OBSTETRICS

Performance of a first-trimester screening of preeclampsia in a routine care low-risk setting

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OBJECTIVE: We sought to evaluate the effectiveness of an integrated first-trimester screening test to predict preeclampsia (PE).

STUDY DESIGN: A prospective cohort of singleton pregnancies underwent routine first-trimester screening from 2009 through 2011 (n = 5759). A logistic regression-based predictive model for early- and late-onset PE was constructed based on: maternal characteristics; levels of pregnancy-associated plasma protein-A and free β-human chorionic gonadotropin at 8-12 weeks; and blood pressure and uterine artery Doppler at 11.0-13.6 weeks.

RESULTS: Of the 5170 enrolled participants, 136 (2.6%) developed PE (early PE: 26 [0.5%]; late PE: 110 [2.1%]). At 5% and 10% false-positive rates, detection rates were 69.2% and 80.8% for early PE (area under the curve, 0.95; 95% confidence interval, 0.94–0.98) and 29.4% and 39.6% for late PE (area under the curve, 0.71; 95% confidence interval, 0.66–0.76), respectively.

CONCLUSION: First-trimester screening combining maternal factors with uterine artery Doppler, blood pressure, and pregnancy-associated plasma protein-A is useful to predict PE in a routine care setting.

Key words: blood pressure, preeclampsia, screening, uterine artery Doppler

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Preeclampsia (PE) occurs in approximately 2-8% of pregnancies.[1] In developed countries, PE is the primary cause of maternal admission to intensive care units[2] and causes approximately 15% of all pregnancy-related deaths.[3] Additionally, PE is associated with an increased risk of perinatal mortality and is the cause for approximately 10% of stillbirths[4] and 15% of preterm births.[5]

In recent years, the results of several studies indicate that a combination of maternal history, biochemical markers, and biophysical markers effectively predicts PE in the first trimester of pregnancy,[6] a period in which prophylactic strategies with aspirin have been demonstrated to be more effective.[7] The performance in the prediction of early-onset PE, which is the clinical form that contributes most significantly to adverse outcomes,[8] is substantially higher than that for late forms of the disease. Thus detection rates (DR) for early PE ranged from 41% when using combinations of maternal history with pregnancy-associated plasma protein-A (PAPP-A),[9] to 96%, when maternal factors, uterine artery (UtA) Doppler, and angiogenic factors were combined.[10] In contrast, the DR for late PE ranges around 31–45%.[9,11]

One gap in the current literature on the prediction of PE is that most studies have been performed in Anglo-Saxon populations and have been carried on under similar research settings.[9,11-16] Another study carried out on a Mediterranean population, with smaller sample size, did not differentiate early and late PE.[17] Thus there is a need to confirm the effectiveness of first-trimester screening for PE when applied under typical clinical conditions and to populations different from those of the original studies.[6] The composition of the population under study may strongly influence maternal a priori risk. For instance, in south-European countries the proportion of black race and the rates of obesity and chronic hypertension are lower than in the United Kingdom.[18]

In this study, we evaluated the effectiveness of an integrated first-trimester screening test for PE when performed under usual care conditions and in a south-European population. The screening strategy combined maternal history, blood pressure (BP), UtA Doppler, and biochemical markers (free β-human chorionic gonadotropin [fβ-HCG] and PAPP-A). The testing was conducted for 3 years in a clinical setting during routine first-trimester ultrasound and was performed by usual clinical staff. We evaluated the DR for early and late PE in 5759 patients.

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TABLE 1
Epidemiological and clinical characteristics of study population according to study groups

