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Clinical implementation of the sFlt-1/PlGF ratio to identify preeclampsia and fetal growth restriction: A prospective cohort study

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ABSTRACT

Objective: To analyze the usefulness of a clinical protocol for early detection of preeclampsia and/or fetal growth restriction (PE/FGR) using, in previously selected pregnancies, the measurement of the sFlt-1/PlGF ratio at 24–28 weeks of gestation.

Study design: Prospective observational cohort study carried out in a single tertiary hospital in Spain. 5601 consecutive singleton pregnancies with complete follow-up were included. High-risk women for PE/FGR were selected by combining data from maternal history and second trimester uterine artery Doppler. Subsequently these patients underwent intensive monitoring, including the measurement of the sFlt-1/PlGF ratio at 24–28 weeks to predict PE/FGR.

Main outcome measures: Early, intermediate and late PE/FGR (delivery $< 32+0$, $32+0 - < 36+0$ and $\geq 36+0$ weeks, respectively).

Results: Overall incidence of early, intermediate and late PE/FGR was 0.3%, 0.7% and 3.2%, respectively, being higher in the 4.3% of women selected for intensive monitoring: 5.8%, 8.7% and 15.4%, respectively (all $p < 0.001$). The area under the curve (AUC) with 95%CI of the sFlt-1/PlGF ratio for detecting early PE/FGR was 0.98 (0.97–1.00), and the sFlt-1/PlGF ratio > 95th centile showed a sensitivity (%) of 100 (95%CI, 78.5–100) and specificity (%) of 80.6 (95%CI, 75.0–85.2). The AUC of the sFlt-1/PlGF ratio for detecting intermediate and late PE/FGR was of 0.87 (95%CI, 0.77–0.97) and 0.68 (95%CI, 0.58–0.79), respectively.

Conclusion: A contingent strategy of measuring the sFlt-1/PlGF ratio at 24–28 weeks in women previously selected by clinical factors and uterine artery Doppler enables an accurate prediction of PE/FGR. This performance is optimal to predict PE/FGR requiring delivery before 32 weeks.

1. Introduction

Preeclampsia (PE) and fetal growth restriction (FGR) are placental dysfunction-related complications that are associated with increased maternal and perinatal morbidity and mortality, especially when early delivery is required. These conditions share risk factors and often coexist, increasing the adverse outcomes [1] Prompt identification and correct allocation of women with early PE or FGR in centers where perinatal care can be optimized are critical for reducing complications. However, diagnosis of PE is still based on nonspecific clinical symptoms and laboratory findings, and FGR identification by routine ultrasound or symphysis-fundal height is also suboptimal, leading to delayed diagnosis [2]. The addition of markers based on the identification of placental dysfunction such as the mean uterine artery pulsatility index (mUtA-PI) and the sFlt-1/PlGF ratio improves the detection of early PE and FGR [3,4]. Universal screening with mUtA-PI at the second trimester scan has 60–80% sensitivity for the detection of early or severe PE and FGR with 90–95% specificity, but suffers from low positive predictive values of 10–20% [5,6]. The sFlt-1/PlGF ratio has the potential to provide optimal positive and negative predictive values in selected populations [7,8] and has been recommended in the UK to help rule-out PE in women with suspected PE between 20 and 34 + 6 weeks' gestation [9]. However, an issue to be elucidated is when to measure these markers in pregnancies with high mUtA-PI.

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In this study, we have designed and analyzed a strategy for the rational implementation of the sFlt-1/PlGF ratio in the clinical practice to identify early, intermediate and late PE or FGR, consisting firstly in the selection of high-risk women by maternal history and second trimester mUtA-PI and, secondly, in the determination of the sFlt-1/PlGF ratio at 26 weeks' gestation.

2. Methods

2.1. Study design

This is an observational prospective cohort study of consecutive women with a viable singleton pregnancy attending our hospital for the routine fetal anomaly scan at 19 + 0 − 22 + 0 weeks (19–22 weeks) of pregnancy and with an estimated date of delivery between March 2014 and February 2016. A subgroup of pregnant women at risk for PE and/or FGR (PE/FGR) according to maternal history and mUtA-PI were selected for intensive monitoring starting at 24 + 0 − 28 + 6 weeks (24–28 weeks), including the sFlt-1/PlGF ratio measurement, as detailed later. The exclusion criteria were multiple pregnancies, fetuses with chromosomal anomalies, major malformations or congenital infections, unknown pregnancy outcome and lack of informed consent. All women received written information about the study at the time of the first ultrasound scan, and those who agreed to participate in the intensive monitoring provided written informed consent. The local Ethics Committee approved the study.

