes.

Intrauterine devices

Other clinical practice guidelines

Given that the rate of expulsion of intrauterine devices can be higher if insertion is performed after childbirth and to reduce the risk of perforation, insertion is suggested from 4 weeks after childbirth. Its use is appropriate regardless of the type of delivery (vaginal or caesarean section) or whether breast-feeding has been performed or not. The "Medical eligibility criteria for the use of contraceptives" by the WHO (WHO, 2011) suggest no restriction on the insertion of an IUD when performed 4 weeks after childbirth. If an insertion of a device is made, before 48 hours have gone by after delivery, a levonorgestrel-releasing IUD should be avoided in women who are breastfeeding.

Women, who are going to have and IUD inserted, should be informed about expulsion signs and that, they should come to the clinic for a review or if any problems are detected.

Barrier methods

Other clinical practice guidelines

Condoms (male or female) can be used at any time after childbirth. Even in cases where another method of contraception is being used, couples should be advised of their correct use to prevent sexually transmitted diseases.

Due to the anatomical changes during the puerperium, the use of diaphragms should start 6 weeks after childbirth. If a woman wants to use this method, she should be warned that she might need to resize the diaphragm during this period. In cases in which the diaphragm will not fit correctly, she must use other contraceptive methods. The use of a diaphragm with spermicide should also be recommended.

The "Medical eligibility criteria for the use of contraceptives" by the WHO (WHO, 2011) state no contraindication for this method after childbirth.

Sterilisation

Other clinical practice guidelines

Male or female sterilisation is considered a definitive contraceptive method, for this reason detailed information on the procedure (the drawbacks and the potential risk of pregnancy) and all other appropriate contraceptive methods in each case should be provided. It should be emphasized that some methods like IUDs and contraceptive implants have a pregnancy rate similar to female sterilisation with the advantage that they are reversible. Men should be informed that vasectomy is associated with greater efficacy and fewer complications compared to tubal ligation.

Emergency methods

Other clinical practice guidelines

Emergency contraception with oral progestogens may be used after day 21 following childbirth, both in the case of women doing breastfeeding and those who do not.

Impregnated copper IUDs as emergency contraception with oral progestogens may be used during the puerperium. Therefore, women should be informed about these methods as well the non-requirement in the case of an unprotected sexual relationship before day 21 after childbirth.

Impregnated copper IUDs should not be inserted before day 28 after childbirth. In the case of an unprotected sexual relationship between day 21 and 27 after childbirth, these devices can be used between day 28 and up to 33 days after childbirth. The device can remain until the next menstrual period or be used as contraception method, without being removed and according to the type, up to 5 years.

Before indicating an emergency contraception method, the potential risks should be discussed with women in case of a still undetected pregnancy and therefore, a follow-up visit is recommended after the third week of the unprotected sexual relationship.

LAM Method

Other clinical practice guidelines

The use of breastfeeding as a protective method against unwanted pregnancy is known as the LAM method (Lactational amenorrhea method). This method can be started immediately after childbirth, and it implies the association of the following conditions:

- That breastfeeding is performed fully or virtually during the whole day and night,
- Amenorrhea,
- And less than 6 months since the last childbirth.

The guide published by the Faculty of Sexual & Reproductive Healthcare of Great Britain (Postnatal Sexual and Reproductive Health) (FSRH, 2009) recommends that women who decide to choose this method should be informed that the effectiveness of this method decreases as the frequency of breastfeeding decreases when menstruation appears or when more than 6 months after childbirth have gone by.

Summary of evidence

Low quality	Most women have their first ovulation and their first menstruation long after the first 45 days after childbirth. (Jackson, 2011)
Low quality	The pregnancy rate after 6 months for women doing exclusive breastfeeding and remain amenorrheic is less than 1.2%. (Van der Wijden 2003)
Other clinical practice guidelines	The puerperium is an opportunity for health professionals, women, and their partners to create an appropriate environment where they can address adequately the advice on contraception and their experiences about sexuality (MSPSI, 2011).

Other clinical practice guidelines	The "Medical eligibility criteria for the use of contraceptives" by the WHO provide a series of recommendations for medical eligibility criteria, designed to encourage guidance on which indications the different types of contraception have under specific circumstances (WHO, 2011).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The literature assessed in this section corresponds to observational studies and in no case has been considered to increase the quality of the evidence.
2. Balance between benefits and risks. The population of women who have no risk of transmitting or acquiring a sexually transmitted disease has been considered. Should there be any risk factors, the clinical decision should be based on choosing the most effective method to prevent the disease transmission and not based on the time until the introduction of contraceptive methods.
3. No studies examining the costs and use of resources or values and preferences of pregnant women were identified.

The direction of the following recommendations was formulated considering that the literature available shows that the vast majority of women, who do not perform breastfeeding, are infertile before 21 days. Among women doing exclusive breastfeeding and who are amenorrheic until 6 months after childbirth, the risk of pregnancy is low. This determined the strength of the recommendations.

Recommendations

√	Health professionals should promote during the puerperium, visits where aspects regarding contraceptive advice and experience of sexuality issues at this stage can be dealt with women and their partners.
√	The "Medical Eligibility Criteria for Contraceptive Use", created by the World Health Organisation (WHO) should be referred to in order to identify the most appropriate choice of contraceptive method according to the characteristics and medical history of each woman.
Strong	Women planning their future pregnancies, and who do not maintain exclusive breastfeeding should be informed about the need for contraception and the introduction of the method that best suits their situation, starting 21 days after childbirth.
Weak	In women with no risk of transmitting or acquiring a sexually transmitted infection, the lactational amenorrhea method (LAM) might apply until 6 months after childbirth if amenorrhea persists and exclusive breastfeeding is done.

6.6. Mental health during the puerperium

Key Questions:

- What are the tools with better performance in the detection of mental disorders during the puerperium?
- Does the contact of the mother with other mother networks and support groups reduce the risk of mental problems and postpartum depression?

Tools for the detection of mental disorders in the puerperium

To answer this key question, an SR on the diagnostic performance of two screening questions on postpartum depression (Mann, 2011) and a report on health technology assessment methods available to identify women at risk for postpartum depression has been assessed (Hewitt, 2009).

An SR on the literature (Mann, 2011) identified a cohort study in which the diagnostic performance of two simple questions posed to women after childbirth to discriminate the risk of postpartum depression was found. These two questions are included in the NICE CPG to detect women at risk for postpartum depression, and are formulated as follows:

– "During the last month, have you often worried because you felt down, depressed or hopeless?"

– "During the last month, have you been worried because you often felt that you had little interest in activities and that these did not provide you any pleasure?"

If the answer was yes to both questions, it is suggested to make one last question: 'Do you think this feeling needs support or help? The study included in the SR by Mann (2011) found the diagnostic performance of the two initial questions to diagnose depression, establishing as a benchmark the structured clinical interview of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) in 506 women with a mean age of 29 years old who came to their puerperium control visit.

A report on health technology assessment (Hewitt, 2009) that evaluated the methods available to identify women at risk of postpartum depression, the acceptability of these methods, their effectiveness in improving outcomes for mothers and their children was identified. It also conducted an economic evaluation of its use. This report was also assessed to answer the question about the mental disorders detection tools during pregnancy, a section whose features are described herein.

Of the 64 studies included in the SR on the performance of the methods available to detect women at risk of postpartum depression, 53 focused on assessing the risk of postpartum depression (including 10,651 women). The studies showed mostly being free of significant bias though half of them were not sufficiently explicit in describing how participants were selected in the studies, the time when the measuring instrument was administered, or if the score of the instrument assessed,was performed without knowledge of the score in the benchmark. The studies were developed over a period of 20 years in a wide number of countries and included a number of women with postpartum depression that varied between 0.3 and 76% depending on the diagnostic gold standard, which generally were the criteria from the DSM (Diagnostic and Statistical Manual).

Thirteen instruments were evaluated in these studies, but the Edinburgh Postnatal Depression Scale (EPDS) was the one that was evaluated in most studies (48). This scale has

a validated Spanish language version included in Appendix 5 (Garcia-Esteve, 2003). The rest of the evaluated instruments were: Beck Depression Inventory (BDI, 10 studies), Postpartum Depression Screening Scale (PDSS, 5 studies), General Health Questionnaire (GHQ, 4 studies), Zung's Self-rating Depression Scale (SDS, 2 studies) and the HRSD, MADRS, Raskin, SCL-90-R and EPDS- GHQ evaluated in one study each.

In 21 studies the performance of eight different tools for the diagnosis of major depression were assessed (EPDS, 18 studies; PDSS, 3; BDI, 4, and MADRS, Raskin, SCL-90-R, and Zung SDS, a study with each scale). In other 35 studies, the same tools for the diagnosis of both major and minor depression were assessed, although only 28 studies on the EPDS offered enough data to make a joint analysis of the results. The selected studies did not assess other mental disorders.

Low quality

The SR by Mann (2011) showed that the two screening questions on postpartum depression had a sensitivity of 100% (95% CI 0.79 to 1) and therefore a negative predictive value of 100% (95% 0.98 to 1) both 1 month and 9 months after childbirth. These results mean that it could be safely ruled that a woman who answered "no" to both questions suffered from postpartum depression.

However, the positive predictive value of the two questions was only 11% (95% CI 0.07 to 0.17) per month or 15% (95% CI from 0.11 to 0.19) 9 months after childbirth, meaning that up to 98% of women who replied affirmatively to the questions would be diagnosed incorrectly.

Moderate quality

The sensitivity of the instruments for the detection of major depression in women after childbirth ranged from 0.60 (95% CI 0.47 to 0.71) and 0.96 (CI 95% 0.90 to 0.98) and specificity from 0.45 (95% CI from 0.26 to 0.66) and 0.97 (95% CI 0.92 to 0.99). For an optimal cut-off diagnosis of major depression in the EPDS of 12 points, in terms of sensitivity and specificity, it was estimated that the scale had a sensitivity and specificity of 0.86 (95% CI 0.81 to 0.89) and 0.87 (95% CI 0.80 to 0.92) respectively. A sensitivity analysis showed that the tool revealed a greater capacity for discrimination when administered within the first 6 weeks after childbirth.

The measuring instruments showed a highly variable sensitivity and specificity for the detection of both minor and major depression (sensitivity between 0.31 (95% CI 0.19 to 0.47) and 0.91 (95% CI 0.80 to 0.96), specificity between 0.67 (95% CI 0.57 to 0.76) to 0.99 (95% CI 0.98 to 0.99). The optimal cut-off for diagnosing both minor and major postpartum depression within the EPDS scale was set at 10 points where the sensitivity and specificity was of 0.82 (95% CI 0.76 to 0.86) and 0.86 (95% CI 0 79 to 0.91) respectively.

