OBSTETRICS

First trimester risk of preeclampsia and rate of spontaneous birth in patients without preeclampsia

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BACKGROUND: First-trimester screening for preeclampsia using a combination of maternal risk factors and mean arterial pressure, uterine artery pulsatility index, and placental growth factor, as proposed by the Fetal Medicine Foundation, provides effective prediction of preterm preeclampsia. Placental dysfunction is a potential precursor of spontaneous birth.

OBJECTIVE: The objective of this study was to examine if the estimated risk of preeclampsia is associated with the gestational age at onset of spontaneous delivery in the absence of preeclampsia.

STUDY DESIGN: This was a secondary analysis of the data from the Screening programme for pre-eclampsia trial in which there was a comparison of the performance of first-trimester screening for preterm preeclampsia using the Fetal Medicine Foundation model vs a traditional history-based risk scoring system. A subgroup of women from the trial with spontaneous onset of delivery (labor with intact membranes or preterm prelabor rupture of membranes) was included in this study and was arbitrarily divided into 3 groups according to the risk for preterm preeclampsia as determined by the Fetal Medicine Foundation model at 11 to 13 weeks' gestation as follows: group 1 low risk (<1/100); group 2 intermediate risk (1/50 to 1/100); and group 3 high risk (>1/50). A survival analysis was carried out using a Kaplan-Meier estimator and a Cox regression analysis with stratification by the 3 preeclampsia risk groups. Occurrence of spontaneous birth in the study groups was compared using log-rank tests and hazard ratios.

RESULTS: The study population comprised 10,820 cases with delivery after spontaneous onset of labor among the 16,451 cases who participated in the Screening programme for pre-eclampsia trial. There were 9795 cases in group 1, 583 in group 2, and 442 in group 3. The gestational age at delivery was <28, <32, <35, <37, and <40 weeks in 0.29%, 0.64%, 1.68%, 4.52%, and 44.97% of cases, respectively, in group 1; 0.69%, 1.71%, 3.26%, 7.72%, and 55.23% of cases, respectively, in group 2; and 0.45%, 1.81%, 5.66%, 13.80%, and 63.12% of cases, respectively, in group 3. The curve profile of gestational age at spontaneous birth in the 3 study groups was significantly different overall and in pairwise comparisons (*P* values <.001). The Cox regression analysis showed that risks increased for spontaneous birth by 18% when the intermediate-risk group was compared with the low-risk group (*P*<.001) and by 41% when the high-risk group was compared with the low-risk group (*P*<.001).

CONCLUSION: In this study that investigated birth after spontaneous onset of labor in women without preeclampsia, there were 2 major findings. First, the duration of pregnancy decreased with increasing first-trimester risk for preeclampsia. Second, in the high-risk group, when compared with the low-risk group, the risk for spontaneous birth was 4 times higher at a gestational age of 24 to 26 weeks, 3 times higher at 28 to 32 weeks, and 2 times higher at 34 to 39 weeks. These differences present major clinical implications for antepartum counselling, monitoring, and interventions in these pregnancies.

Key words: competing risks model, first-trimester screening, labor, mean arterial pressure, placental growth factor, preeclampsia, preterm birth, SPREE study, survival analysis, uterine artery Doppler

Introduction

Screening for preterm preeclampsia (PE), as proposed by the Fetal Medicine Foundation (FMF) method in which the patient-specific risk is derived from a combination of maternal risk factors and the uterine artery Doppler pulsatility index (UtA-PI), the mean arterial pressure (MAP), and the serum placental growth factor (PIGF) level, provides an effective prediction of the risk for the major form of placental dysfunction that leads to preterm PE.[1–3] This method substantially outperforms screening based on maternal history alone as recommended by the National Institute for Health and Care Excellence (NICE) guidelines. An observational study that compared the FMF method with the NICE guidelines reported that at the same screen positive rate of about 10%, the detection rate for preterm PE was 82% when using the FMF method and 41% when using the NICE guidelines.[2] The FMF method is now endorsed by several international organizations, including the International Federation of Gynaecology and Obstetrics (FIGO).[4]

Placental dysfunction is also thought to be a potential precursor of spontaneous preterm birth (sPTB), demonstrated by a lower mean birth weight percentile among premature neonates[5,6] and by evidence suggestive of impaired placentation in a substantial proportion of cases with sPTB.[7–11] There is also some contradictory evidence that showed that among patients who received low-dose aspirin prophylaxis for different indications, the risk for sPTB was decreased.[11–21] The mechanism responsible for initiating term or preterm parturition among humans is largely unknown, although there is a common inflammatory pathway that is shared by spontaneous term and preterm labor.[22] However, it was proposed that the placenta and membranes play a

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Why was this study conducted?