Variable	Unaffected (n = 5034)	Late PE (n = 110)	Early PE (n = 26)
Age, y, median (IQR)	32 (28–35.4)	33.2 (29–36.3)	31.3 (29.9–36.5)
BMI, kg/m^2, median (IQR)	24 (22.7–24.7)	24.6 (23.5–26.4)[a]	24.4 (22.7–28)
Ethnicity, n (%)			
White European	3757 (74.6)	73 (66.4)	15 (57.7)
Black	22 (0.4)	1 (0.9)	1 (3.8)
South American	784 (15.6)	28 (25.5)	6 (23.1)
Other	471 (9.4)	8 (7.3)	4 (15.4)
Smoking status, cigarettes/d, n (%)			
0	4637 (92.1)	100 (90.9)	24 (92.3)
<10	107 (2.1)	4 (3.6)	0 (0)
10-20	245 (4.9)	4 (3.6)	1 (3.8)
>20	45 (0.9)	2 (1.8)	1 (3.8)
Medical history, n (%)			
Chronic hypertension	48 (1)	10 (9.1)[a]	4 (15.4)[b]
Diabetes mellitus	88 (1.7)	7 (6.4)[a]	0 (0)
Renal disease	6 (0.1)	0	3 (11.5)[b,c]
Autoimmune disease	68 (1.4)	4 (3.6)	1 (3.8)
Coagulation disorders	40 (0.8)	4 (3.6)[a]	0 (0)
Obstetric history, n (%)			
Nulliparous	2971 (59)	70 (63.6)	14 (53.8)
Previous PE	28 (0.6)	10 (9.1)[a]	5 (19.2)[b]
Previous IUGR[d]	28 (0.6)	1 (0.9)	3 (11.5)[b,c]
Mean BP, mmHg, median (IQR)	78.5 (74.1–83.1)	79.4 (74.9–84.1)	85.7 (80–89.7)[b,c]
Mean UtA-PI, median (IQR)	1.67 (0.53–1.25)	1.68 (1.54–1.84)	2.23 (1.75–3)[b,c]
Maternal serum biochemistry (MoM), median (IQR)			
PAPP-A	1.06 (0.53–1.25)	0.55 (0.28–1.05)[a]	0.87 (0.44–1.24)
β-HCG	1 (0.63–1.16)	0.96 (0.55–1.15)	0.92 (0.5–1.04)

BMI, body mass index; *BP*, blood pressure; *HCG*, human chorionic gonadotropin; *IQR*, interquartile range; *IUGR*, intrauterine growth restriction; *MoM*, multiple of expected normal median; *PAPP-A*, pregnancy-associated plasma protein-A; *PE*, preeclampsia; *PI*, pulsatility indices; *UtA*, uterine artery.

[a] Significant comparison between unaffected and late PE; [b] Significant comparison between unaffected and early PE; [c] Significant comparison between late and early PE; [d] Birthweight <10th centile that required delivery <37 wk.

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Materials and Methods

Subjects

In this study, a prospective cohort composed of singleton pregnancies underwent routine first-trimester screening at the Department of Maternal-Fetal Medicine at Hospital Clinic Barcelona. The local ethics committee approved the study protocol and each patient provided written informed consent. Gestational age in all pregnancies was calculated based on the crown-rump length (CRL) at first-trimester ultrasound.[19] Maternal characteristics and medical history was recorded and BP, UtA Doppler and plasmatic concentrations of PAPP-A, and fβ-HCG were measured in the first trimester.

From May 2009 through October 2011, a total of 5759 women underwent examination. Of these participants, a total of 589 (10.2%) were excluded for the following reasons (nonexclusively): missing outcome data (n = 525), major fetal defects or chromosomopathies (n = 25), miscarriage or fetal death <24 weeks (n = 80), and termination of pregnancy in the absence of medical indication (n = 21). After these participants were excluded, 5170 cases remained.

Predictive variables

Maternal characteristics and medical history were prospectively recorded at the time of first-trimester ultrasound (11.0-13.6 weeks) via a patient question-

naire. Characteristics recorded were: medical and obstetric history, maternal age, ethnicity, smoking status, parity, height, and weight.

A nurse measured BP automatically with a calibrated device (M6 Comfort; Omron Corp, Kyoto, Japan) in our outpatient clinics according to standard procedure. BP was measured in 1 arm (right or left) without distinction while women were seated and after a 5-minute rest. Mean arterial pressure (MAP) was calculated as: diastolic BP + (systolic – diastolic)/3.

UtA evaluation was performed transvaginally during the first-trimester ultrasound, as previously described.[20] Both UtA-pulsatility indices (PI) were automatically measured and mean UtA-PI was calculated.

Maternal serum PAPP-A and fβ-HCG were measured using the DELFIA Xpress analyzer (Perkin-Elmer, Turku, Finland) between 8-12 weeks of gestation. Thereafter, these levels were converted to multiples of the expected normal median (MoM), which were corrected for CRL, maternal age, body mass index (BMI), smoking and diabetes status, and ethnicity according to local references.[21]

Outcome measures

PE was defined as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg on at least 2 occasions 4 hours apart, developing >20 weeks of gestation in previously normotensive women, and proteinuria >300 mg in a 24-hour urine specimen.[22] Early PE was defined as PE requiring delivery <34 weeks. Doctors who made the diagnosis were blinded to the study parameters obtained during the first trimester.