Summary of evidence

Low quality	Using two simple questions after childbirth to screen postpartum depression have shown a very good result in being able to dismiss this problem in women who say no to both questions, but have a very significant proportion of false positives in women responding affirmatively (Mann, 2001).
Moderate quality	The Edinburgh Postnatal Depression Scale (EPDS) is the most evaluated scale in the diagnosis of postpartum depression, being the one that has shown better results in the detection of women with minor or major depression after childbirth (Hewitt, 2009). This scale has a validated Spanish language version included in Appendix 5 (Garcia-Esteve, 2003).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The quality of the evidence regarding the use of the two postpartum depression-screening questions has been decreaseddue to the inaccuracy of the results. The only available study that has evaluated the performance of this test simplymanagedto evaluate 33% of the participants, which can imply an unreliable estimate. The literature available on the performance of the Edinburgh Postnatal Depression Scale (EPDS) for identifying women at risk for postpartum depression is moderate quality due to the high variability between the results of the studies (I2 values greater than 70%).
2. Balance between benefits and risks. The identification of women at risk of postpartum depression can ensure the proper approach to this affective disorder resulting in an impact on women and on the relationship established with their children and their environment. No relevant side effects of a screening of these features, beyond the possible impact of the determination of false positives, were derived.
3. Costs and use of resources. The HTA report by Hewitt (2009) conducted an SR on the literature to identify economic evaluation studies, but found no studies related to this matter. The authors developed their own analytical model (Paulden, 2009). The model included the costs of the questionnaires, the treatment of women diagnosed and those resulting from the incorrect diagnosis, with data obtained from NHS reference costs sources. The analytical model was designed from Monte Carlo simulations. The study estimated a QALY of 0.8461 for regular care, 0.8468 for screening with the BDI, and 0.8461 or 0.8472 for screening with the EPDS depending on the cut-off established for the diagnosis of depression. The estimated costs were 49.29 £ for regular care, 121.51 £ for screening with the BDI, and between 73.49 and 215.05 £ for screening with the EPDS. When considering regular care as the strategy of reference, the most favourable incremental cost per QALY was, the 41.1 £ derived using the EPDS with a cut-off of 16 points (all other values ranged between 49.9 and 272.46 £). The likelihood of regular care being the most cost-effective was 87% with a reference of 20,000 £ per QALY and 58% with the reference of 30,000 £ per QALY. The authors concluded that these data did not show that regular screening was cost effective for the parameters in the NHS. Although no studies have been identified in this regard, the workload involved in regular monitoring of pregnant women and the availability of trained health personnel for proper evaluation should be assessed.
4. Values and preferences of pregnant women. The report evaluating health technologies (Hewitt, 2009a) and a subsequent publication of its results (Brealey, 2010) developed an SR on qualitative studies and observational studies to rate the acceptability of the EPDS scale among pregnant women and healthcare professionals. The results of 16 studies, synthesized from a narrative and textual approach, showed that in general the EPDS is accepted by women and healthcare professionals, although there are some factors to consider related to its administration. Women need to feel comfortable in the process of screening the risk of postpartum depression, so it is important that the test be carried out by a person who has an established link and is familiar to her. If possible, women should be given the opportunity to complete it at home. The review showed that women expressed their difficulty in responding to the last item of the instrument related to the possibility of self-injurious behaviours.

The direction of the following recommendations was formulated considering the large

number of studies that have evaluated the diagnostic performance of the EPDS and its good results regarding sensitivity. Therefore, a favourable recommendation for its use was formulated. A favourable recommendation was given on the performance of two screening questions as it has shown a negative predictive value of 100%, being a good triage tool. In relation to both opportunistic questions screening for depression, although the results of the SR by Mann (2011) showed a negative predictive value of 100% of the two questions, these were based on a single study, whichcould only evaluate a third of the initial sample of interest. The high rate of false positives caused the test to be proposed as a triage of those women who require further evaluation. The benefits that can be derived from the correct diagnosis of a woman with postpartum depression after childbirth justify the formulation of a strong recommendation for the use of the EPDS scale.

Recommendations

Weak	We suggest, after childbirth, asking to women the following question during the visits to identify the possibility of puerperal depression: "During the last month, have you often worried because you felt down, depressed or hopeless?" "During the last month, have you been worried because you often felt that you had little interest in activities and that these did not provide you any pleasure?"
Weak	We suggest not continuing with the diagnosis of postpartum depression if she says 'no' to the previous questions.
Strong	The Edinburgh Postnatal Depression Scale (EPDS, Appendix 5) should be used to confirm the diagnosis of postpartum depression in women who have answered 'yes' to the previous questions.
√	A score of over 12 points in the EPDS should be taken as a reference point for the diagnosis of postpardum depression
Weak	We suggest the use of the EPDS scale in the first six weeks after childbirth to ensure that the risk of depression in women is correctly discriminated.

Support groups during the puerperium

A Cochrane SR (Dennis, 2004) evaluating the effect of psychosocial and psychological interventions in the risk of postpartum depression has been identified.

Two additional RCTs published after the search date of the SR (PRIMS, 2006; Dennis, 2009) have also been included. The PRISM study (Lumley, 2006) is a community RCT assessing the effect of a resource, information, and support program for mothers in reducing depression and improving physical health six months after childbirth. The RCT (Dennis, 2009) evaluated the effectiveness of peer support in the prevention of postpartum depression in women at high risk.

Psychosocial interventions for preventing postpartum depression.

A Cochrane SR (Dennis, 2004) evaluated the effect of psychological and psychosocial preventive interventions compared with regular care in the risk of postpartum depression.

For this key question, the studies evaluating psychosocial interventions (8 RCTs, 5,908 participants) were taken into account. The interventions considered in this study were: antepartum and postpartum classes (3 RCTs), home visits by health professionals (2 RCTs), home visits by community postnatal support workers (1 RCT), continued hospital care (1 RCT), early postpartum

follow-up (1 RCT). While these interventions cannot be considered as strict contact between the mother and other networks of mothers and support groups, they are the only available studies evaluating the effectiveness of psychosocial interventions in preventing mental health of mothers.

Antepartum and postpartum classes versus regular care

The SR by Dennis (2004) included 2 RCTs (Brugha, 2000; Stamp, 1995) that assessed the effectiveness of antepartum and postpartum classes compared to regular care (311 participants). Both studies included women at risk of postpartum depression, so their results may not have direct application in women without risk. In the RCT (Stamp, 1995) a series of group sessions led by midwives (two sessions antepartum and one postpartum) were carried out and in the other RCT (Brugha, 2000) a trained nurse and an occupational therapist performed six antepartum classes and one postpartum session. **Very low quality**

There were no differences in the number of participants within the study with depressive symptoms between the two study groups (RR 1.02, 95% CI 0.61 to 1.72). Both studies used the same definition of postpartum depression: Stamp (1995) defined the presence of depressive symptoms from a score higher than 12 on the Edinburgh Postnatal Depression Scale (EPSD); on the other hand, Brugha (2000) used 10 as the cut-off point on the same scale.

Postpartum home visits by health professionals versus regular care

The same SR included two RCTs (1,663 women) evaluating the effectiveness of performing postpartum home visits by health professionals [(nurses in Armstrong (1999) and midwives in MacArthur (2002)]. **Low quality**

16 weeks after childbirth, it was noted that home visits reduced the risk of depressive symptoms by 32% (RR 0.68, 95% CI 0.55 to 0.84). Both studies defined the presence of depressive symptoms as a score higher than 12 on the EPDS scale.

Postpartum home visits by non-health professionals versus regular care

One RCT (Morrell, 2000; 623 participants) evaluated the effectiveness of postpartum home visits by community midwives and a community worker, with no differences being observed in depressive symptomatology (EPDS score>12) at 24 weeks postpartum between the group of women under treatment and the group receiving regular care (RR 0.89, 95% CI 0.62 to 1.27). **Very low quality**

Cxontinuing care versus regular care

One study (Waldestrom, 2000, n=1000) compared the administration of antepartum and postpartum care continuously in the hospital by a team of midwives with regular care, and no differences were found regarding depressive symptoms in mothers (RR 1 34, 95% CI 0.97 to 1.85). **Low quality**

Telephone peer support versus regular care

One RCT evaluated the effectiveness of telephone peer support in the prevention of postpartum depression. The study included 701 women in the first two weeks after childbirth who had a high risk of postpartum depression. The criterion to determine the risk of women suffering from postpartum depression was to have a score higher than 9 points in the EPDS scale between 24 and 48 hours after childbirth. The women were randomised to a control group receiving regular care or the same care with telephone contact by women volunteers who had suffered and overcome postpartum depression. Telephone contact was to be started between 48 and 72 hours after randomisation and consisted of a minimum of four telephone contacts and then the interaction was performed if it was deemed necessary. All the women included had a high risk of postpartum depression: 38% of women in the intervention group and 41% of the control group had already a score higher than 12 in the EPDS scale at the beginning of the study. It was possible to objectify the start of the intervention in 94% of the women in the intervention group.

12 weeks after childbirth, women in the intervention group were less likely to have symptoms of postpartum depression compared with the control group (percentage of women with EPDS score >12: 14% versus 25%; OR 2.1; 95% CI 1.38 to 3.20; NNT = 8). The mean EPDS score was lower in the intervention group compared to the control group: 7.93 (SD 4.68) versus 8.89 (SD 5.24).

Very low quality

After 12 weeks, women in the intervention group also had a lower risk of having a score >44 on the STAI anxiety questionnaire: 21% versus 27%; OR 1.44; 95% CI 0.99 to 2.10) but showed no differences in mean scores (35.10 (SD 11.85) versus 36.88 (SD 12.84); p = 0.08).

There were no differences in the mean score of the UCLA loneliness scale at 12 weeks postpartum between the intervention groups.

Strategies to facilitate mothers making friends

The PRISM study (Lumley, 2006) is a community RCT assessing the effect of the PRISM (Program of Resources, Information and Support for Mothers) program in reducing depression and improving the physical health of women six months after childbirth.

This study included 18,555 women from 16 rural and urban districts of the Australian state of Victoria. Each of the districts were randomised to apply or not the PRISM program. This program had objectives at primary care and community level. Among many other key strategies of the program, it emphasized the mother-to-mother support based on the principle of making friends. These strategies were not based on group participation, but to increase the chances that women make friends by gathering in places, taking part in activities where they could meet people, through a facilitator (e.g.a maternal and child health nurse) or other community groups offering mutual and reciprocal links.

The results were evaluated by questionnaires mailed after 6 months (61.6% of women in the intervention group and 60.1% in the control group replied). It was noted that this program had no effect in reducing the prevalence of postpartum depression: the proportion of women with probable depression (EPDS ≥13) was 15.7% and 14.9% (intervention and control groups, respectively) (OR 1.06, 95% CI 0.91 to 1.24). There were no differences in the mean EPDS score (6.9 (SD 0.11) versus 6.8 (SD 0.11); DM 0.08; p = 0.61).

Low quality

Summary of evidence

-	Psychosocial interventions to prevent postpartum depression. The studies available suggest that overall psychosocial interventions compared with regular care did not reduce significantly the number of women who develop postpartum depression, except intensive postpartum support provided by health professionals.
Very low quality	Antepartum and postpartum classes. The interventions in the form antepartum and postpartum classes aimed at women at high risk of postpartum depression had no effect in preventing this disease compared to regular care.
Low quality	Postpartum home visits by health professionals. Postpartum home visits by health professionals (nurses and midwives) compared to regular care reduced the risk of depressive symptoms at 16 weeks postpartum.
Very low quality	Postpartum home visits by non-health professionals. Postpartum home visits by non-health professionals had no effect in reducing postpartum depression.
Low quality	Antepartum and postpartum continuing care. The administration of antepartum and postpartum continuing care during the hospital stay by a team of midwives has not shown an effect in reducing postpartum depression compared with regular care.
Very low quality	Peer telephone support. The telephone support to mothers with high risk of postpartum depression by volunteers, who have suffered and overcome this condition, halved the risk of postpartum depression symptoms. This intervention had no effect compared to regular care in reducing anxiety or loneliness.
Low quality	Strategies to make friends. The combination of interventions in primary and community care, among which the strategies to facilitate establishing friendship among mothers stand out, were not effective in preventing postpartum depression.

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The main causes that limit the confidence in the results are on the one hand, the methodological limitations of some studies and secondly, the inaccurate results. This is due to the low number of events of the studies and the inability to combine their results due to the variability of the interventions evaluated, the populations included (women with or without increased risk of postpartum depression) as well as different diagnostic criteria applied in the different studies (despite using the same scale, EPDS, the studies disagree on the threshold for considering that there are signs of postpartum depression). It is also noteworthy that most of the available evidence is indirect and comes from studies evaluating psychosocial interventions but do not fit the definition of interventions based on the contact of mothers with other

networks of mothers or support group. In some case, the studies have included women at high risk for postpartum depression.