The objective of this study was to assess the extent to which the risk of preeclampsia (PE), calculated by the FMF model, may be associated with gestational age at onset of spontaneous birth among women delivering without PE, at term or preterm.

Key findings

There is a direct association between increasing semiquantitative risk for preterm preeclampsia (PE) and the rates of spontaneous birth among women with no PE when using the Fetal Medicine Foundation method of screening for PE, which combines maternal risk factors with mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor.

What does this add to what is known?

Screening for PE according to the Fetal Medicine Foundation method provides additional benefit beyond PE prediction. Patients with an increased risk for PE deliver earlier and have a greater risk for spontaneous birth at term or preterm that may warrant additional screening and eventually opportunities for timely prophylaxis or treatment. These results support the hypothesis that subclinical forms of dysfunctional placentation associated with the risk for PE may be an etiologic precursor of spontaneous human parturition.

major role and that cellular senescence also contributes to a large extent.[23]

A prediction of the gestational age at spontaneous birth is challenging, particularly when attempted in the first trimester. Moreover, the optimal or expected timing of delivery based on the risk for PE and placental dysfunction was not explored extensively before, and individualization of the optimal time for delivery is one of the targets to address with future research to improve maternal-fetal outcomes. The objective of our study was to assess the extent to which the risk for PE, calculated by the FMF model, may be associated with gestational age at onset of spontaneous birth among women who delivered without PE at term or prematurely.

Materials and Methods

Study design, setting, and participants

This was a secondary analysis of the Screening program for pre-eclampsia (SPREE) study,[2] which was a multicenter cohort investigation involving 16,747 women with singleton pregnancies, conducted across 7 maternity hospitals within the National Health Service in England between April 2016 and December 2016. The primary objective of this study was to assess the effectiveness of screening for preterm PE using the FMF model by comparing it with risk scoring as recommended by the NICE. The outcomes obtained through screening were not disclosed to the patients or their obstetricians. Low-dose aspirin prophylaxis was administered from the first trimester to 36 weeks' gestation according to individual policies at each local hospital.

In this study, we excluded women who delivered before 24 weeks' gestation and those who developed PE, had iatrogenic deliveries (including induction of labor and elective or prelabor cesarean delivery), severe maternal diseases, and major fetal abnormalities detected at 11 to 13 weeks' gestation. Only cases with spontaneous onset of birth (labor with intact membranes or preterm prelabor rupture of membranes) were included.

The study population was arbitrarily divided into 3 groups according to the risk for preterm PE determined by the FMF model at 11 to 13 weeks' gestation as follows: group 1 was the low-risk group (<1/100); group 2 was intermediate risk (1/50 to 1/100); and group 3 was high risk (>1/50). The risk was estimated from a combination of maternal demographic characteristics, elements from the medical history, and measurements of MAP, UtA-PI, and PlGF.

Variables and outcomes

The primary outcome was gestational age at spontaneous onset of labor with no PE. Spontaneous onset of birth was defined as any prelabor rupture of membranes (at term or preterm) or any progressive and significant cervical modification and ripening, coupled with regular uterine activity or a cervical dilation >6 cm.[24]

The definition of PE used was that proposed by the American College of Obstetricians and Gynecologists in 2019.[25] It requires the presence of chronic or gestational hypertension, together with development of ≥1 of the following conditions: new-onset proteinuria, serum creatinine exceeding 97 μmol/L in the absence of underlying renal disease, serum transaminase levels exceeding twice the normal range (≥65 IU/L for our laboratory), platelet count dropping below 100,000/μL, the occurrence of headaches or visual symptoms, or the onset of pulmonary edema. Chronic hypertension was defined as having a systolic blood pressure measurement of ≥140 mm Hg and/or a diastolic blood pressure measurement of ≥90 mm Hg, recognized either before pregnancy or at a gestational age of before 20 weeks. In contrast, gestational hypertension was characterized as new-onset hypertension arising at ≥20 weeks' gestation in a woman who was previously normotensive.[26]

Data sources and measurements

Data were retrieved from the electronic database of the SPREE study. Gestational age was determined in the first trimester by ultrasound measurements of the fetal crown-rump length.[27] In all cases, screening for PE was performed at 11+0 to 13+6 weeks' gestation. In the same visit, we also recorded the maternal demographic characteristics and medical history, fetal anatomy, measurement of

nuchal translucency, and the concentrations of MAP, UtA-PI (according to standardized protocols),[1–4,28] and serum PlGF using automated analyzers (DELFIA Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, MA; and BRAHMS KRYPTOR analyzer, Thermo Fisher Scientific, Hennigsdorf, Germany).