Statistical analysis

The Mann-Whitney *U* test and Pearson χ^2 test were performed to make univariate comparisons of quantitative and qualitative variables, respectively, between groups. A post hoc Bonferroni correction was conducted to maintain a type I error of 0.05 ($P = .025$).

Logarithmic transformation was performed to normalize mean UtA-PI and MAP. In 52 cases, (1%) mean UtA-PI could not be calculated and these values were replaced by the average value of the whole cohort. Expected log values were calculated for all cases using a linear regression analysis of unaffected cases and included the following covariables: maternal age at first-trimester ultrasound (years), CRL at first-trimester ultrasound (millimeters), maternal height (centimeters) and weight (kilograms) at examination, parity (nulliparous vs multiparous), smoking status upon examination (0, 1-9, 10-19, and ≥20 cigarettes/d), and ethnicity (white European, South American, black, and other). Each individual observed value was expressed as a MoM of the expected value.

Logistic regression was used to estimate each woman's a priori risk with respect to the following covariates: medical history of diabetes; chronic hypertension; renal or autoimmune diseases; congenital and acquired thrombophilic conditions; obstetric history of PE or intrauterine growth restriction; maternal age; BMI (kg/m^2); smoking (cigarettes/d); and ethnicity and parity.

Logistic regression analysis was performed to estimate the individual risks for early and late PE with respect to the following covariables: a priori risk (log transformed), log MoM mean UtA-PI, log MoM MAP, log MoM PAPP-A, and log MoM fβ-HCG.[21] Receiver operating characteristic curves were performed to analyze model performance, which was expressed as DR for different cutoffs of false-positive rates (FPRs).

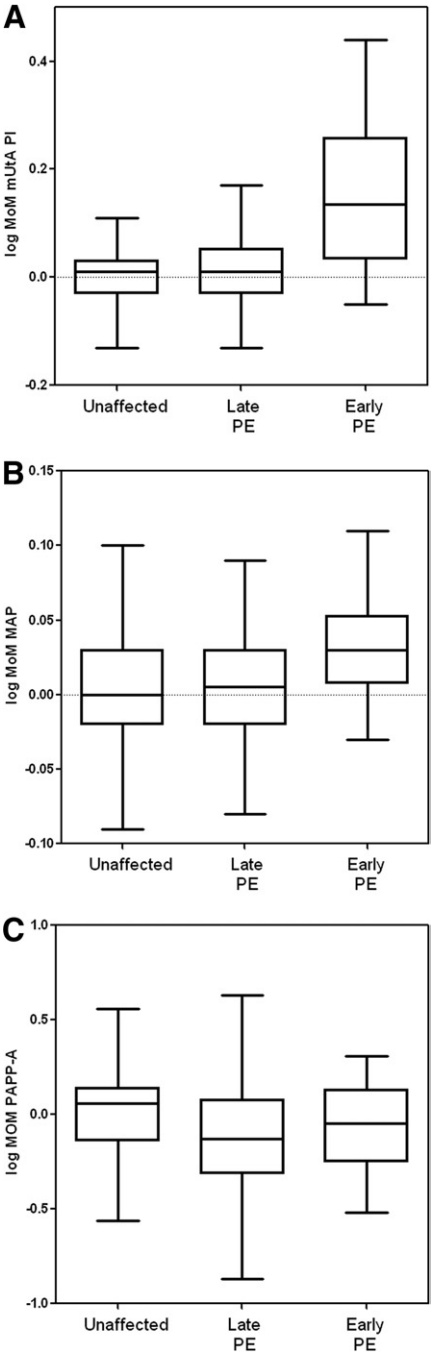
In all regression models, stepwise forward algorithms were performed to select variables at a *P* value cutoff of .05. Goodness-of-fit models were assessed by calculating Nagelkerke R^2.

The statistical package SPSS 18.0 (IBM Corp, Armonk, NY) was used to conduct all the statistical analyses and graphs were generated with MedCalc (MedCalc Software, Mariakerke, Belgium).