2. Balance between benefits and risks. No studies assessing the risks associated with interventions to facilitate contact of mothers with other networks of mothers or support groups have been identified. A priori, there appears to be no apparent risk in implementing such interventions.

3. Costs and use of resources. One study (Petrou, 2006) evaluated the cost-effectiveness of a preventive intervention aimed at women at high risk of developing postpartum depression (specific advice and support to the mother-child relationship) compared with regular care in primary care. Women in the intervention group suffered depressive symptoms for less time than women in the control group (mean 2.21 months versus 2.7 months), although the difference was not statistically significant (p = 0.41). The health and social costs were estimated at £ 2396.9 per mother-child pair in the group of preventive intervention and 2277.5 £ in the regular care group, with a mean cost difference of 119.5 £ (95% CI -535.4 to 784.9; p = 0.72). The preventive intervention resulted in no significant increase in the mean of months free of postpartum depression and in a non-significant increase in social and health costs, resulting in an incremental cost per month free of depression of 43.1 £. Assuming a willingness to pay of 1,000 £ per month free of postpartum depression, the likelihood that preventive intervention is cost-effective is 0.71.

4. Values and preferences of pregnant women. In the RCT by Dennis (2009) evaluating the effect of peer support in preventing postpartum depression, a sectional survey among the participants was conducted to describe their perceptions of the intervention received. The maternal perceptions were assessed at 12 weeks postpartum using a peer support validated assessment inventory (PSEI. Dennis, 2003). The evaluation was answered and sent by 63.3% (n = 221) of women in the intervention group. The women described a high percentage of positive relationship qualities such as trust (82.6%) and the care perceived (79.1%). Most women (80.5%) indicated that they were very satisfied with the experience of peer support. Maternal satisfaction was associated with the number and duration of the contacts.

The direction of the following recommendations was formulated considering that the psychosocial interventions, except home visits by health professionals, and the strategies to facilitate the establishment of friendships have no effect in preventing postpartum depression. It seems that peer telephone support for women who already have depressive symptoms at 24 to 48 hours postpartum reduces the risk of postpartum depression but has no effect on the scales of anxiety and loneliness. The apparent absence of risks and the values and preferences of patients are factors that are considered to make a strong recommendation. However, there are no studies assessing the cost of all the interventions and moreover, the information available from the only study identified does not show a clearly favourable cost-effectiveness ratio. This, coupled with the low quality of the evidence and the limited efficacy at a single intervention applied to women who already have depressive symptoms, determine a weak recommendation, due in part to the limited applicability of the results of the trials that included women with high risk of depression.

Recommendation

√	Puerperium support groups should be created in primary care, offering psychological support during the period and enhancing the acquisition of knowledge and skills that have already been worked on in preparation for childbirth groups during the pregnancy.

6.7. Breastfeeding

Key Questions:

- What practices favour the establishment of breastfeeding during the puerperium?
- What practices help to maintain breastfeeding during the puerperium?
- What is the most appropriate treatment for the cracks in the nipple, breast engorgement and mastitis?

Practices to promote the establishment of breastfeeding

Four SRs were identified (Ingram, 2010; Pate, 2009), of which two were Cochrane SRs (Dyson, 2007; Lumbiganon, 2011).

Lumbiganon (2011) aimed to evaluate the effectiveness of different prenatal education schemes on breastfeeding (LM) to promote its inception and continuity. The aim of the review by Dyson (2007) was to assess the effectiveness of interventions to promote breastfeeding prior to its start. This SR evaluated the results in terms of the number of women starting to breastfeed. The review by Ingram (2010) assessed the effect of prenatal care in pairs at the start of breastfeeding. The aim of the review by Pate (2009) was to determine the probability of a successful breastfeeding comparing interventions based on information technology versus face-to-face interventions.

Interventions for promoting the initiation of breastfeeding

The Review by Dyson (2007) identified 11 studies (1,553 women) evaluating the effect of the intervention in terms of the number of women who initiated breastfeeding. Nine studies were conducted in the USA, one in Australia and one in Nicaragua. Nine studies involved women with low incomes.

The interventions measured were: health education for pregnant women (5 RCTs), peer assistance (1 RCT), programs to promote breastfeeding (1 RCT), early contact with the mother and child (1 RCT).

Health education for pregnant women

A combined analysis of the results of 5 RCTs showed that compared to regular care, interventions in health education for pregnant women increase in a statistically significant way the proportion of women who start breastfeeding (5 RCTs, 582 women; RR 1, 57, 95% CI 1.15 to 2.15). The interventions assessed in these studies consisted of formal and structured activities in which women dealt with different aspects of breastfeeding. The interventions had different formats ranging from one session to longer programs of up to 4 sessions, each lasting between 15 and 40 minutes. In most cases, the workshops were led by a person skilled in breastfeeding, who tailored the sessions to the needs and concerns of women. Some of the interventions were supplemented with information leaflets.

Low quality

Taking into consideration that the results showed a moderate heterogeneity (I2 = 53.4%), two subgroup analyses were performed to assess the effect of repeating the intervention according to the needs of women, and to compare the different types of educational meetings (generic from textbooks, or lectures, formally given by an assistant, and done individually).

In both subgroup analyses,the heterogeneity disappeared. In the group of women who had repeated the intervention it was observed that they initiated breastfeeding more (two RCTs, 162 women; RR 2.40, 95% CI 1.57 to 3.66; I2 = 7%). However, no significant differences were observed when comparing different modalities in the number of women who initiated breastfeeding (3 RCTs, 420 women; RR 1.26, 95% CI 1.00 to 1.60; I2 = 0%). These results should be considered with caution due to the variability between studies (e.g. in the definitions of regular care, and the methods, content and duration of the interventions evaluated) (Dyson, 2007).

Peer assistance for women to consider breastfeeding

Compared with regular care, prenatal, perinatal and postnatal peer assistance was effective to increase the rate of initiation of breastfeeding in an RCT involving predominantly Latin women in the United States (1 RCT, 165 women; RR 2.02 95% CI 2.63 to 6.14). The peers were women from the community who had completed high school, had breastfed for sixmonths, and had received 30 hours of formal training. The support services included at least one prenatal visit at home, postpartum daily visits during hospitalisation and at least three visits at home. The study showed that women who had the role of peers had not expected adherence to the protocol, particularly in home visits (Dyson, 2007; Ingram, 2010). **Moderate quality**

Promotional packs to promote breastfeeding

One RCT compared if distributing a promotional pack designed in the hospital (with information on breastfeeding and infant development, coupons, and gifts) encouraged further the start of breastfeeding than a commercial promotional pack. The study showed no difference in the onset of breastfeeding in a group of women from middle and high income in the United States (1 RCT, 547 women; RR 0.93, 95% CI 0.80 to 1.08) (Dyson, 2007). **Moderate quality**

Immediate contact between the mother and the newborn

An RCT conducted in Nicaragua compared the impact on the start of breastfeeding to facilitate immediate contact between the mother and the newborn and subsequent separation during hospitalisation compared with regular care, without showing that this practice increased the number of women initiating breastfeeding (1 RCT, 259 women; RR 1.05, 95% CI 0.94 to 1.17) (Dyson, 2007). **Moderate quality**

In a previous section the results of the Cochrane SR by Moore (2012), which included 34 RCTs with 2,177 mother-child dyads, showing that women who performed a skin-to-skin presented better results on several variables regarding breastfeeding have been mentioned. **Moderate quality**

The number of women who performed skin contact maintained more breastfeeding up to four months after childbirth (13 RCTs, 702 participants, RR 1.27, 95% CI 1.06 to 1.53) than in the case of exclusive breastfeeding, which remained at three to six months after childbirth (3 RCTs, 149 participants, RR 1.97, 95% CI 1.37 to 2.83).

The duration of breastfeeding was also higher in women who performed a skin-to-skin contact (6 RCTs, 264 mothers – infants couples; DM 63.73 days; 95% CI 37.96 to 89.50). **Low quality**

Educational interventions based on information technologies

The review by Pate (2009) aimed to assess the impact on the establishment of breastfeeding based on information technology interventions, although some of his studies do not describe explicitly the use of these technologies. The SR identified 21 clinical trials carried out in developed countries, some of which were also included in the SR by Dyson (2007).

One RCT compared the impact on the establishment of exclusive breastfeeding in a group of US Latin women with few resources within a program including prenatal and postnatal peer advice compared to a program promoting breastfeeding without peer support, which showed a benefit in the number of women who initiated exclusive breastfeeding (1 RCT, 182 women; OR 2.9, 95% CI 1.1 to 8.0) (Pate, 2009). **Low quality**

In an RCT developed in two urban hospitals in Finland, an information and support breastfeeding online program, compared to a standard promotion program, showed an increase in the rate of initiation of breastfeeding (1 RCT, 863 women; OR 2.7, 95% CI 2.1 to 3.7). In another American RCT, a computer audio-visual and prenatal breastfeeding support intervention showed a higher rate of establishment of breastfeeding than a program of regular care (1 RCT, 993 women; OR 1.6, 95% CI 1.3 to 2, 1). The combined analysis of these studies showed a favourable impact of the breastfeeding establishment programs which take advantage of the information technology potential (OR 2.2, 95% CI 1.9 to 2.7) (Pate, 2009).

Prenatal education aimed at improving breastfeeding and its duration

The SR by Lumbiganon (2011) included 17 studies involving 7,131 women, mostly conducted in developed countries (Canada, the USA, United Kingdom. Australia). No meta-analyses were performed because each study made several comparisons: five studies compared an educational method in breastfeeding with regular care; three studies compared different educational methods with each other; seven studies compared multiple methods combined against one educational method; and one study compared different combined interventions. The breastfeeding initiation rate was analysed in five studies comparing different interventions with regular care.

A training workshop on breastfeeding did not influence the rate of initiation of breastfeeding in Hispanic women (1 RCT, 86 women; RR 1.19, 95% CI 0.97 to 1.45) (Lumbiganon, 2011). **Moderate quality**

A prenatal program that included the involvement of other parents who offered support and advice showed a significant increase in the rate of initiation of breastfeeding (1 RCT, 59 women; RR 1.82, 95% CI 1.13 to 2.93) (Lumbiganon, 2011). **Low quality**

A program that promoted both education with practical tools for breastfeeding as well as education on attitudes to breastfeeding showed no change in the rate of initiation of breastfeeding or the initiation of exclusive breastfeeding (1 RCT, 616 women; RR 1.01, 95% CI 0.98 to 1.04) (Lumbiganon, 2011). **Moderate quality**

Compared with regular maternal care, the prenatal peer support program showed no difference in the rate of initiation of breastfeeding (1 RCT, 1083 women; RR 1.11, 95% CI 0.86 to 1.43). The results were similar in one RCT comparing two types of educational programs, one promoting skills and other attitudes to breastfeeding (1 RCT, 616 women; RR 1.03, 95% CI 0.99 to 1.07). **Moderate quality**

Summary of evidence

Moderate quality	Interventions in health education and peer support can increase the number of women initiating breastfeeding. Best results have been observed in interventions based on needs expressed by women and during repeated educational sessions (Dyson, 2007).
Moderate quality	Support programs and prenatal and postnatal counselling as well as other interventions carried out through information technologies can improve the rates of initiation of breastfeeding (Pate, 2009).
Moderate quality	Given the methodological limitations, the variability among the available studies and the modest effect observed it is not possible to say that prenatal breastfeeding education programs increase the initiation or duration of breastfeeding (Lumbiganon, 2011).