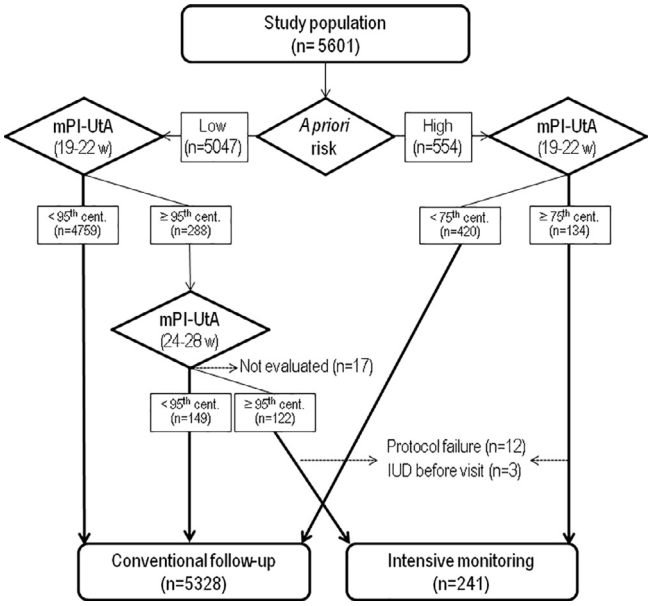

Fig. 1. Flow chart of study population showing the selection of pregnancies for conventional follow-up or intensive monitoring. Cent, centile; FGR, fetal growth restriction; IUD, intrauterine death; mPI-UtA, mean uterine artery pulsatility index; PE, preeclampsia; w, weeks of gestation.

2.2. Study sampling and procedures

Coinciding with the first ultrasound visit, maternal risk factors for PE established by the National Institute for Health and Clinical Excellence (NICE) guidelines [10] were recorded. Pregnant women were categorized as low (no high-risk factors or ≤one moderate-risk factor) or high (at least one high-risk factor or two moderate-risk factors) *a priori* risk. Low-dose aspirin (100 mg/day) prophylaxis from < 16 weeks until 36 weeks was routinely recommended when one or more high-risk factors were present. Gestational age was calculated according to the recommendations of The American College of Obstetricians and Gynecologists, that is, accurate recall of the last menstrual period was respected unless there was a significant discrepancy with the first ultrasound estimation based on measurement of the crown-rump length before 14 + 0 weeks or biparietal diameter from 14 + 0 weeks onwards [11].

Transabdominal Doppler study of mUtA-PI was performed at the anomaly scan as previously described [12]. We selected for intensive monitoring those women with *a priori* high risk for PE and mUtA-PI ≥75th percentile, as well as those with *a priori* low risk for PE and mUtA-PI ≥95th percentile. In the latter, it was additionally required that the mUtA-PI persisted ≥95th percentile at 24–28 weeks. These different mUtA-PI thresholds were used because high-risk patients are more prone to develop PE/FGR even in absence of highly elevated uterine artery resistances [5]. In those selected women we carried out a check-up visit at 24–28 weeks consisting of a fetal growth scan, mean arterial pressure (MAP) measurement and analytical study including assessment of the protein/creatinine index in random urine sample and measurement of the sFlt-1/PlGF ratio in maternal serum. Previously described cut-off values of 10 (95th centile for gestational age) [13], 38 (high suspicion of PE) [7], and 85 (aid in diagnosis of PE) [13], were used for interpretation of results. Thus, in absence of clinical disease, the cadence of new check-up visits depended on the previous result: under the rule out cut-off point of 38 no additional visits were made unless a suspicion of PE/FGR further arose, while between 38 and 85, and above 85 the next check-up visit was planned within 2 weeks and every 48–96 h, respectively. This scheme of surveillance followed experts' recommendations that were based on the observation that the likelihood of complications in the short-term is higher as the ratio increases, but when the values are < 85 this probability in the following two weeks is still low [14,15]. A full description of this protocol has been published elsewhere [2], including the rationale for selecting the cut-offs of the mUtA-PI and sFlt-1/PlGF ratio, as well as the time intervals between visits. Women not selected for intensive monitoring as well as those with sFlt-1/PlGF ratio below 38 underwent conventional follow-up that in our country includes routinely growth scan at 34–36 weeks. Whenever PE/FGR was diagnosed, current protocols were followed as described below. Physicians were aware of the results of the sFlt-1/PlGF ratio but the test was only used to guide the frequency of visits, the need for additional test and of hospitalization, in concurrence with other clinical and analytical data. Therefore, indication of delivery was guided by current protocols, and it was not directly influenced by the biomarkers.

The sFlt-1 and PlGF concentrations (picograms per milliliter) in maternal serum samples were performed using an automated assay system (Cobas® 6000 e701 module, Roche Diagnostics, Penzberg, Germany). This is the same platform for which the aforementioned cutoffs have been validated. The sFlt-1/PlGF ratio was calculated and expressed in absolute values.