RESULTS

Among the 5170 women included in the study, 136 (2.6%) developed PE, including 110 (2.1%) cases of late PE and 26 (0.5%) cases of early PE. Table 1 shows the epidemiological and clinical charac-

FIGURE 1
Box plots of log MoM of predictive variables among study groups



A, Mean uterine artery (*UtA*) Doppler pulsatility indices (*PI*); **B**, Mean arterial pressure (*MAP*); and **C**, pregnancy-associated plasma protein-A (*PAPP-A*) levels.
MoM, multiple of expected normal median; *mUtA-PI*, mean uterine artery-pulsatility indices; *PE*, preeclampsia.

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teristics of the population by study group.

Scatterplots showing mean UtA-PI and MAP (in log MoM values) against gestational age at delivery and the correlation between UtA-PI and MAP are provided in the Supplemental Figures in the Appendix.

The following formula best fit the expected log mean UtA-PI: 0.668018 – (0.002772 * CRL) – (0.001536 * height) – (0.001151 * maternal age); R^2 = 4.6%.

The following formula best fit the expected log MAP: 1.803485 + (0.002990 * BMI) + (0.000645 * maternal age) – (0.00421 if South American); R^2 = 13.1%.

Figure 1 shows the distribution in log MoM of mean UtA-PI, MAP, and PAPP-A among the different study groups. The log MoM mean UtA-PI was significantly greater in the early PE group compared to unaffected ($P < .001$) and late PE ($P = .001$) groups. Similarly, log MoM MAP was significantly higher in the early PE group than in the unaffected ($P = .001$) and late PE ($P < .001$) groups. Log MoM PAPP-A was significantly lower in the late PE group compared to the unaffected group ($P < .001$).

The following model best fit the a priori risk for late and early PE [a priori risk = $e^y/(1 + e^y)$]:

Late PE Y = –6.135 + (2.124 if previous PE) + (1.571 if chronic hypertension) + (0.958 if diabetes mellitus) + (1.416 if thrombophilic condition) – (0.487 if multipara) + (0.093 * BMI); R^2 = 7.9%.

Early PE Y = –7.703 + (0.086 * BMI) + (1.708 if chronic hypertension) + (4.033 if renal disease) + (1.931 if parous, previous PE) + (0.005 if parous, no previous PE); R^2 = 13%.

The following models best fit the patient-specific a posteriori risk (a posteriori risk = $e^y/[1 + e^y]$):

Late PE Y = 0.328 + (2.205 * log a priori risk) – (1.307 * log MoM PAPP-A); R^2 = 10.1%

Early PE Y = –0.320 + (2.681 * log a priori risk) + (13.132 * log MoM mean UtA-PI) + (25.733 * log MoM MAP); R^2 = 36.8%.

One example of the application of these models is a 35-year-old woman with a prothrombin gene mutation, but no other medical conditions, who underwent her first pregnancy. At the time of the first-trimester ultrasound (CRL, 65 mm), her height was 165 cm and weight was 65 kg (BMI 23.8 kg/m^2). She had a mean UtA-PI of 1.85, a MAP of 90 mm Hg, and a PAPP-A of 0.87 MoM.

The expected log mean UtA-PI is: 0.668018 – (0.002772 * 65) – (0.001536 * 165) – (0.001151 * 35) = 0.194.

The log MoM mean UtA-PI is: log (1.85) – 0.194 = 0.073.

The expected log MAP is: 1.803485 + (0.00299 * 23.8) + (0.000645 * 35) = 1.897.

The log MoM MAP is: log (90) – 1.897 = 0.057.

The a priori odds for early PE is: Y = –7.703 + (0.086 * 23.8) = –5.656.

The a priori risk = $e^{-5.656}/(1 + e^{-5.656})$ = 0.0034

The a posteriori odds for early PE is: Y = –0.320 + (2.681 * log(0.0034)) + (13.132 * 0.073) + (25.733 * 0.057) = –4.4945.

The a posteriori risk = $e^{-4.4945}/(1 + e^{-4.4945})$ = 0.011 = 1/91.

The same woman with a mean UtA-PI of 2.5 would have a risk of 1/18 for early PE.