From evidence to recommendation

The strength and direction of the recommendation were established considering the following aspects:

1. Quality of the evidence. The studies included in the review by Pate (2009) presented a moderate methodological quality due to losses in the follow-up and the fact that they were not blind. The studies included in the review by Dyson (2005) had limitations such as lack of blinding, loss of follow-up and heterogeneity in populations and interventions. Regarding the review by Lumbigamon (2011), most of the studies included had methodological and small effect size limitations. The variability in the design of the study has determined, in many cases, to reduce the quality of evidence due to inconsistency. The RCTs assessed have evaluated many interventions in women with very different characteristics, and have been compared with different modes of control group.
2. Balance between benefits and risks. Since there are more benefits than risks when performing interventions that promote the initiation of breastfeeding, strategies for women should be developed. Prenatal educational interventions do not generate risks to breastfeeding.
3. Costs and use of resources. An economic study (Bartick, 2012; updated by Ball, 2001), aimed at determining the impact of breastfeeding maintained for 6 months in the incidence of otitis media, necrotizing enterocolitis, gastroenteritis, hospitalisation for lower respiratory tract infections, atopic dermatitis, sudden death syndrome, asthma, leukaemia, diabetes mellitus type I and childhood obesity. The breastfeeding data were obtained from the 2005 birth cohort CDC "Disease Control and prevention." The burden of disease for each event was obtained from the "Agency for Healthcare Research and Quality." The direct and indirect costs of each disease were calculated in dollars with 2007 as the reference date. This analysis determined that if 90% of American families breastfed for 6 months, US $13 billion would be saved and 911 excess deaths would be avoided, being mostly babies (10.5 billion and 741 deaths with 80% compliance). According to the authors, the major limitation of this study was the possible inconsistencies arising from the data used to estimate the cost and duration of breastfeeding.
4. No studies examining the values and preferences of pregnant women were identified.

The direction of the following recommendation was made taking into account the clinical

benefit derived from this habit, much higher than the possible consequences of vertical transmission of infections.

Recommendation

Strong	All pregnant women should be provided with information and support for the establishment of breastfeeding.

Practices to promote the maintenance of breastfeeding

Three Cochrane SRs (Lumbiganon, 2011; Jaafar, 2011; Renfrew, 2012) were identified. The review by Lumbiganon (2011) aimed to evaluate the effectiveness of different prenatal breastfeeding education schemes to promote its inception and continuity. The aim of the review by Jaafar (2011) was to evaluate the use of pacifiers to maintain breastfeeding. The review by Renfrew (2012) assessed the effectiveness of support or assistance in maintaining breastfeeding.

Support or assistance to breastfeeding

The review by Renfrew (2012) included 52 RCTs with 54,451 pairs of mothers and babies from 21 countries. Most studies were conducted in countries with low income (49). The main limitation of the evaluated studies was that they did not describe in detail the characteristics of the intervention on the support provided to mothers, nor details on training or qualifications of the people who performedthese support tasks.

The interventions evaluated in this review consisted in contact with healthcare professionals or volunteers who offered additional support to regular care in healthcare or community centres. The support consisted of any activity related to the reinforcement of breastfeeding or mothers requiring information on the subject. These activities could be provided in groups or individually and were offered both actively or demanded by the mothers. Support was offered in person or by telephone at a single contact or a series of meetings that were carried out for several months.

Compared with regular care, support for breastfeeding showed benefit for its maintenance (both exclusive and non-exclusive) after 6 months (40 RCTs, 14,227 participants, RR 0.91, 95% CI 0.88 to 0.96). This result should be interpreted with caution due to the moderate heterogeneity of the studies (I2 = 56%), but the results remained significant when restricting the analysis to studies with a low risk of bias. The results were also significant up to nine months of follow-up. No significant differences were identified when interventions were compared depending on the number of contacts with the professional who provided the support (4 contacts, 4 to 8 contacts or more than 8 contacts) (Renfrew, 2012). Support interventions also contributed to maintaining exclusive breastfeeding after six month of follow-up (33 RCTs, 11,961 women; RR 0.86, 95% CI 0.82 to 0.91).

Moderate quality

The support of breastfeeding favoured its maintenance after 6 months regardless of who provided the care tasks (5 RCTs; 1,474 participants; RR 0.97, 95% CI 0.91 to 1.03), although the intervention appears to have a greater effect when provided by non-healthcare volunteers (9 RCTs, 3,109 participants; RR 0.85, 95% CI 0.77 to 0.93) than by health professionals (26 RCTs, 9,644 participants; RR 0.94; 95% CI 0.88 to 0.99). The results were the same when the benefit of breastfeeding support in the proportion of mothers who achieved maintaining exclusive breastfeeding was evaluated.

Moderate quality

The breastfeeding support increases the number of women who maintained exclusive breastfeeding regardless of the person providing the support (3 RCTs, 1,074 participants; RR 0.76, 95% CI 0.44 to 1.32), although the effect is stronger when assistance comes from non-healthcare volunteers (12 RCTs, 4,350 participants; RR 0.74, 95% CI 0.64 to 0.87) than when it comes from healthcare professionals (18 RCTs, 6,537 participants; RR 0 93, 95% CI 0.88 to 0.98).

The SR highlighted a greater impact on the maintenance of breastfeeding after six months when breastfeeding support is done in person (16 RCTs, 7,859 participants; RR 0.90, 95% CI 0.84 to 0.96) than by telephone (3 RCTs, 677 participants, RR 0.87, 95% CI 0.65 to 1.17); or both approaches are combined to the provision of support (21 RCTs, 5,691 participants RR 0.93; 95% CI 0.87 to 0.99), although these results showed a high heterogeneity probably explained by the variability of approaches of the support activities evaluated in the studies. **Low quality**

As in previous analyses, the results were the same for the percentage of women who achieved a maintenance of exclusive breastfeeding after six months, which was higher with a face to face breastfeeding support (17 RCTs, 7113 participants, RR 0.81, 95% CI 0.75 to 0.88) than by telephone (2 RCTs, 419 participants, RR 1.00, 95% CI 0.99 to 1.01).

The authors of the SR could not conduct a formal analysis to assess whether breastfeeding support had a greater effect when offered proactively or on demand by mothers. However, five of the studies, which considered the possibility that it was the mothers who requested support for breastfeeding, did not show significant results in terms of maintenance (Renfrew, 2012). **Very low quality**

All the aspects commented led the authors of the SR to conclude that women should be offered direct support in a series of contacts programmed and adapted to the characteristics of each mother (Renfrew, 2012). **Very low quality**

Prenatal education

The review by Lumbiganon (2011) identified 17 RCTs (7,131 participants), of which 14 contributed to the analyses (6,932 participants), mostly conducted in high-income countries (Canada, the USA, United Kingdom, Australia). Given that each of the evaluated RCTs included a comparison of different interest to other studies, it was not possible to conduct a meta-analysis.

Overall, seven studies compared educational methods in breastfeeding versus regular care. Three studies compared two educational methods with each other. In eightRCTs, a combination of multiple educational methods against one method was compared.

Educational interventions on breastfeeding versus regular care

Among the studies included in the SR by Lumbiganon (2011), an RCT compared the impact of a training workshop on breastfeeding versus regular care, without showing any benefit on the number of mothers who continued breastfeeding (1 RCT, 185 participants, RR 1.07, 95% CI 0.92 to 1.24) or exclusive breastfeeding (1 RCT, 185 participants, RR 1.08, 95% CI 0.84 to 1.38) after 3 months. There no benefit observed either after 6 months of follow-up (Kluka, 2004). **Low quality**

Another RCT compared regular care with an educational intervention aimed at providing practical skills to women and improve their knowledge and attitudes about breastfeeding in sessions lasting up to two hours (Forster, 2004). This educational model showed no benefit either when compared with regular care regarding women who maintained breastfeeding (1 RCT, 596 participants, RR 1.01, 95% CI 0.87 to 1.7), or exclusive breastfeeding after six months (1 RCT, 596 participants, RR 1.19, 95% CI 0.69 to 2.05).

Educational interventions compared with each other

The RCT by Foster (2004) showed no difference between the mothers who maintained breastfeeding after six months when the component of its intervention based on the promotion of practical skills related to breastfeeding was compared to the component based on the promotion of knowledge and attitudes on this issue (1 RCT, 596 participants, RR 1.21, 95% CI 0.87 to 1.67). **Low quality**

A small RCT (Kistin, 1990; 74 participants) comparing an intervention based on the discussion of issues related to group breastfeeding versus an individual mode, showed no difference in maintaining breastfeeding afterthree months (RR 2, 84, 95% CI 0.61 to 13.18).

One RCT compared an intervention that combined a training video with a formal educational program on breastfeeding with a simple intervention based on the dispensation of brochures (Rossiter, 1994), without finding any differences between the two methods in the number of women who kept breastfeeding after six months (175 participants, RR 1.59, 95% CI 0.86 to 2.94). Only 25% of the women who participated in the intervention combining the educational program with the video kept breastfeeding after six months, compared with 12% of women who received the training brochures. **Low quality**

A subsequent RCT evaluated the impact of adding a formal training program on breastfeeding to the regular training, without this additional aspect showing any benefit in the number of women still breastfeeding after six months (1,250 participants; RR 0.97, 95% CI 0.79 to 1.19) which was around 20% in both groups (Lavender, 2005).

A program that combined audio-visual materials (brochure and video) with the possibility to consult with a healthcare professional aspects related to breastfeeding, did not show a higher percentage of women who maintained breastfeeding after three months when compared with a group of women receiving only audio-visual materials (1 RCT, 150 participants, RR 1.29, 95% CI 0.80 to 2.06). After sixmonths, the number of women who kept breastfeeding was higher in the group that besides audio-visual materials had the ability to perform queries on this aspect (RR 2.23, 95% CI 1.01 to 4.92). Breastfeeding was maintained in 20% of the mothers of the latter group compared to 9% of mothers who had received only audio-visual materials (Mattar, 2007). The benefit was also observed when compared to the group of women who had participated in this intervention with a group of women who had received formal education after three months but not after six months.

Use of the pacifier

The review of Jaffar (2011) identified three studies that included 1,915 healthy babies including mothers with considerable motivation for breastfeeding. Two of the studies could be combined in a meta-analysis: the first was a multicentred, non-inferiority RCT that evaluated the use of pacifiers in babies, once breastfeeding had been established; the second was a double-blind RCT that evaluated whether the regular use of the pacifier was related to the end of breastfeeding at three months. The third study was not evaluated in the analysis of the results since it showed losses greater than 20% in its follow-up.

High quality

A combined analysis of the results of two RCTs showed that the use of the pacifier compared with not using it, had no effect on the proportion of babies who exclusively breastfed after three months (2 RCTs, 1,228 participants, RR 1.00 CI 95% 0.95 to 1.06) or four months (1 RCT, 970 participants, RR 0.99, 95% CI 0.92 to 1.06).

Similarly, the use of the pacifier did not affect the proportion of babieswho exclusively breastfed after three months (2 RCTs, 1,128 participants; RR 1.00, 95% CI 0.97 to 1.02) and four months (1 RCT, 970 participants, RR 1.01, 95% CI 0.98 to 1.03) (Jaffar, 2011).

Other clinical practice guidelines

Moreover, the Birth and Breastfeeding Humanisation Initiative (BFHI) was launched by the WHO and UNICEF to encourage hospitals, healthcare services, particularly maternity wards to adopt practices that protect, promote and support exclusive breastfeeding from birth. The 10 criteria for the BFHI hospitals are (BFHI, 2008):

1. Have a written breastfeeding policy that is routinely communicated to all staff.
2. Train all healthcare staff in skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.In addition to training on the most relevant aspects of breastfeeding to provide the best start of breastfeeding after childbirth.
4. Help mothers initiate breastfeeding within one half-hour after childbirth. This step is now interpreted as: place babies in skin contact with their mothers immediately after birth for at least an hour and encourage mothers to recognize when their babies are ready to breastfeed and offer help if necessary.
5. Show mothers how to breastfeed and maintain lactation, even if they should be separated from their babies.
6. Give newborn infants no food or drink other than breastmilk, unless medically indicated.
7. Practice rooming in - that is, allow mothers and infants to remain together 24 hours a day.
8. Encourage breastfeeding on demand.
9. Give no feeding bottles, teats or pacifiers to breastfeeding babies.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital (and provide the mother with breastfeeding support resources available in her area).