2.3. Outcomes

FGR was defined as an estimated fetal weight (EFW) by ultrasound [16] < 3rd centile, or EFW < 10th centile plus abnormal fetal Doppler (PI > 95th centile in the umbilical artery, PI < 5th centile in the middle cerebral artery, or cerebroplacental ratio < 5th centile) [17]. EFW and birth weight were converted into a percentile after correction for gestational age, fetal gender and customization by maternal characteristics, using the GROW software [18]. Fetal surveillance was based on a previously defined stage-based protocol to monitor fetal wellbeing and decide the timing and route of delivery in FGR [19]. PE was defined according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [20]. Maternal indications for expeditious delivery at 33 + 6 weeks or less were the presence of clinical conditions that contraindicate expectant management [21]. Immediate delivery was also indicated in severe PE at 34 + 0 weeks or later, while in non-severe forms expectant management was recommended until 37 + 0 weeks.

Table 1
Incidence of early, intermediate and late preeclampsia and/or fetal growth restriction (PE/FGR) in the study population and relative risks (RR) for these outcomes depending on being selected for conventional follow-up or intensive monitoring.

Outcome group	Study population (n = 5601)		Follow-up allocation after selection process [a]					
	n	% Incidence (95% CI)	Conventional (n = 5328)		Intensive (n = 241)		RR (95%CI)	P value
			n	% Incidence (95%CI)	n	% Incidence (95%CI)		
Early PE/FGR	17	0.3 (0.2–0.5)	2	0.04 (0.01–0.14)	14	5.8 (3.4–9.5)	146.3 (33.4–640.4)	< 0.001
Intermediate PE/FGR	37	0.7 (0.5–0.9)	16	0.3 (0.2–0.5)	21	8.7 (5.8–13.0)	26.8 (14.1–50.7)	< 0.001
Late PE/FGR	182	3.2 (2.8–3.7)	141	2.6 (2.2–3.1)	37	15.4 (11.3–20.4)	5.2 (3.7–7.3)	< 0.001
All PE/FGR	236	4.2 (3.7–4.8)	159	3.0 (2.6–3.5)	72	29.9 (24.4–35.9)	10.0 (7.8–12.8)	< 0.001

CI, confidence interval.
Early PE/FGR: delivery < 32 weeks; Intermediate PE/FGR: delivery 32 – < 36 weeks; Late PE/FGR: delivery ≥36 weeks.
[a] 32 cases were not allocated to any mode of follow-up, as detailed in the text.

Outcome data were recorded on clinical electronic databases: ultrasound scans and check-up visits during pregnancy were stored in Viewpoint® 5 (GE Healthcare), biochemical tests and data from delivery and neonatal care were recorded in HP-HCIS (Hewlett-Packard Development Company, L.P.) and a specific database for data collection of women selected for intensive monitoring was created on the Research Electronic Data Capture (REDCap) tool hosted at our institution [22]. Careful review and definitive classification of PE and FGR cases was assessed by two investigators (I.H. and E.S).

We have presented PE and FGR as a single outcome since the sFlt-1/PlGF ratio is a surrogate of placental dysfunction, and is not specific to either of the two entities separately [2] Thus, our outcome groups were "early PE/FGR" (those pregnancies with PE and/or FGR requiring delivery < 32 weeks), "intermediate PE/FGR" (delivery at 32– < 36 weeks), and "late PE/FGR" (delivery ≥ 36 weeks). The "no PE/FGR" group was used for comparisons.

2.4. Statistical analysis

The reporting of this study conforms to the STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology) statement. Baseline characteristics were expressed in mean and standard deviations (SD) or percentage (%). The non-normally distributed values of sFlt-1 (pg/mL), PlGF (pg/mL) and the sFlt-1/PlGF ratio were expressed in median and interquartile range (IQR). Box plots were generated to represent the values of these analytes in the different outcome groups. Comparisons between the characteristics of the PE/FGR outcome groups and the no PE/FGR group were performed using chi-square or Fisheŕs exact testing for categorical variables and by *T*-test or Mann-Whitney *U* test both with post-hoc Bonferronís adjustment (critical statistical significance $p < 0.017$). P-values for all tests were two-sided. The accuracy of the predictive variables to predict early, intermediate and late PE/FGR was assessed using the areas under the receiver-operating characteristic curves (AUC), and derived sensitivities, specificities, positive/negative predictive values (PPV/NPV) and positive likelihood ratios (LR+) were calculated with 95% confidence intervals (CI). Kaplan-Meier curve was produced to represent the cumulative incidence of delivery with PE/FGR from the time of sFlt-1/PlGF measurement (deliveries without PE/FGR were censored). Data were carefully entered and analyzed after data cleansing, using statistical package IBM SPSS Statistics 20.

3. Results

A total of 6983 women with singleton pregnancies attended our centre for routine anomaly scan during the study period. Late miscarriage was diagnosed in 7 (0.1%), mPI-UtA was not measured in 17 (0.2%), major congenital anomalies were detected in 65 (0.9%) cases, and 1293 (18.5%) were lost to follow up since they delivered elsewhere. Baselines characteristics of included and lost to follow up patients are shown in the Supplementary Table S1, showing that pregnant women who decided to deliver elsewhere had a lower risk profile for PE/FGR, based on clinical and sonographic factors, than those who remained with us. Moreover, among the losses, only 8 women (0.6%) fulfilled criteria for intensive monitoring.