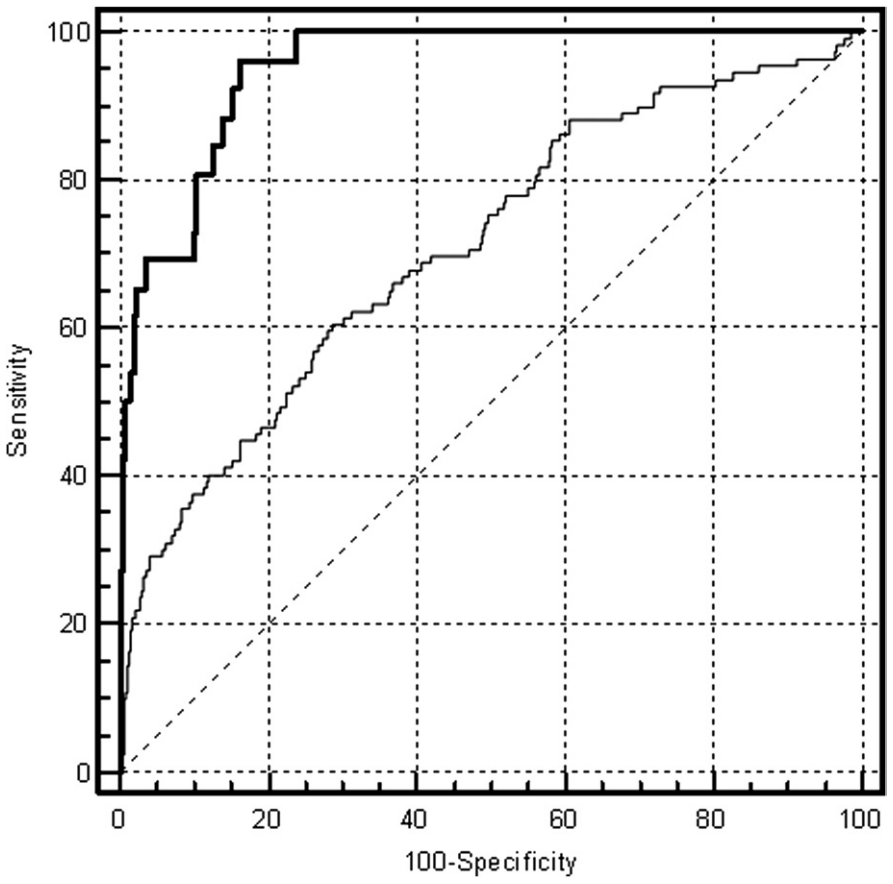
Figure 2 shows the receiver operating characteristic curve for late PE (area under the curve, 0.710; 95% confidence interval, 0.658–0.763) and early PE (area under the curve, 0.96; 95% confidence interval, 0.94–0.98) models. The diagnostic performance for late and early PE for FPRs of 5%, 10%, and 15% is presented in Table 2. Table 3 shows the DR for early PE for a 5% and 10% FPR of each individual predictor and their combinations.

Comment

This study supports previous evidence that integrated first-trimester screening shows a high performance for the detection of early PE. The study evaluated a large sample of patients under typical clinical conditions and suggests that PE screening can be satisfactorily performed in a routine care setting. In addition, screening was performed on European Mediterranean patients, normally associated with lower cardiovascular risks.[18] The a priori risks for PE previously reported had been modeled using patient cohorts from the United Kingdom, with higher proportions of patients with cardiovascular risk factors and Afro-Caribbean origin.[12,23] As previously shown, the maternal risk factors for PE may vary considerably in other populations,[24] which highlights the need to calculate a priori risks in each individual population. The results of this study support that screening for PE is effective even in populations with lower maternal a priori risk.

Early PE is the less prevalent form of the disease, but is a major contributor to maternal and perinatal complications in developed countries.[8] The results of this study demonstrate that a combination of maternal history, BP, and ultrasound data in the first trimester achieves a reasonably high sensitivity, with DR of between 69% and 81% for 5% and 10% FPRs, respectively. These figures are slightly lower than those reported by Poon et al[25] (89.2% DR) in the Fetal Medicine Foundation (FMF) cohort using the same set of predictors. The most obvious difference between the studies performed by the FMF and this one is the performance of the maternal a priori risk. Thus, in our study the DR achieved by maternal factors was 31% for a 10% FPR. This figure is remarkably lower than the 41% obtained in the largest reported study, which was performed in the United Kingdom in 30,784 unselected low-risk women.[23] This higher performance is likely to be explained by differences in the prevalence of risk factors, including mean BMI and the proportions of black women and of patients with a previous PE, which were higher in the United Kingdom study. Aside from differences in a priori risk, it could be argued that some maternal predictors may have been recorded more accurately in previous studies performed in a research setting. Particularly, BP in previous studies reported by the FMF was measured following a strict protocol, in-

FIGURE 2
Receiver operator characteristic curves



Late (*thin line*) and early (*thick line*) preeclampsia.