Summary of evidence

Moderate quality	There is enough literature to say that support for breastfeeding promotes maintenance after six months. The studies available suggest that women benefit more when supported directly by non-healthcare volunteers (e.g., other mothers) in scheduled contacts (Renfrew, 2012).
Low quality	Prenatal educational interventions to promote breastfeeding have shown a very limited effect on the maintenance of breastfeeding until the baby is six months old. Given the multitude of interventions that have been evaluated in the literature, and its modest benefit, it is not possible to know what the components of these educational strategies that may offer a greater benefit are (Lumbiganon, 2011).
High quality	The use of the pacifier has not shown to provide any benefit in maintaining breastfeeding (Jaffar, 2011).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The quality of the evidence has decreased in the section on breastfeeding support due to methodological limitations of several of the studies included in the SR by Renfrew (2012). Despite the heterogeneity shown in some of the analyses, the results have also been significant when only the studies with less risk of bias were analysed. The great variability between the studies that have assessed prenatal educational interventions for maintaining breastfeeding made it impossible to know for sure what type of intervention might offer a greater benefit. On the other hand, the RCTs assessed by Lumbiganon (2011) have generally shown a small sample affecting the accuracy of their results, reflected in estimates of the effect with very large ICs. Although the SR by Jaffar (2011) only includes two RCTs, not enough reasons have been identified to decrease the quality of the evidence.
2. Balance between benefits and risks. None of the evaluated interventions may pose a major risk for mothers or their babies, which in no case would exceed the benefit from breastfeeding.
3. No studies examining the costs and use of resources were identified.
4. Values and preferences of pregnant women. The SR by Renfrew (2012) provided some data on women's satisfaction with programs to support breastfeeding. The RCTs that evaluated this aspect showed that mothers' satisfaction with this support was high but no study showed that it was statistically significantly greater than that in their controls. When the perception of confidence of mothers with breastfeeding was evaluated, no significant difference between the groups compared was observed.

The direction of the following recommendations was formulated considering that there is enough literature to state that support for breastfeeding helps maintain breastfeeding, although it is very difficult to determine which elements of prenatal educational interventions can influence. On the other hand, there is evidence to promote the use of pacifiers as a way to improve the maintenance of breastfeeding. The quality of the evidence is sufficient to reinforce breastfeeding support interventions. Any harmful aspects of this intervention would not exceed in any case to the benefit obtained from breastfeeding. On the other hand, there is not enough information to support strong recommendations regarding the other interventions included in this clinical question.

Recommendations

Strong	All mothers should be offered support in order to maintain the duration and exclusivity of breastfeeding in the long term. Should this support be provided, it is preferable to be done individually following the 10 steps recommended by the Initiative for a more Human Birth and Lactation Care (BFHI).
Weak	We suggest providing information to mothers about the materials and educational activities available to promote breastfeeding.

Treatment of complications of breastfeeding

Two Cochrane systematic reviews (Jahanfar et al., 2010) and a document of recommendations from a systematic review from the Joanna Briggs Institute (Page, 2009) were identified. The review by Jahanfar (2010) aimed to examine the effectiveness of antibiotic therapies to relieve symptoms of breastfeeding women diagnosed with mastitis, following both clinical criteria and laboratory confirmation. The aim of the review by Mangesi (2010) was to assess the treatment for women with breast engorgement. The review by Page (2009) aimed to determine the effectiveness of the interventions when managing pain and the injuries in women's nipples during breastfeeding.

Use of antibiotics for mastitis in breastfeeding women

The review by Jahanfar (2010) included two studies of about 125 breastfeeding women with mastitis symptoms such as increased sensitivity, redness of the breasts, decreased secretion of milk or fever. One study compared the absence of treatment, the emptying of the breast and the emptying of the breast with some of the following 6-day antibiotic treatments: penicillin 500,000 IU three times a day, oral ampicillin 500 mg four times a day, or erythromycin 500 mg twice a day. The other RCT compared two antibiotics (amoxicillin against cephradine) at a dose of 500 mg orally every eight hours for seven days. Sensitivity analyses and subgroup analyses were performed. Although sensitivity analyses were planned to compare the results depending on the doses evaluated in the studies, or the reactions to the treatment of the mother or the baby, the differences among the studies did not allow a meta-analysis.

Both studies evaluated the resolution of symptoms (fever, rash, sensitivity) as the main outcome. On the other hand, one of the RCTs evaluated the maintenance of breastfeeding two weeks after the treatment had ended, and both studies evaluated other outcomes such as persistence of symptoms, problems with the secretion of milk or recurrence of infection.

Very low quality

One RCT showed that treatment with antibiotic treatment and emptying of the breast contributed to the improvement in symptoms of infectious mastitis in a significantly higher proportion (96%) than the failure to treat them (15%) (1 RCT, 110 women; RR 6.63; 95% OR 3.48 to 12.60). The results were also significant when comparing the antibiotic treatment and emptying of the breast compared to emptying of the breast only (RR 1.89; 95% OR 1.45 to 2.47).

The resolution of symptoms was faster in the group of women who received antibiotics and emptying of the breast (average of 2.1 days) than in the other two groups (emptying of the breast: average of 4.2 days; no treatment: average of 6.7 days).

The RCT comparing amoxicillin against cephradine showed no differences between the groups regarding the number of women with improvement of symptoms in the clinical trial (1 RCT, 25 women; RR 0.85, 95% CI 0.65 to 1.12), although almost all women had shown improvement after seven days of treatment. **Low quality**

None of the RCTs described that the use of antibiotics provoked adverse effects.

Treatment of breast engorgement during breastfeeding

The Cochrane SR by Mangesi (2010) identified eight studies that evaluated a wide range of treatments (acupuncture, application of cabbage leaves, cold gel packs, proteases tablets, the use of ultrasound, or subcutaneous oxytocin). The studies were performed during a much extended period and the diversity of outcomes assessed call into question the applicability of their results.

An RCT comparing an acupuncture treatment versus regular care showed no significant difference in the number of women who were prescribed antibiotics (which the authors of the SR took as a secondary outcome of women with mastitis, 210 women; RR 0.61, 95% CI 0.32 to 1.1) or in the number of women with an engorgement (RR 0.20, 95% CI 0.04 to 1.01). **Low quality**

Two other RCTs showed no difference in applying cabbage leaves versus the use of cold gel packs in the score of a pain scale, or the fact of applying a cabbage leaf chilled or at room temperature relative to women with pain. **Very low quality**

In a small RCT (59 participants) in which the administration of a protease complex (a plant enzyme) was compared with placebo, the treatment showed a higher proportion of women with an improvement in pain relief (RR 0.17, 95% CI 0.04 to 0.74) or sensitivity (RR 0.34, 95% CI 0.15 to 0.79). However, the RCT did not specify how many of the participants in the study were breastfeeding at the time when the study was conducted. **Very low quality**

An RCT evaluating the effect of applying thermal ultrasound versus a sham procedure showed no difference at end of the treatment related to pain, sensitivity or the duration of breastfeeding of the participants. The applicability of the results of this study was limited due tothe restrictedsize of the sample (109 women) and the fact that therandomisation unit was the breast and not the woman. **Very low quality**

In a study carried out on 45 women, after three days of treatment with oxytocin, further treatment was required compared to placebo, though the differences were not significant (RR 3.13, 95% CI 0.68 to 14.44). **Very low quality**

Finally, an open RCT (88 women) showed a slight decrease in the score on a pain scale after applying cold gel packs (from 1.84 (0.65) points to 1.23 points (0.68)) compared to an increase in score in the group that had not received any treatment. **Very low quality**

The NICE CPG on care during the puerperium (Demott, 2006) identified a number of preventive measures for engorgement by introducing a systematic review of community interventions to promote the duration of breastfeeding (Renfrew, 2005): early onset of breastfeeding, proper posture and skin-to-skin connection with the baby during feedings and spontaneous breastfeeding.

Expert opinion

The guide mentions another systematic review for another guide from the Ministry of Health of Singapore which highlights the following determinants for managing engorgement: ensure that the mother is comfortable to continue breastfeeding and producing milk, and ensure continued breastfeeding considering that the baby's sucking is the best way to ensure proper drainage of the breast ducts while breast milk production increases. The paper also highlights the role of massaging the breasts or stimulation for the manual ejection of milk (Singapore Ministry of Health, 2002).

Nipple pain and injury management associated with breastfeeding

The SR by Page (2009) aimed to determine the effectiveness of the interventions available to prevent or reduce the pain or nipple injuries associated with breastfeeding. The review evaluated data from 12 studies that examined a variety of non-comparable interventions, so no meta-analysis was performed. The specificity of the design of some of these studies, usually with small study samples, limits the applicability of any of its results.

One RCT compared regular training during hospitalisation to a single structured educational intervention given for 30 minutes in the first 24 hours after childbirth. Although those women who received the intervention reported less pain than the women in the control group, no significant differences were observed regarding nipple injuries.

Moderate quality

Another RCT evaluated the effectiveness of a 1-hour prenatal training session aimed at showing how to hold the baby and how to put it to prevent pain and injury to the nipple. . In this study, the mothers who participated in the training session registered lower scores on a pain scale four days after childbirth, and continued breastfeeding at a higher rate after six weeks of follow-up than women who received regular care (70 participants; RR 3.10, 95% CI 1.81 to 5.30).

A final RCT evaluated the effectiveness of a training intervention after childbirth aimed at educating mothers about the positioning of the baby during feedings when mothers were provided verbal and written information. In this trial women who received training showed less pain values on a visual analogue scale.

Several RCTs have compared the application of warm compresses, tea bags or breastmilk manually pumped to control pain and nipple trauma. Placing warm compresses has shown the best results.

Moderate quality

An RCT carried out in 73 women compared these three systems to control pain as a complement to training on breastfeeding from verbal and written information. The women were encouraged to use the system to which they had been assigned four times a day to breastfeed their babies. The group, which showed a greater decrease of pain measured with a visual scale, was the one, which used warm compresses. The results were similar in another clinical trial conducted in 65 mothers who used compresses or tea bags and thus showed a greater reduction in pain than breastmilk manually pumped.

An RCT comparing the application of chlorhexidine (0.2%) versus a placebo of distilled water in 200 mothers showed a significant reduction in the general discomfort in the group that had used chlorhexidine although no significant differences were observed in the number or the severity of the injuries which were significantly reduced in both groups. **Moderate quality**

The SR by Page (2009) did not provide sufficient evidence to support the use of polyethylene or hydrogel dressings, ointments or lanolin, collagenase or dexpantenol protective disks.

Summary of evidence

Low quality	Although two small RCTs have shown an effect of the antibiotics for the relief of symptoms caused by infectious mastitis, there is not enough information to assess the impact of this treatment (Jahanfar, 2009).
Low quality	A series of interventions assessed in humans as acupuncture, a protease complex, oxytocin, ultrasound, cabbage leaves or cold gel bags have shown no clinically relevant benefit for breast engorgement (Mangesi, 2010).
Early initiation of breastfeeding and proper acquisition of positions and connection with the baby during breastfeeding have been highlighted as two aspects that help to prevent breast engorgement (Demott, 2006). On the other hand, continued breastfeeding and breast massage or stimulation for manual pumping of milk may be two alternatives to avoid engorgement (Singapore Ministry of Health, 2002).	
Moderate quality	Despite the unavailability of sufficient evidence, participation in training activities aimed at instructing on how to hold the baby and its positioning during breastfeeding and the use of warm compresses help reduce the pain in the nipples due to breastfeeding (Page, 2009).