The resultant is a study population of 5601 pregnancies with complete outcomes available. Of them, 554/5601 (9.9%) had *a priori* high risk and 5047 (90.1%) had *a priori* low risk for PE. Fig. 1 summarizes the process for selecting women for intensive monitoring. During this process, 32 additional women were excluded: in 17 cases with *a priori* low risk for PE and high mPI-UtA at 19–22 weeks, the mPI-UtA at 24–28 weeks could not be measured due to a citation error or non-attendance and three of them developed late FGR. Moreover, 15 cases initially selected for intensive monitoring (7 with *a priori* high risk and 8 with *a priori* low risk) were excluded because the results of the sFlt-1/PlGF ratio were not available. As detailed in Fig. 1, in 3 of them an intrauterine death was detected prior to the measurement of the ratio, having one an early PE/FGR.

The incidence of PE/FGR in the whole population was of 236/5601 (4.2%, 95%CI, 3.7%-4.8%), while in those selected for intensive monitoring was of 72/241 (29.9%, 95%CI, 24.4%-35.9%). The majority of these PE/FGR cases had mPI-UtA ≥ 95th centile at 19–22 weeks (62/72, 86%) and in 10 it was ≥ 75th centile. Table 1 describes the incidences and relative risks of early, intermediate and late PE/FGR in women selected for intensive monitoring when compared to those with conventional follow-up.

The main baseline characteristics and predictive variables at 24–28 weeks in the group of selected women for intensive monitoring are shown in table 2. Maternal and perinatal outcomes are shown in the Supplementary Table S2. The main characteristics and outcomes of the study population are shown in the Supplementary Tables S3 and S4. None of the baseline characteristics were significantly different between women who did not develop PE/FGR and those who did, whether early, intermediate or late. However, differences were found in all predictive variables that were assessed at 26.2 (0.8) weeks, except for the protein/creatinine index. Distribution of the values of the sFlt-1/PlGF at 24–28 weeks in the different outcome groups is shown in the Supplementary Fig. S1. In six cases, PE/FGR was already present at the time of the 24–28 visit and delivery occurred before 32 weeks in all but one case. In them, the sFlt-1/PlGF ratio was > 85 in all, with a median (IQR) value of 208.1 (127.4–555.7).

The AUC of the predictive variables at 24–28 weeks for the prediction of early, intermediate and late PE/FGR are given in Fig. 2. The best performance for detecting early and intermediate PE/FGR corresponded to the sFlt-1/PlGF ratio and PlGF alone. The AUC (95%CI) for early PE/FGR was of 0.98 (0.97–1.00) and 0.98 (0.95–1.00), respectively, and for intermediate PE/FGR of 0.87 (0.77–0.97) and 0.87 (0.77–0.97), respectively. AUC for detecting late PE/FGR performed modestly, all being below 0.70.

Diagnostic accuracies of the sFlt-1/PlGF ratio cutoffs of > 95th

Table 2
Description of maternal characteristics and predictive variables at 24 + 0 − 28 + 6 weeks visit of women selected for intensive monitoring that developed pre-eclampsia or fetal growth restriction requiring delivery < 32 weeks (early PE/FGR), at 32 – < 36 weeks (intermediate PE/FGR) or ≥ 36 weeks (late PE/FGR), compared with pregnant women who did not developed preeclampsia or fetal growth restriction (No PE/FGR).