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cluding >1 measurement in both arms, and recording as final an average of these measurements. While this protocol is optimal for measuring BP,[26] it is not current practice in most clinical settings. In the present study, BP was measured once in 1 arm following routine protocols by health care staff serving at pregnancy clinics, and recorded in the patient's medical record. In any event, the DR achieved by combining maternal factors and BP in this study (46%) was remarkably similar to that reported by the FMF (48.6%) with the use of strict recording protocols.[25]

TABLE 2
Diagnostic performance for late and early preeclampsia

Variable	Risk cutoff	Prevalence of positives %	DR, %	FPR, %	+LHR	–LHR
Late PE	>1/14	5.5	29.4	5	5.88	0.74
	>1/18	10.6	39.6	10	3.96	0.67
	>1/22	15.6	42.2	15	2.81	0.68
Early PE	>1/73	5.1	69.2	5	13.84	0.32
	>1/178	10.1	80.8	10	8.08	0.21
	>1/278	15.1	96.2	15	6.41	0.04

DR, detection rate; *FPR*, false-positive rate; *LHR*, likelihood ratio; *PE*, preeclampsia.

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TABLE 3
Detection rate for early preeclampsia of each individual predictor and their combinations

Variable	5% FPR	10% FPR
A priori risk	25%	31.4%
MAP	38.5%	61.5%
Mean UtA-PI	46.2%	57.7%
A priori risk + MAP	46.3%	69.2%
A priori risk + mean UtA-PI	65%	73.3%

FPR, false-positive rate; *MAP*, mean arterial pressure; *PI*, pulsatility indices; *UtA*, uterine artery.

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UtA Doppler was the strongest predictor of early PE in this study. It improved the DR achieved by maternal factors from 31% to 73%. This is in line with previous studies. In a study performed by the FMF Poon et al[13] reported that the addition of UtA measurements to maternal factors improved the DR from 37% to 65%, a slightly lower figure than that found in the present study. We speculate that the opportunity for improvement may be greater when the DR achieved by maternal factors is smaller. Important information provided by the current study is that the performance of UtA Doppler seems to be high regardless of the method of measurement. Poon et al,[13] and in general all studies reported by the FMF, evaluated the UtA by transabdominal ultrasound while we predominantly used a vaginal approach. Additionally, the authors reported that the best DR was obtained using the lowest PI of any UtA, while the highest predictive value in our study was achieved using the mean PI of both arteries.[13]

This study evaluated 2 biochemical markers now used for the screening of Down syndrome. As expected, fβ-HCG was not associated with an increased risk of PE. The findings concerning PAPP-A may seem more surprising, since previous studies had suggested an association between this biomarker and the subsequent risk of PE. However, the association of PAPP-A with PE is weak and it becomes nonsignificant when combined with other markers. Thus, the FMF,[10] in

a nested case-control study published in 2010 and including 90 PE and 180 unaffected controls, in which various combinations of maternal factors, soluble endoglin, placental growth factor, and PAPP-A were explored, concluded that PAPP-A did not contribute to the prediction of PE. In another study from the same group Akolekar et al[27] explored a combination of maternal factors, UtA-PI, inhibin A, and PAPP-A and reached similar conclusions, that is, PAPP-A did not improve prediction. Finally, and also from the FMF, Poon et al[9] reported a study addressing the differential contribution of several factors to the prediction of PE, and concluded that PAPP-A added virtually no value to the prediction of PE when used in combination with UtA Doppler. We acknowledge that a potentially additional reason influencing the performance of PAPP-A is that 70% of the cases in this present study were measured at 8-10 weeks. It is biologically plausible that the predictive value for biochemical markers is later in the first trimester. Recent data concerning the longitudinal trends of several biochemical markers demonstrate that they correlate with UtA Doppler only late in the first trimester.[28] This may generate some conflict on designing combined strategies for the prediction of aneuploidy and PE. While the best performance for predicting trisomy 21 is achieved at 9-10 weeks, this might be detrimental to the prediction of PE. If the value of other biochemical markers such as angiogenic factors is confirmed in prospective large studies, an optimal trade-off between aneuploidy and PE screening should be determined.