From evidence to recommendation

The strength and direction of the recommendations were established considering the following aspects:

1. Quality of the evidence. The studies included in the review by Jahanfar (2012) were of poor methodological quality and evaluated two very heterogeneous treatments. The small size of the sample of the two RCTs affected the imprecise results. The studies included in the review by Mangesi (2010) had serious methodological limitations and very modest results regarding the interventions evaluated. The studies of the SR by Page (2009) evaluated very heterogeneous interventions, which limits the ability to draw firm conclusions.
2. Balance between benefits and risks. The available studies on the use of antibiotics to treat mastitis show not to cause complications or significant adverse effects. The strategies to prevent or relieve engorgement according to the NICE CPG cannot be expected to cause major complications for women. This would apply equally to the interventions evaluated for pain and nipple trauma.
3. No studies examining the costs and use of resources or values and preferences of pregnant women were identified. The SR by Renfrew (2012) provided some data on women's satisfaction with the programs to support breastfeeding. The RCTs that evaluated this aspect showed that mothers' satisfaction with this support was high but it was not observed in any study that it was significantly greater from a statistical point

of view than their controls. When the perception of confidence of mothers regarding breastfeeding was evaluated, no significant differences were observed between the groups compared.

The direction of the following recommendations was formulated considering that the exact impact of using antibiotics to treat mastitis is unknown. The outcomes assessed come from two small studies with methodological limitations that evaluate very different treatments (Jahanfar, 2009). However, they have shown benefit in the treatment of infectious mastitis, without causing significant adverse effects. The strategies to relieve engorgement do not come from studies with an appropriate design that assessed their effectiveness, as they have been collected from various documents that have formulated recommendations in this regard. Finally, there are limited data on the effectiveness of interventions aimed at the management of pain or nipple trauma resulting from breastfeeding data, although the results of some RCTs support training on the positioning of the baby during breastfeeding and the use of warm compresses. The uncertainty associated with the interventions evaluated in this clinical question does not allow the formulation of strong recommendations.

Recommendations

Weak	We suggest using an antibiotic treatment and maintenance of breastfeeding with frequent voiding to solve infectious mastitis.
Weak	We suggest encouraging to Women to start breastfeeding as soon as possible to prevent complications such as engorgement or pain and injury to the nipple.
Weak	We suggest providing advice to omen with breast engorgement aboutbreastfeeding their babies frequently and on a continuous basis, with the possibility of performing massages in the breast and stimulate it for milk to be ejected manually.

Weak	We suggest offering educational activities on the position of the mother and baby during breastfeeding, signs of proper latch and effective signs of milk transfer.
Weak	We suggest using warm compresses after breastfeeding for those women who breastfeed with pain or nipple lesions .
√	At least one observation of breastfeeding should be done before hospital discharge to check it is done properly, and if there are any complications such as engorgement, sore and cracked nipple to help correct the difficulties in latching of the baby.

7.1 Number, content and timing of visits during pregnancy

Week of gestation	Medical history	Exploration	Blood tests, serologies, testing and clinical practices	Information
1st visit 6-10 fw	– Anamnesis – Risk Assessment – Gender-based violence assessment – Psychological state assessment – Review thevaccinationschedule – Eating habits assessment – Register in computerisedmedical history	– Weight*, height and body mass index (BMI) – Measure blood pressure (BP) * Individualise assessment of weight, although avoiding routine weightings in all prenatal visits.	Offer: Blood test – CBC – Urine culture – Blood type, Rh factor, indirect Coombs test. – Serology HbsAg - HIV – LUES – Rubella – Screening for Chagas disease in women from, or who have resided for a period of time in an endemicarea – Screening for gestational diabetes inwomen at high risk – Screening for Chlamydia in asymptomatic women at risk of STIs – Consider selective screening of hepatitis C in women at risk of administration of the inactivated influenza vaccineduring theflu season	– Characteristics, targets and limitations of the ultrasound-screeningtest andchromosomal abnormalities. – Dietary and hygiene measures to reduce the risk of infections (toxoplasma, cytomegalovirus) – A pregnant woman seronegative to the varicella zoster virus: avoid contact with a person affected and consult a healthcare professional in case of contact – On the risks to the foetus and newborn of certain vaccine-preventable diseases. – Lifestyles during pregnancy (eating habits, pharmacological supplements, alcohol, smoking, other addictive substances) medication, alcohol, smoking,exercise, stress, sexuality, travelling.) – Management of common problems during pregnancy

Week of gestation	Medical history	Exploration	Blood tests, serologies, testing and clinical practices	Information
11-13 fw	– Update medical history – Risk Assessment	– BP	Offer: – Screening of chromosomal abnormalities: Combined test – 1sttrimester ultrasound	– Features, targets, constraints and implications of pathological findings of ultrasound screening and chromosomal abnormalities test.
16-17fw	– Update medical history – Risk Assessment	– BP – Customise weight follow up avoiding weighing routinely in all prenatal visits	Offer: – Screening of chromosomal abnormalities: Quadruple screening only to pregnant women who have not been able to conduct a screening test in the first trimester, if available in the Healthcare Centre – The administration of diphtheria and tetanus for pregnant women without a full vaccination regimen	
20-21 fw	– Update medical history – Risk Assessment	– BP	– Ultrasound of the 2nd semester – Determination of the length of the cervix	– Features, targets, constraints and implications of pathological findings of ultrasound screening
25-26 fw	– Update medical history – Risk Assessment	– BP – Measurement of fundal height.	Offer*: – Screening for gestational diabetes of pregnant women at risk – CBC to investigate an haemoglobin level below 10.5g / 100 ml and consider iron supplements. – Determination of uric acid – Repeat the determination of HIV in women at risk – Repeat the determination of anti-Rh antibodies to Rh negative pregnant women – Administration of anti-D gamma globulin to Rh-negativepregnant women with unsensitised Rh-incompatible. * The assessment, recording and communication of results to the pregnant woman are subject to the internal organisation of the healthcare centre.	– Offer the opportunity to participate in a childbirth preparation program and start practising pelvic floor exercises – Breastfeeding: educational activities and materials: advantages, start, support and techniques.

Week of gestation	Medical history	Exploration	Blood tests, serologies, testing and clinical practices	Information
29-30 fw	– Update medical history – Risk Assessment	– BP – Measurement of fundal height.		Report on: – The possibility of alabour and childbirth plan. – Labour and pain relief methods.
34-36 fw	– Update medical history – Risk Assessment	– BP – Measurement of fundal height. – Exploration of foetal position to assess the possibility of ECV in case of breech presentation.	Offer: – Universal screening for Group B streptococcus.	
38-40 fw	– Update medical history – Risk Assessment	– BP – Measurement of fundal height.		Report on: Signs and symptoms of antepartum and, of labour and alarm signs and symptoms. – Baby care, skin-to-skin contact. – Postpartum care of the mother and advice on emotional changes – Postpartum appointments calendar
41 fw	– Update medical history – Risk Assessment	– BP – Foetal monitoring	Offer pregnant women the opportunity to induce labour after 41 weeks at the time deemed most appropriate, and before reaching week 42 of gestation.	– Report on the different methods to induce labour.

FW: follow-up week BP: Blood pressure CPG: Clinical Practice Guideline. BMI: Body Mass Index.

2. Number, content and timing of visits during the puerperium				
Puerperium period	**Intervention**	**Exploration**	**Clinical practice**	**Information and health promotion**
24 hours after childbirth - discharge	– Immediate placement of the baby on the abdomen or chest of the mother with the supervision of a healthcare professional. – Correct identification of the baby – Avoid mother-baby separation	–Physical examination of the newborn –Identify signs that can warn of any complications.	– Clean the umbilical cord with soap and water. – Administer an intramuscular dose of 1mg ofvitamin K. – In the event that parents do not accept intramuscular administration, 2 mg of vitamin K can be administered orally followed in the case of babies totally or partially breastfed by 1mg weekly up to 12 weeks of age. – Conductophthalmic topical antibiotic prophylaxis – Administer paracetamol orally (500 mg-1 g/8-12 hours) if perineal pain, with topical application of cold as second-line treatment.	– Encourage self-care of the mother and baby care – Encourage the mother-baby bonding – Provide information on baby care and warning signs. – Ensure continuity of care for the woman and her baby after discharge. – Provide advice on intake of natural fiber and fluids to prevent constipation. – Promote the practice of pelvic floor exercises. – Provide information and support for the initiation and maintenance of breastfeeding – Recommend activities and educational materials on self-care, baby care and breastfeeding.

Puerperium period	Intervention	Exploration	Clinical practice	Information and health promotion
24-48 hours after hospital discharge.	- Promote spaces in which women can address issues related to advice on contraceptive choice and identify the most appropriate contraceptive method.	– Explore the emotional state of women, her family support and coping strategies for daily life situations. – Ask questions to identify the development of a possible postpartum depression.	– Arrange the first contact with the midwife in Primary Care. – Provide home visits to provide assistance in the care of the mother and the baby – If the woman does not want home visits, provide visits in a primary care centre or hospital.	– Encourage the creation of postpartum groupsin Primary Care – Encourage self-care of the mother and baby care – Encourage the mother-baby bonding – Provide information on baby care and warning signs. – Provide advice on intake of natural fiber and fluids to prevent constipation. – Promote the practice of pelvic floor exercises. – Provide information and support for the initiation and maintenance of breastfeeding. – Recommend activities and educational materials on self-care, baby care and breastfeeding.
4-6 weeks after childbirth		– Explore the emotional state of women, her family support and coping strategies for daily life situations.		– Provide information on baby care and warning signs. – Provide information and support for the maintenance of breastfeeding. – Recommend activities and educational materials on self-care, baby care and breastfeeding.

8. Dissemination and implementation

8.1 Format of the guide, dissemination and implementations

CPGsare useful to improve the quality of care and the outcomes in people for whom they are addressed. The big challenge now is to achieve the adherence of healthcare professionals to them. For this reason, an implementation strategy aimed at overcoming the existing barriers in the environment in which they will be applied is crucial.

The dissemination and implementation strategies of the plan to put into practice the Clinical Practice Guideline on Care Pregnancy and Puerperium include the following interventions:

- Presentation of the CPG to the media by the healthcare authorities.
- Presentation of the CPG to the Directorate and Sub-directorate of Primary and Specialised Care of the different regional healthcare services.
- Institutional Presentation of the CPG in collaboration with the General Department of Quality and Cohesion of the Ministry of Health to the various scientific societies, social organisations and professionals involved.
- The materials prepared for users in order to facilitate its distribution to all healthcare professionals and, in turn, pregnant women and mothers will be highlighted in all the presentations.
- Effective and targeted distribution aimed at professional groups involved in both Primary care and Hospital care to facilitate its dissemination.
- Dissemination of this CPG in electronic form on the website of the Ministry of Health, Social Services and Equality, GUIASALUD, AETSA, the Spanish Network for Health Technology Assessment and Medical Care of the National Healthcare System (SNS), scientific societies and associations of users involved in the subject.
- Mailing of individualised copies to professionals and potential users.
- Publication of this CPG in medical journals.

For the implementation of the recommendations within this guide, the constitution of local multidisciplinary teams to assume the coordination and leadership of the process may be necessary. These teams should perform an implementation planning, in which the analysis of potential barriers and facilitators, proposals to address them according to scientific knowledge about the effectiveness of the various options as well as the design of the evaluation plan, the recommendations of the guide and the corresponding indicators to assess both the development of the process of implementation, such as the adequacy and results of clinical practices should be included.The Working Group proposed as implementation strategy for a better transfer the usual practice of healthcare professionals, the development of multicomponent interventions, as those that have shown greater effectiveness. Among the components previously described, the following should be included:

- Interactive training sessions with clinical management and target healthcare professionals.
- Review of the adequacy of clinical practices to the guide recommendations. Self-assessment of healthcare and medical history, conducted by the professional team with

the support of clinical management units to facilitate knowledge transfer and inmprove quality, providing healthcare professionals the feedback of the results from the audit.