Characteristics	No PE/FGR (n = 169)	Early PE/FGR (n = 14)	Intermediate PE/FGR (n = 21)	Late PE/FGR (n = 37)
Maternal baseline variables				
Age (y)	32.8 (6.8)	34.6 (5.9)	32.4 (6.2)	33.3 (5.7)
Height (cm)	161.8 (6.6)	160.0 (4.4)	157.3 (5.3)	161.4 (6.5)
Prepregnancy weight (kg)	67.0 (15.0)	67.8 (13.2)	66.1 (16.0)	63.6 (15.1)
Prepregnancy BMI (kg/m^2)	25.1 (5.1)	25.9 (5.2)	26.1 (6.1)	24.1 (5.8)
Current Smoker	13 (7.7)	2 (14.3)	3 (14.3)	8 (21.6)
Race or ethnic group				
White or Caucasian	110 (65.1)	8 (57.1)	12 (57.1)	30 (81.1)
Hispanic	43 (25.4)	4 (28.6)	5 (23.8)	5 (13.5)
Asian	4 (2.4)	1 (7.1)	2 (9.5)	1 (2.7)
North African	8 (4.7)	0 (0.0)	1 (4.8)	0 (0.0)
Black or African American	4 (2.4)	1 (7.1)	1 (4.8)	1 (2.7)
Risk factors for placental dysfunction				
High				
Previous PE	26 (15.4)	2 (14.3)	5 (23.8)	4 (10.8)
Chronic hypertension	17 (10.1)	1 (7.1)	6 (28.6)	4 (10.8)
Prepregnancy diabetes	7 (4.1)	1 (7.1)	1 (4.8)	1 (2.7)
Chronic kidney disease	8 (4.7)	0 (0.0)	1 (4.8)	0 (0.0)
Thrombophilia	12 (7.1)	0 (0.0)	0 (0.0)	1 (2.7)
SLE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Moderate				
Pregnancy interval > 10 y	101 (59.8)	11 (78.6)	12 (57.1)	24 (64.9)
Age ≥ 40 y	29 (17.2)	3 (21.4)	2 (9.5)	4 (10.8)
Prepregnancy BMI ≥ 35 kg/m^2	10 (5.9)	1 (7.1)	2 (9.5)	3 (8.1)
Family history of PE[a]	15 (8.9)	2 (14.3)	2 (9.5)	1 (2.7)
At least 1 high-risk or 2 moderate-risk factors	96 (56.8)	6 (42.9)	10 (47.6)	14 (37.8)
Mode of conception				
Spontaneous	163 (96.5)	14 (100.0)	21 (100.0)	36 (97.3)
ART (own oocyte)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
ART (oocyte donation)	4 (2.4)	0 (0.0)	0 (0.0)	1 (2.7)
Low-dose aspirin intake (100 mg/day)				
No	126 (74.6)	12 (85.7)	13 (61.9)	29 (78.4)
Starting at or before 16 weeks	42 (24.9)	2 (14.3)	7 (33.3)	8 (21.6)
Starting after 16 weeks	0 (0.00)	0 (0.0)	1 (4.8)	0 (0.00)
Low dose heparin prophylaxis				
No	159 (94.1)	14 (100.0)	21 (100.0)	35 (94.6)
Starting at or before 16 weeks	7 (4.2)	0 (0.0)	0 (0.0)	2 (5.4)
Starting after 16 weeks	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Predictive variables at 24 + 0 − 28 + 6 weeks visit				
Estimated fetal weight				
In grams	949 (130)	735 (168)[a]	839 (133)[a]	865 (135)[a]
Customized centile, median (IQR)	70 (37)	8 (30)[a]	40 (27)[a]	48 (46)[a]
< 10th customized centile	3 (1.8)	8 (57.1)[a]	2 (9.5)	1 (2.7)
UA-PI	1.09 (0.15)	1.36 (0.25)[a]	1.17 (0.20)	1.11 (0.17)
MCA-PI	2.00 (0.31)	1.60 (0.29)[a]	1.90 (0.27)	1.98 (0.36)
CPR	1.88 (0.37)	1.23 (0.36)[a]	1.65 (0.24)[a]	1.82 (0.43)
mUtA-PI	1.22 (0.32)	1.87 (0.49)[a]	1.71 (0.74)[a]	1.48 (0.33)[a]
sFlt-1 (pg/mL), median (IQR)	1341 (8 8 0)	8627 (6262)[a]	2196 (1594)[a]	1832 (5 6 2)
PlGF (pg/mL), median (IQR)	378.1 (264.5)	38.9 (41.2)[a]	96.2 (121.6)[a]	262.5 (357.2)
sFlt-1/PlGF ratio, median (IQR)	3.7 (3)	239.8 (264.1)[a]	22.4 (30.2)[a]	6.1 (10.5)
Mean blood arterial pressure (mmHg)	84.8 (8.1)	103.5 (11.2)[a]	97.5 (14.1)[a]	88.4 (8.3)
Protein/Creatinine index	0.18 (0.44)	0.24 (0.19)	0.14 (0.05)	0.13 (0.05)

Data are given as mean (standard deviation) unless otherwise stated for continuous variables and n (%) for categorical variables. Statistical analysis was made comparing each PE/FGR group with no PE/FGR. For significant differences, contrasts between groups have been made using chi-square or Fisherś exact testing for categorical variables and *T*-test or non-parametric Mann-Whitney *U* testing for continuous variables, all with post-hoc Bonferronís adjustment. [a]Critical significance level p < 0.017.

ART, assisted reproductive technology; BMI, body mass index; CPR: cerebro-placental ratio; MCA-PI: medium cerebral artery pulsatility index; mUtA-PI: mean uterine arteries pulsatility index; PlGF, placental growth factor; sFlt-1: soluble fms-like tyrosine kinase-1; SLE, systemic lupus erythematosus; UA-PI, umbilical artery pulsatility index.

centile, > 38 and > 85 for early, intermediate and late PE/FGR are detailed in Table 3. Finally, Fig. 3 shows the cumulative incidence of delivery with PE/FGR, according to the sFlt-1/PlGF value at 24–28 weeks. The incidence of PE/FGR in women with normal sFlt-1/PlGF ratio was lower than in those with values between > 95th centile – ≤38, > 38 – ≤85, and > 85, being of 15.3% (95%CI 10.9% – 21.3%), 64.1% (95%CI, 48.4–77.3%), 100% (95%CI, 56.5–100%) and 93.3% (95%CI, 70.2–98.8%), respectively (all p < 0.001). Furthermore, gestational age in weeks at delivery was higher, being of 38.7 (1.9), 36.3 (2.9), 35.3 (2.6) and 29.9 (2.5), respectively (all p < 0.001).