The DR of late PE was much lower than that of early PE. The prevalence of late PE is significantly greater than that of early PE. While it remains a serious maternal-fetal health problem in developing countries, late PE is associated with normal perinatal outcomes in the vast majority of cases in the Western world and other developed countries. The development of late PE is thought to be significantly influenced by maternal predisposition with little or negligible placental component, which explains a much lower presence of the intrauterine growth restriction that occurs in virtually all cases of early PE.[29] The low degree or absence of placental insufficiency, and the fact that maternal predisposition may occur due to a wide variety of subclinical conditions, makes predicting PE in the first trimester quite challenging. Consequently, the predictive value of screening at such early gestational age in previous studies has been consistently low.[11-13,23,25]

This study was conducted in a large unselected population under usual clinical care conditions. This is a strength of the study and reinforces the notion that screening for PE is feasible and effective in populations with a lower a priori risk. Among the limitations of the study, we acknowledge that the performance of the screening here proposed should be validated in further prospective studies. In addition, while the personnel taking part in the study were indeed clinical staff, we acknowledge that, being a large tertiary center, the skills of the clinicians recording UtA Doppler, and consequently the reproducibility of the measurements, could have been higher than the average. Finally, the study did not evaluate any angiogenic factors, which currently have become strong candidates for the prediction of PE and have been shown to improve the performance of screening strategies.[10,11] Assessment of placental growth factor in a future study in the same population is warranted.

To conclude, our study suggests that first-trimester screening combining maternal factors with UtA Doppler, BP, and PAPP-A is useful to predict PE in a routine care setting. Further studies evaluating the addition of other predictors are required. In addition, studies assessing the implementation of a screening strategy at first trimester to select women for prophylactic interventions are also needed. ■

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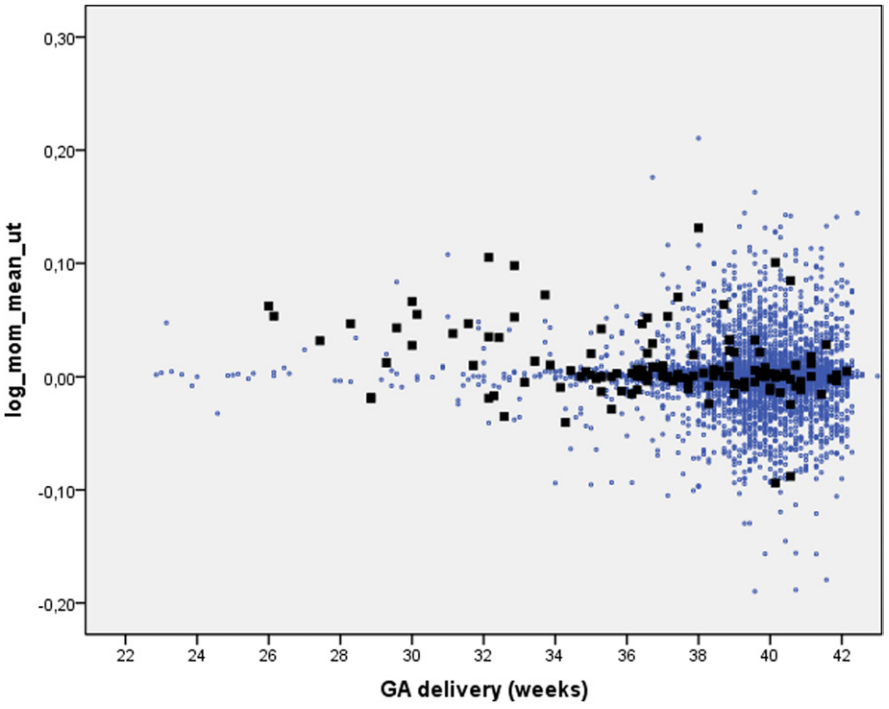
APPENDIX

SUPPLEMENTAL FIGURE 1
Mean uterine artery PI (in log MoM values) against GA at delivery



Blue dots = unaffected; *Black squares* = affected by preeclampsia.

GA, gestational age; *MoM,* multiple of expected normal median; *PI,* pulsatility indices.