- Inclusion of the targets and recommendations of the guide in the care protocols.

The CPG consists basically of two versions for healthcare professionals: a complete one, an abridged one, and an adapted version for pregnant women. All versions are available in HTLM format and in PDF format on the website of GuíaSalud (www.guisalud.es). The abridged version is published on paper and contains the CD-ROM with the full version.

9. Future lines of research

The proposals for future research identified in the creation process of the CPG were as follows:

9.1 Pregnancy

9.1.1 Visits and monitoring during pregnancy

Qualitative studies on the perception of pregnant women about who provides prenatal care are needed.

Lifestyles during pregnancy

Studies are needed to determine the amount of alcohol from which it can put the foetus at risk.

9.1.2 Management of common symptoms during pregnancy

Double-blind RCTs, with a longer follow-up are needed to investigate the efficacy and safety of therapeutic ultrasound for acute or persistent perineal pain after childbirth.

Qualitative studies are needed to explore how some minor symptoms during pregnancy (vomiting, heartburn, back pain) can interfere with daily activities and social relationships.

9.1.3 Managing breech pregnancy from week 35

Double-blind RCTs with larger sample sizes, high quality and a longer follow-up are needed to investigate the efficacy and safety of other treatments to increase the success rate of the external cephalic version (ECV) (foetal acoustic stimulation, regional analgesia, amnioinfusion or systemic opioids).

Double-blind RCTs with larger sample sizes, high quality and a longer follow-up are needed to investigate the efficacy and safety of alternative interventions to ECV (postural management or moxibustion).

9.2 Puerperium

9.2.1 Management of common problems during the puerperium

Therapeutic ultrasound should be used for acute or persistent perineal pain after childbirth in the context of clinical research.

9.2.2 Support groups during the puerperium

Double-blind RCTs with larger sample sizes, high quality and a longer follow-up are needed to investigate the efficacy and safety of the interventions involving the contact of mothers with other mother networks or support groups.

Appendixes

Appendix 1. Declaration of interests

The following members of the development group have declared no conflict of interests*: Longinos Aceituno, Margalida Alomar, Carmen Beltrán, Carmen Barona, Isabel Corona, Dolors Costa, Isabel Espiga, Manuel Fillol, Laura García, Juliana Ester Martín, Dolores Martínez, Ángela Elisabeth Müller, Ibone Olza, Marta Parra, Ivan Solà, Carmen Tejero, Rosario Quintana y Casilda Velasco.

Yolanda Martin Seco has declared to have a close family member (partner) related to the pharmaceutical company GSK.

Rafael Torrejón states having received funding for clinical trials but not personally linked to the Fundación Seville (Hospital Universitario Virgen del Rocío de Seville), which are not related to the issue addressed by this guide.

*In the methodological materials, available both on the web page GuíaSalud as in AETSA, and which presents in detail the information with the methodological process of this CPG, the standard form used is included to facilitate the collection of the declaration of interests.

Appendix 2. Rating the quality of evidence and grading of the strength of the recommendations through the GRADE system

When formulating recommendations, the guide development group should consider to what extent they can rely on the fact that carrying out a recommendation will bring more advantages than disadvantages. This decision is not easy and is influenced by multiple factors that make this stage one of the most complex in the preparation of a guide.

The formulation systems to make recommendations were proposed more than two decades ago. These systems already differed initially the level of scientific evidence (the adaptation of different study designs to answer different types of questions) on the strength of the recommendations. Since then, the different systems have evolved and incorporated other aspects beyond the design of the studies and which must be taken into account when making recommendations.

To rate the quality of the evidence and grade the strength of the recommendations, the guidelines by the GRADE Working Group have been followed. This Working Group seeks to establish a method of making explicit and transparent recommendations, which are easily handled by the CPG Working Groups, in order to overcome the drawbacks of other systems that make recommendations (Guyatt, 2008a, 2008b, 2011a).

The main steps in the GRADE system (*Grading of Recommendations Assessment of Development and Evaluation*) are described below:

A) Rating the quality of the evidence

Grading the quality of the evidence is performed for each of the outcomes of interest relevant to the decision making and therefore for every clinical question it is possible that various outcomes of interest reflect a classification of different quality (Guyatt, 2011b). Initially, it is considered that the RCTs have a "high quality" and the observational studies have a "low quality." However, a number of aspects that can decrease the quality of the RCTs or that may increase it in the case of the observational studies are suggested. The quality of the evidence is rated as high, moderate, low or very low (Balshem, 2011). The quality of the evidence presented in the right margin of the text of the guide is suitably modified if the classification of the evidence changes for any other outcome of interest is discussed in the summary of the evidence. In rating the overall quality of the evidence, the development group has considered:

- The relevant variables in the decision making process.
- When these have shown inconsistent results (for a benefit or harm) the overall quality as the lowest among the different variables has been considered.
- When these have shown a consistent result (for a benefit or a harm) the overall quality as the highest among the different variables has been considered.
- When these have shown a consistent result but the balance between benefits and adverse effectsis uncertain the overall quality and the lowest among the different variables has been considered.

The following aspects have been considered to reduce the quality of the RCTs (Balshem, 2011):

- **Limitations in the design or implementation of the RCT:** such as the lack of concealment

of randomisation of the sequence, improper masking, severe losses, lack of analysis due to an intention to treat, study completion earlier than planned for beneficial reasons.

- **Inconsistent results:** discrepant estimates of the effect of a treatment (heterogeneity or variability in the results) on available studies suggest real differences in these estimates. These may be due to differences in the population, the intervention, the outcomes of interest or the quality of the study. Where there is unexplained reasonable heterogeneity, the quality decreases.
- **Absence of direct scientific evidence:** the absence of direct comparisons between two treatments (each treatment compared with placebo, but not between them) or extrapolating the results of a study of a particular drug to other drugs belonging to the same family in the absence of a demonstrated effect of class, is also considered indirect evidence. Often there are large differences between the population on which the recommendations are implemented and included in the studies evaluated. Finally, the aspects of the potential applicability in our environment or the external validity of the available scientific evidence should also be taken into consideration.
- **Inaccuracy:** if the available studies include relatively few events and few women and therefore have wide confidence intervals, the quality decreases.
- **Reporting bias:** the quality can decrease if there is a reasonable doubt about whether the authors have included or not all studies (e.g., publication bias in the context of an SR) or if the authors have included or not all the relevant outcome variables (outcome reporting bias).

On the other hand, when observational studies have been evaluated, a number of factors that can increase their quality have been taken into account:

- **Important effect:** when the observed effect shows a consistent strong association (RR>2 or <0.5) or very strong (RR>5 or <0.2) and, based on studies without confounding factors. On these occasions,the quality can be considered as moderate or even high.
- The presence of a gradient-dose response.
- Situations in which all potential confounding factors could have reduced the observed association. In cases where women receiving the intervention of interest have a worse prognosis and still have better outcomes than the control group, it is likely that the actual observed effect is greater.

The members of the development group have worked in different clinical questions which included the summary of the available evidence for each of the questions, and in which a reasoned justification of the main aspects that have changed the quality of the evidence has been included. Also as an appendix to this justification some GRADE tables summarizing the findings in the literature available for each outcome of interest have been included, and the detailed aspects and reasons which have changed the quality of evidence have been synthesized (Guyatt 2011c).

B) Grading the strength of the recommendations

The strength of recommendations informs us to what extent conducting a recommendation carries more benefits than harm in women. There are several factors to be considered in the grading of recommendations (Guyatt, 2008b; Brożek, 2011):

- **Balance between benefits and risks:** To make a proper assessment of the balance between benefits and risks it is necessary to consider the baseline risk of the population to which

the recommendation is addressed, and the effect in both relative and absolute terms.

- **Quality of scientific evidence:** Before performing a recommendation, it is necessary to know the certainty of the estimate of the observed effect. If the quality of the scientific evidence is not high, although the magnitude is important, the confidence should diminish and therefore the force with which to conduct a recommendation.
- **Values and preferences:** the uncertainty about the values and preferences of the target population that are addressed in the CPG is another factor to be taken into account. Healthcare professionals, the group of women or society in general should see their values and preferences that should influence when grading the recommendations.
- **Costs:** unlike other outcome variables, the costs are much more variable over time, in different geographical areas and according to various implications. Thus, although a high cost reduces the probability to grade the recommendation as strong, the context will be critical in the final assessment.

When grading the strength of the recommendations two categories are considered: strong and weak recommendations.

In strong recommendations, the guideline development group is confident that the benefits outweigh the adverse effects or vice versa, that the adverse effects outweigh the benefits. In the first case, the recommendation is strongly in favour. In the second one, it is strongly against. The recommendation is presented with the expression 'is recommended'.

Weak recommendations may also be in favour or against. One recommendation is weak in favour when the development group concluded that the beneficial effects of carrying out the recommendation probably outweigh the detrimental ones, although it is not completely sure. However, the recommendation is weak against, when the adverse effects are likely to outweigh the benefits. The recommendation is presented with the expression 'can be assessed' or 'should'.

For the interventions with no available evidence and for which the development group wants to highlight a particular aspect, there are a number of recommendations based on the clinical experience and the consensus of the development group, which have been identified with the √ symbol.

The members of the development group have formulated the recommendations from the working papers discussed previously in which for each clinical question a summary of the evidence and justification for the classification of the quality of evidence has been included. This working document also included a section in which issues identified in the literature regarding the factors to be taken into account in the grading of the recommendations are discussed. Moreover, the recommendations are headed with a section in which both aspects determining both the direction and the strength of recommendations are justified. All these papers were distributed among the components of the development group for consideration and review, and the final wording of the recommendations was adopted in a series of workshops held at different times of the process.

Appendix 3. Tables

Table 1. Maternal risk factors associated with risk of stillbirth

Factors	Prevalence	Proportion of intrauterine foetal deaths	OR
All pregnancies		6.4/1.000	1.0
Low-risk pregnancies	80 %	4.0-5.5/1.000	0.86
Hypertensive disorders			
Chronic hypertension	6 % - 10 %	6 - 25/1.000	1.5 - 2.7
Pregnancy-induced hypertension:			
- Average	5.8 % 7.7 %	9 - 51/1.000	1.2 - 4.0
- Severe	1.3 % - 3.3 %	12 - 29/1.000	1.8 - 4.4
Diabetes			
Treatment with diet	2.5 % - 5 %	6 - 10/1.000	1.2 - 2.2
Treatment with insulin	2.4 %	6 - 35/1.000	1.7 - 7.0
Systemic lupus erythematosus	<1 %	40 - 150/1.000	6 - 20
Kidney disease	<1 %	15 - 200/1.000	2.2 - 30
Thyroid disorders	0.2 % - 2 %	12 - 20/1.000	2.2 - 3.0
Thrombophilia	1 % - 5 %	18 - 40/1.000	2.8 - 5.0
Cholestasis of pregnancy	<0.1 %	12 - 30/1.000	1.8 - 4.4
Smoking (> 10 cigarettes)	10 % - 20 %	10 - 15/1.000	1.7 - 3.0
Obesity (pre-pregnancy)			
BMI 25-29.9 kg / m2	21 %	12 - 15/1.000	1.9 - 2.7
BMI ≥30 kg / m2	20 %	13 - 18/1.000	2.1 - 2.8
Low education (<12 years versus. ≥12 years)	30 %	10 - 13/1.000	1.6 - 2.0
Prior stunting in infants (<10%)	6.7 %	12 - 30/1.000	2 - 4.6
Previous stillbirth	0.5 % - 1.0 %	9 - 20/1.000	1.4 - 3.2
Multiple gestation	2 % - 3.5%		
Twins	2.7 %	12/1.000	1.0 - 2.8
Triplets	0.14 %	34/1.000	2.8 - 3.7
Advanced maternal age (reference <35 years)			
35 - 39 years	15 % - 18 %	11 - 14/1.000	1.8 - 2.2
≥40 years	2 %	11 - 21/1.000	1.8 - 3.3
Black women versus white women	15 %	12 - 14/1.000	2.0 - 2.2

Abbreviations: BMI: Body Mass Index.