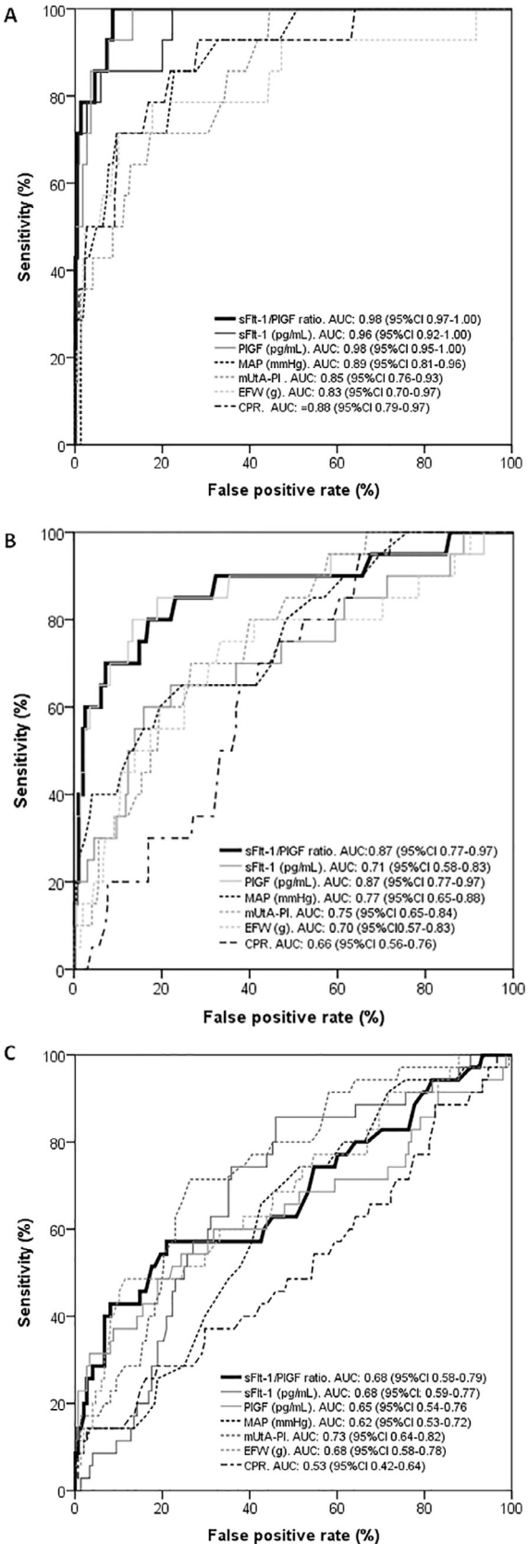

Fig. 2. Receiver-operating characteristic curves for the prediction of (a) early PE/FGR, (b) intermediate PE/FGR* and (c) late PE/FGR† with the sFlt-1/PlGF ratio, sFlt-1, PlGF, mean arterial pressure (MAP), mean uterine artery pulsatility index (mUtA-PI), estimated fetal weight (EFW) and cerebral-placental ratio (CPR). All tests were measured at 24–28 weeks in women selected for intensive monitoring. The area under the receiver operating characteristic curve (AUC) with 95% confidence interval is given for each test in the legend. *Only ongoing pregnancies were considered for analysis (16 pregnancies with delivery < 32 weeks were excluded). †Only ongoing pregnancies were considered for analysis (49 pregnancies with delivery < 36 weeks were excluded).

4. Discussion

4.1. Main findings

Our study has demonstrated the usefulness of the clinical implementation of the sFlt-1/PlGF ratio measurement at 24–28 weeks in previously selected high-risk women for placental dysfunction-related complications (PE/FGR). In a screening strategy based on the maternal history, the mPI-UtA at 19–22 weeks and the sFlt-1/PlGF ratio at 24–28 weeks, the PPV of the sFlt-1/PlGF ratio > 38 and > 85 was 55.0% and 73.3%, respectively, for PE/IUGR requiring delivery before 32 weeks. Optimal sensitivity/specificity accuracy of 100%/80.6% was reached when using the sFlt-1/PlGF ratio > 95th centile as the cut-off. Beyond 32 weeks, the sensitivity and specificity are poorer but those cases with sFlt-1/PlGF ratio > 95th centile that remain pregnant still retain a LR + > 5 for developing intermediate or late PE/FGR.

Overall, this approach allows a better stratification of the real risk of PE/FGR in this selected group of women, delineating two possible ways: first, those with values > 95th centile should undergo intensified feto-maternal care during the remaining pregnancy. Moreover, the higher the ratio the closer the surveillance, given the inverse relationship between the value of the ratio and the time to delivery. Second, pregnancies with sFlt-1/PlGF ratio ≤ 95th centile can be reassured avoiding unnecessary tests, scans and visits in the next 4–6 weeks.