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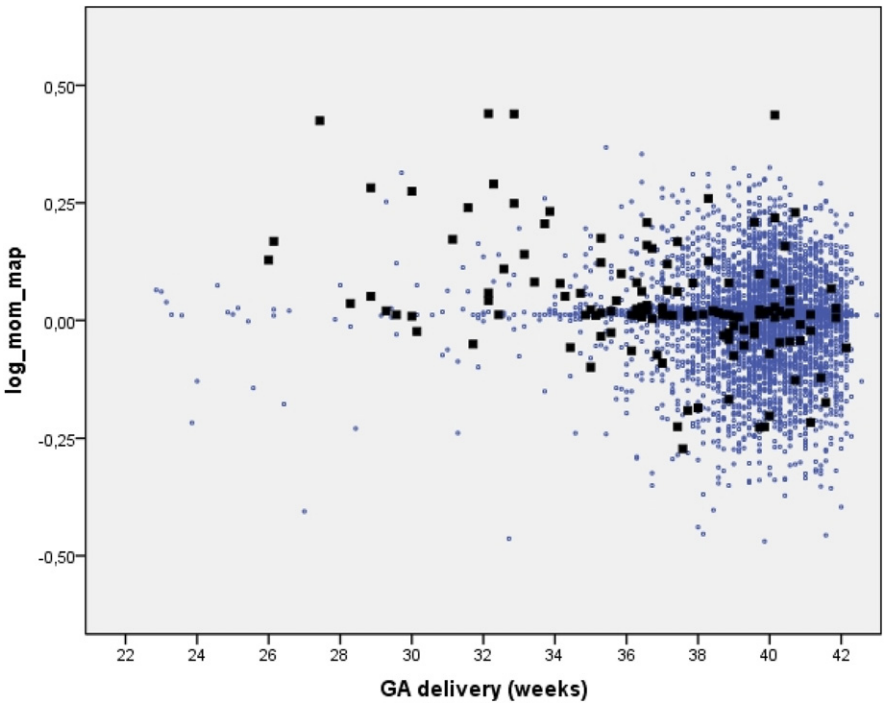
SUPPLEMENTAL FIGURE 2

MAP (in log MoM values) against GA at delivery



Blue dots = unaffected; *Black squares* = affected by preeclampsia.

GA, gestational age; *MAP,* mean arterial pressure; *MoM,* multiple of expected normal median.

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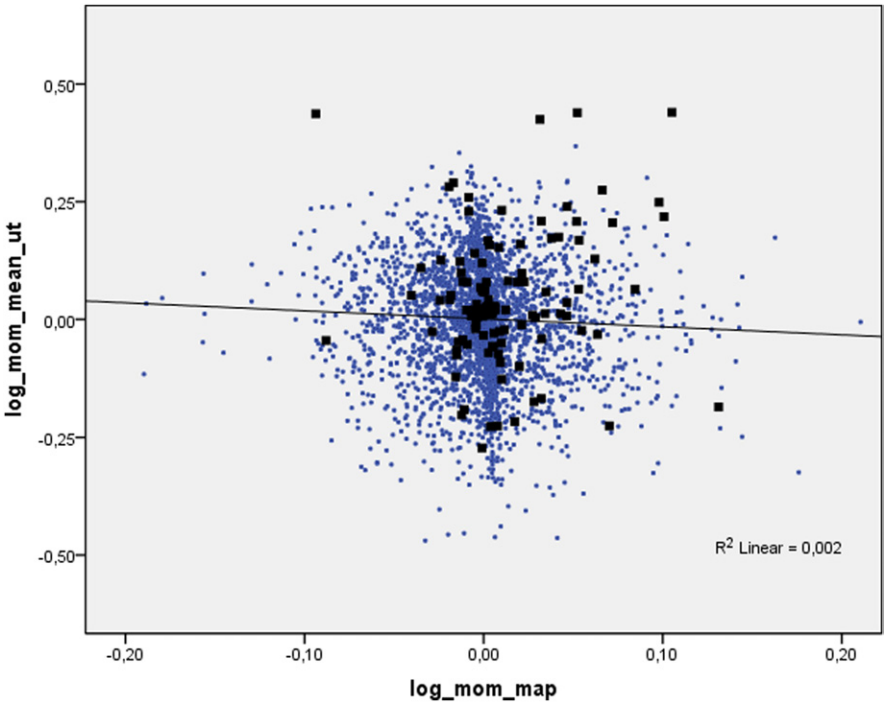
SUPPLEMENTAL FIGURE 3

Correlation between uterine artery PI and MAP (in log MoM)



Blue dots = unaffected; *Black squares* = affected by preeclampsia.

MAP, mean arterial pressure; *MoM,* multiple of expected normal median; *PI,* pulsatility indices.

Scazzocchio. First-trimester preeclampsia screening in routine care. Am J Obstet Gynecol 2013.