Source: Fretts RC. Aetiology and prevention of stillbirth. Am J Obstet Gynecol. 2005;193(6):1923-35.

Table 2. Composition of drug tablets used for each study

	Multi vitamin (Czeizel, 1994)	Trace elements (Czeizel, 1994)	Multi vitamin (ICMR, 2000)	Placebo (ICMR, 2000)	Folic acid (Kirke, 1992)	Multi vitamin (Kirke, 1992)	Folic acid + Multi vitamin (Kirke, 1992)	Folic acid (Laurence, 1981)	Folic acid (MRC, 1991)	Folic acid + Multi vitamin (MRC, 1991)	Multi vitamin (MRC, 1991)	Placebo (MRC, 1991)
Vitamin A	4.000 –6.000 UI/day		4.000 UI/day			4.000 UI/day	4.000 UI/day			4.000 UI/day	4.000 UI/day	
Folic acid	0.8 mg/day		4 mg/day		0.36 mg/day		0.36 mg/day	4 mg/day	4 mg/day	4 mg/day		
Vitamin B1 (thiamine)	1.6 mg/day		2.5 mg/day			1.5 mg/day	1.5 mg/day			1.5 mg/day	1.5 mg/day	
Vitamin B12	4 µg/day											
Vitamin B2 (riboflavin)	1,8 mg/day		2,5 mg/day			1,5 mg/day	1.5 mg/day			1.5 mg/day	1.5 mg/day	
Vitamin B6 (pyridoxine)	2,6 mg/day		2 mg/day			1 mg/day	1 mg/day			1 mg/day	1 mg/day	
Biotin	0,2 mg/day											
Vitamin C (ascorbic acid)	100 mg/day	7.5 mg/day	2 mg/day			40 mg/day	40 mg/day			40 mg/day	40 mg/day	
Calcium	125 mg/day											
Copper	1 mg/day	1 mg/day										
Vitamin D (calciferol)	500 UI/day		400 UI/day			400 UI/day	400 UI/day			400 mg/day	400 mg/day	

Table 2. Composition of drug tablets used for each study

	Multi vitamin (Czeizel, 1994)	Trace elements (Czeizel, 1994)	Multi vitamin (ICMR, 2000)	Placebo (ICMR, 2000)	Folic acid (Kirke, 1992)	Multi vitamin (Kirke, 1992)	Folic acid + Multi vitamin (Kirke, 1992)	Folic acid (Laurence, 1981)	Folic acid (MRC, 1991)	Folic acid + Multi vitamin (MRC, 1991)	Multi vitamin (MRC, 1991)	Placebo (MRC, 1991)
Vitamin E	15 mg/day											
Calcium phosphate			240 mg/day	240 mg/day		480 mg/day	480 mg/day					240 mg/day
Phosphorus	125 mg/day											
Iron	60 mg/day											
Magnesium	100 mg/day											
Manganese	1 mg/day	1 mg/day										
Nicotinamide	19 mg/day		15 mg/day			15 mg/day			15 mg/day	15 mg/day		
Calcium pantothenate	10 mg/day											
Ferrous sulfate			120 mg/day	120 mg/day		252 mg/day	252 mg/day					120 mg/day
Zinc	7,5 mg/day	7,5 mg/day	10 mg/day									

Table 3. Results of the SR by Thangaratinam 2006

Outcome of interest	Uric acid value	Number of studies	LR+	LR-
Eclampsia	350 µmol/L	3	2.1 (IC 95 %:1.4 to 3.5)	0.38 (IC 95 %:0.18 to 0.81)
Severe hypertension	≥350 µmol/L	6	1.7 (IC 95 %:1.3 to 2.2)	0.49 (IC 95 %:0.38 to 0.64)
Caesarean section	350 µmol/L	4	2.4 (IC 95 %:1.3 to 4.7)	0.39 (IC 95 %:0.20 to 0.76)
PEG	350 µmol/L	5	1.3 (IC 95 %:1.1 to 1.7)	0.60 (IC 95 %:0.43 to 0.83)
Neonatal death	≥350 µmol/L	7	1.5 (IC 95 %:0.9 to 2.6)	0.51 (IC 95 %:0.20 to 1.30)

Table 4. Diagnostic criteria for gestational diabetes

Organisation	OGTT	Plasma glucose concentrationmg/dl			
		Fast	1h	2h	3h
WHO	75 g	126		140	
ACOG	100 g	105	190	165	145
IADPSG – ADA	75 g	92	180	153	

Table 5. Aims of ultrasound scans

Modality and gestational age	Aims
1st trimester ultrasound 12 weeks (Between 11 and 14 weeks)	Identify the number of embryos Diagnosis of zygosity and amnionicity for multiple gestation Identification of embryonic heartbeat Estimation of gestational age Detection and measurement of nuchal translucency (marker of foetal chromosopathy) Observation of embryo morphology Identifying the existence of uterine and / or adnexal pathology
2nd trimester ultrasound 20 weeks (Between 18 and 22 weeks)	Diagnosis of structural abnormalities Determination of chromosomal markers Include the objectives of the previous ultrasound, if not performed
3rd trimester ultrasound 32 weeks (Between 32 and 36 weeks)	Identification of foetal vitality and position Estimation of foetal growth Diagnosis of placental position abnormalities Diagnosis of amniotic fluid abnormalities Fetoplacental volume flow study in the cases identified

Table 6. Drugs that have been shown to be safe at any time during pregnacy (adapted from protocols SEGO, 2005 [Consider requesting for permission to reproduce])

Ammonium	Clotrimazole	Lincomycin
Ammonium chloride	Codeine	Liothyronine (triiodothyronine)
Amoxicillin	Cholecalciferol (vitamin D3)	Nystatin
Ampicillin	Dexchlorpheniramine	Methyldopa
Amphotericin B	Digoxin	Miconazole (topical)
Antacids	Diphenhydramine	Minerals (at recommended doses)
Anti-D immunoglobulin	Diphtheria vaccine	
Atropine	Dihydrotachysterol	Nalidixic acid
Bisacodyl	Doxylamine	Pantothenic acid
Bromhexine	Econazole (topical)	Paracetamol
Calcium folinate	Ergocalciferol (vitamin D2)	Penicillins
Cephalosporins	Erythromycin	Pyridoxine
Cyclizine	Etambutol	Riboflavin
Cyproheptadine	Fenoterol	Sulfasalazine
Clindamycin	Folic acid	Thiamine
Chlorpheniramine	Insulin	Thyroglobulin
Chloride	Iron	Tetanus immunoglobulin
Chlorhexidine	Isoniazid	Tetanus vaccine
Chloroquine (prophylaxis)	Levothyroxine	Vitamins (at recommended doses)

Table 7. Teratogenic drugs (adapted from protocols SEGO, 2005 [Consider requesting for permission to reproduce])

Contraindicated drugs
Androgens
Diethylstilboestrol
Misoprostol
Retinoids (isotretinoin, etretinate, and tretinoin)
Retinol (vitamin A) at a dose of 5,000 U
Thalidomide
Drugs frequently used, teratogenic or with severe adverse effects, whose use could be justified in certain circumstances:
Aminoglycosides
Aminopterin, methotrexate
Anticoagulants (warfarin or acenocoumarol)
Carbamazepine
Chloramphenicol
Cyclophosphamide
Enzyme inhibitors of angiotensin converting
Lithium
Penicillamine
Phenobarbital
Phenytoin
Progestogens
Quinine and Chloroquine
Tetracyclines
Valproic acid

Table 8. Risk classification of drugs during pregnancy by the FDA (adapted from Larrubia 2010)

Category A	Controlled studies in pregnant women have not shown an increased risk of foetal abnormalities.	Studies performed in pregnant women have shown no risk to the foetus during the first trimester or in the rest of the pregnancy.
Category B	No risk to the human foetus has been identified.	Animal studies have shown no teratogenic risk, but there are no controlled studies carried out in pregnant women. Animal studies have shown unconfirmed side effects in pregnant women. Their use is accepted during pregnancy.
Category C	Foetal risk is not excluded.	Animal studies have shown foetal side effects and there are no controlled studies in pregnant women. There are no studies in animals or women. Their use is accepted if the benefits outweigh the potential foetal risks.
Category D	There is evidence of foetal risk.	The teratogenic risk to the foetus, has been demonstrated although in certain situations the benefits in pregnant women may be acceptable despite these risks (e.g. in the face of a disease or condition that threatens life or a serious disease for whichother safer drugs may not be used).
Category X	Contraindicated	Both studies in animals and humans have shown a clear risk to the foetus.

Appendix 4. Abbreviations

ACOG: *College of Obstetrics and Gynaecology*
ADA: *American Diabetes Association*
BMI: Body Mass Index
BSGD: *Brazilian Study of Gestational Diabetes*
CMV: Cytomegalovirus
CT: Congenital Toxoplasmosis
DM: Diabetes Mellitus
ECV: External cephalic version
EPDS: *Edinburgh Postnatal Depression Scale*
GD: Gestational Diabetes
Hb: Haemoglobin
HBP: High Blood Pressure
HIV: Human Immunodeficiency Virus
IADPSG: *The International Association of Diabetes and Pregnancy Study Group*
OGTT: Glucose tolerance test
PFMT: Pelvic Floor Muscle Training
RCT: Randomised Clinical Trial
RRR: Relative Risk Reduction
SR: Systematic Review
STAI: *State-trait anxiety inventory*
TSH: Thyroid-stimulating hormone
UCLA: *University of California at Los Angeles*
USPSTF: *United States Preventive Services Task Force*
WHO: World Health Organisation

Appendix 5. Edinburgh Postnatal Depression Scale (EPDS)

Validated Spanish version (adapted from Garcia-Esteve 2003)

Instructions

As you are pregnant or have recently had a baby, we would like to know how you are feeling now. Please UNDERLINE the answer that comes closest to how you have felt in the past 7 days.
In the past 7 days:

1. I have been able to laugh and see the funny side of things
   - As much as I always could
   - Not quite so much now
   - Definitely not so much now
   - Not at all
2. I have looked forward with enjoyment to things
   - As much as I ever did
   - Rather less than I used to
   - Definitely less than I used to
   - Hardly at all
3. I have blamed myself unnecessarily when things went wrong
   - Yes, most of the time
   - Yes, some of the time
   - Not very often
   - No, never
4. I have been anxious or worried for no good reason
   - No, not at all
   - Hardly ever
   - Yes, sometimes
   - Yes, very often
5. I have felt scared or panicky for no good reason
   - Yes, quite a lot
   - Yes, sometimes
   - No, not much
   - No, not at all
6. Things have been getting on top of me
   - Yes, most of the time I haven't been able to cope at all
   - Yes, sometimes I haven't been coping as well as usual
   - No, most of the time I have coped quite well
   - No, I have been coping as well as ever

7. I have been so unhappy that I have had difficulty sleeping
    - Yes, most of the time
    - Yes, some of the time
    - Not very often
    - No, not at all
8. I have felt sad or miserable
    - Yes, most of the time
    - Yes, some of the time
    - Not very often
    - No, not at all
9. I have been so unhappy that I have been crying
    - Yes, most of the time
    - Yes, quite often
    - Only occasionally
    - No, never
10. The thought of harming myself has occurred to me
    - Yes, quite often
    - Sometimes
    - Hardly ever
    - Never

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