4.2. Interpretation

PE and FGR are the major obstetric concerns related to placental dysfunction, and both are associated with similar abnormally elevated values of the sFlt-1/PlGF ratio, especially in the early forms [2,23]. There is no universal consensus to define early and late PE or FGR. While the cutoff of 34 weeks is more commonly used for PE, this limit is usually lowered to 32 weeks for FGR [24]. Recently, the group of Nicolaides has proposed to distinguish between early PE (< 32 weeks), intermediate PE (32–36 weeks) and late PE (> 36 weeks). This differentiation is intended to identify the cases that occur before the gestational age windows (30–33 weeks and 35–37 weeks) in which they propose to perform controls on pregnant women at risk for PE [25]. We assumed this last proposal since our strategy has many similarities.

Recently, the “PROGNOSIS” study has established the sFlt-1/PlGF value of > 38 as a unique cutoff for assessing suspected PE between 24 and 37 weeks. In this high-risk population with 19% PE cases, the NPV and PPV for rule-out and rule-in PE in the next 4 weeks were of 94.3% and 36.7%, respectively [7,26]. These figures are in accordance with ours of 98.6% and 55.0% for rule-out and rule-in early PE/FGR, respectively, using the same cutoff and despite we have combined PE and/or FGR, which results in a higher prevalence of events (29.9%). Moreover, lowering the threshold limit to 10 at 24–28 weeks (95th centile) the sensitivity is improved from 79% to 100%, keeping a good specificity of 80.6%. This may be explained by the distribution of the normal values of the sFlt-1/PlGF ratio across gestation, which reaches a nadir at 24–28 weeks [13].

The use of the sFlt-1/PlGF ratio in the second half of pregnancy has proven to be cost efficient when applied in women with suspected PE [9]. However, its application as a single test in universal screening may

Table 3
Diagnostic accuracy of established cutoff values of the sFlt-1/PlGF ratio (measured at 24–28 weeks) for the detection of early, intermediate and late preeclampsia/fetal growth restriction (PE/FGR) in women selected for intensive monitoring.

Outcome group	Cutoff of the sFlt-1/PlGF at 24–28 w	n	Sn (%)(95%CI)	Sp (%)(95%CI)	PPV (%)(95%CI)	NPV (%)(95%CI)	LR (+)(95%CI)
Early PE/FGR	> 95th centile	14	100 (78.5–100)	80.6 (75.0–85.2)	24.1 (15.0–36.5)	100 (97.9–100)	5.2 (4.0–6.7)
(n = 14)	> 38	11	78.6 (52.4–92.4)	96.0 (92.6–97.9)	55.0 (34.2–74.2)	98.6 (96.1–99.5)	19.8 (9.9–39.8)
	> 85	11	78.6 (52.4–92.4)	98.2 (95.6–99.3)	73.3 (48.1–89.1)	98.6 (96.1–99.5)	44.6 (16.3–122.3)
Intermediate PE/FGR[a]	> 95th centile	15	71.4 (50.0–86.2)	86.8 (81.4–90.7)	35.7 (23.0–50.8)	96.7 (93.0–98.5)	5.4 (3.5–8.4)
(n = 21)	> 38	6	28.6 (13.8–50.0)	99.0 (96.5–99.7)	75.0 (40.9–92.8)	93.1 (89.0–95.8)	29.1 (6.3–135.4)
	> 85	3	14.3 (5.0–34.6)	100 (98.2–100)	100 (43.8–100)	91.9 (87.6–94.8)	–
Late PE/FGR[b]	> 95th centile	15	40.5 (26.3–56.5)	92.9 (87.7–96.0)	57.7 (38.9–74.5)	86.7 (80.7–91.1)	5.7 (2.9–11.4)
(n = 37)	> 38	2	5.4 (1.5–17.7)	100 (97.6–100)	100 (34.2–100)	81.6 (75.5–86.4)	–
	> 85	0	0 (0–9.4)	100 (97.6–100)	–	80.7 (74.6–85.7)	–

CI, confidence interval; LR(+), positive likelihood ratio; NPV, negative predictive value, PPV, positive predictive value; Sn, sensitivity; Sp, specificity; w, weeks.
[a] Only ongoing pregnancies were considered for analysis (16 pregnancies with delivery < 32 weeks were excluded).
[b] Only ongoing pregnancies were considered for analysis (49 pregnancies with delivery < 36 weeks were excluded).

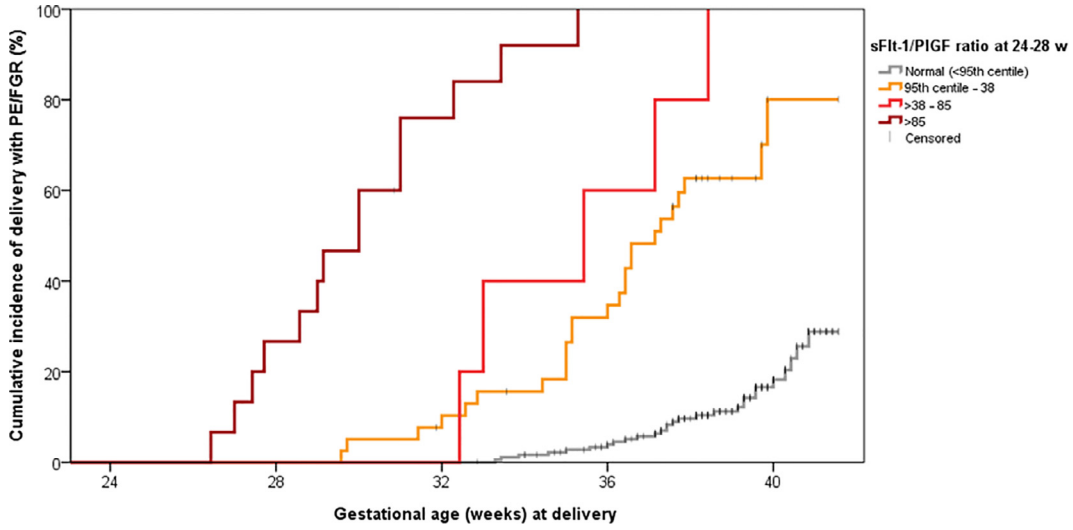

Fig. 3. Kaplan-Meier plot of cumulative incidence of delivery with preeclampsia/fetal growth restriction (PE/FGR) according to the sFlt-1/PlGF ratio at 24–28 weeks (≤95th centile, 95th centile – 38, > 38 – 85 and > 85). Censored cases are those who delivered without PE/FGR.

not be as efficient [27,28]. Thus, we have applied a contingent strategy whereby we measured the sFlt-1/PlGF ratio to < 5% of our population, which had a high risk of developing PE/FGR of nearly 30%. The group of Nicolaides has recently proposed to apply a universal screening at 11–14 weeks and 19–24 weeks, combining the *a priori* risk from maternal characteristics with adjusted values of MAP, mPI-UtA and PlGF (also incorporating sFlt-1 at 19–24 weeks). These screening tests selected 10% and < 1% of the total population, respectively, containing > 95% cases of PE delivering < 32 weeks. Therefore, they achieved even superior results to our selection process, with the additional advantage that first-trimester screening allows effective prevention with low-dose aspirin [25,29]. It could also be argued that our strategy implies missing PE/FGR occurring before 24 weeks but these are very uncommon and usually clinically evident, being unlikely that their earlier detection could provide any benefit in terms of neonatal survival [30]. On the other hand, our approach presents also some advantages, such as its greater simplicity, the lower expenditure on biomarkers and an easier clinical implementation.

We acknowledge some limitations of our study. Firstly, given our losses and their low-risk profile, the prevalence of PE/FGR may be overrepresented, potentially altering in some degree the predictive performance of our strategy. This shortcoming is common in many population-based studies, and in our study it is minimized by the fact that the vast majority of pregnant women eligible for intensive monitoring had a good adherence to our center. Secondly, the selection process was centered in the second trimester of pregnancy, while the first trimester screening for PE is now being implemented in many institutions [29]. However, we believe that both approaches can be complementary, and our proposal has the potential to better reassess the true risk of developing early PE/FGR and reduce the high rate of false positives that affects the first trimester PE screening [31]. Third, we are aware that the 75th centile of the mPI-UtA is an uncommon cutoff point but this allowed the detection of 10 additional PE/FGR cases, confirming thereby that a priori high-risk women are prone to develop these conditions even in absence of highly elevated uterine resistances. Fourth, we cannot extrapolate our data to multiple gestations, in which the values of mUtA-PI and sFlt-1/PlGF ratio differ. Finally, our observational study has not been designed to demonstrate if the clinical implementation of the sFlt-1/PlGF ratio is useful to reduce maternal or fetal adverse outcomes. It seems unlikely that the determination of biomarkers by itself will improve maternal-fetal outcomes, but we do believe that the adequacy of medical care, with a prompt selection and referral of early PE/FGR cases to experienced centers can help to improve maternal and fetal safety.

5. Conclusion

We have observed that the implementation of the sFlt-1/PlGF ratio measurement at 24–28 weeks of gestation in women selected by risk factors and uterine artery Doppler, provides an accurate prediction of PE/FGR, especially for the early forms.

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Disclosure of interests

IH and AG have received lecture fees and consultancy payments from Roche Diagnostics. The other authors did not report any potential conflicts of interest.

Contribution to authorship

IH, AG-B, EAL-J and AG conceived the study concept and design. IH, ES, PG-A and MSQ collaborated in the data collection and completed the data analysis. EAL-J was responsible for the collection and quality control of the laboratory data. IH and ES drafted the manuscript under the supervision of AG-B and AG. All authors aided in the interpretation of the data and critical revision of the manuscript. All authors approved the final version and take full responsibility for the integrity of the data and the accuracy of the data analysis.

Details of ethics approval

The local clinical research ethics committee approved this study (reference number: 13/371, approved 26 November 2013).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.preghy.2018.06.017.

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