Study size

A post hoc power analysis was carried out for the main analysis, taking into account the number of events in each study group, using the Schoenfield formula.[29] The observed statistical power was 99.9% for comparison between group 1 and 3 and 95.4% when comparing group 1 with 2. When adapting the Bonferroni correction for multiple comparisons, the observed statistical power was 99.9% and 92.4%, respectively. The type 1 error rate was set at 5% significance level (2.5% with Bonferroni correction).

Statistical methods

A survival analysis was carried out using a Kaplan-Meier estimator with stratification by the 3 study groups with different risk categories for preterm PE. A log-rank test was applied to compare the gestational age at spontaneous birth in the study groups. Gestational age–specific risks for spontaneous birth were calculated and presented graphically for study groups. A Cox regression analysis was used to calculate the hazard ratio (HR) using the 3 study groups as categorical variables. The low-risk group (group 1) was used as reference for calculating the HRs. The assumption of risk proportionality was evaluated using log minus log plots analysis (results not shown). A subanalysis was carried out using the Kaplan-Meier estimator to explore the effect of aspirin after matching treated and untreaded groups according to the risk for PE.

All statistical analyses were carried out using SPSS Statistics for Windows (version 27.0; IBM Corp, Armonk, NY). Statistical significance was considered for a α error of 0.025 and β error of 0.8.

Results

Participants

The study population comprised 10,820 cases with delivery after spontaneous onset of labor among the 16,451 cases included in the SPREE study. There were 9795 (90.5%) cases in group 1, 583 (5.4%) cases in group 2, and 442 (4.1%) cases in group 3.

Descriptive and outcome data

The distribution of gestational age at delivery is shown in Table 1. Delivery at <28, <32, <35, <37, and <40 weeks' gestation occurred in 0.29%, 0.64%, 1.68%, 4.52%, and 44.97% of the cases, respectively, in group 1; in 0.69%, 1.71%, 3.26%, 7.72%, and 55.23% of the cases in group 2; and in 0.45%, 1.81%, 5.66%, 13.80%, and 63.12% of the cases in group 3.

Main results

The curve profile in Figure 1 depicting the proportion of women still pregnant as gestational increases in the 3 study groups was significantly different overall and in the pairwise comparisons (P values <.001). Overall, the greater the first-trimester risk for PE, the earlier was the gestational age at spontaneous birth, both at term and prematurely.

The smoothed risk for spontaneous birth throughout pregnancy depended on both the gestational age and the study group category (Figures 2, 3, and 4). With advancing gestational age, the risk for spontaneous birth increased and converged among the 3 study groups. The greater the risk for PE, the higher the chance of a spontaneous birth at an earlier gestational age, at term or prematurely. The Cox regression analysis quantified the HRs in the study groups, which were significantly different (P<.001) (Table 2). A subanalysis was performed for 292 cases (2.67%) who were treated with aspirin and who were matched 1:1 with cases who were not treated, based on their risk for PE. The average risk for PE was identical in both cases and controls (mean risk treated group, 1/1084; SD, 1/2028; mean risk untreated group, 1/1084; SD, 1/2027). A Kaplan-Meier survival model indicated that aspirin did not exhibit a significant overall effect (log rank test P=.922) (Supplemental Figure).

Comment

Principal findings

There were 2 major findings in this study in relation to the onset of spontaneous birth. First, the duration of pregnancy decreased with increasing first-trimester risk for PE. Second, in the high-risk group, when compared with the low-risk group, the smoothed risk for spontaneous birth was approximately 4 times higher at 24 to 26 weeks' gestation, 3 times higher at 28 to 32 weeks' gestation, and 2 times higher at 34 to 39 weeks' gestation and became equivalent at 40 weeks' gestation and beyond with an

TABLE 1
Cumulative frequency (proportions) of cases and risk for spontaneous birth in the study groups at different gestational age thresholds

Gestational age (wk)	Group 1: PE risk <1:100	Group 2: PE risk 1:50 −1:100	Group 3: PE risk >1:50
<28	28 (0.29)	4 (0.69)	2 (0.45)
<32	65 (0.64)	10 (1.71)	8 (1.81)
<35	165 (1.68)	19 (3.36)	25 (5.66)
<37	442 (4.52)	45 (7.72)	61 (13.80)
<40	4405 (44.97)	322 (55.23)	279 (63.12)
Total	9795	583	442

The data are presented as number (percentage).
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TABLE 2
Cox Regression model showing the significant effect of PE risk on the risk for spontaneous delivery with no PE in the 3 study groups

Variables	B	SE	Wald	DoF	*P*	HR	95% CI of HR
PE risk <1/100[a]			63.320	2	<.001		
PE risk 1/50—1/100	0.169	0.043	15.635	1	<.001	1.184	1.089—1.287
PE risk >1/50	0.342	0.049	49.282	1	<.001	1.407	1.279—1.548

The hazard ratios for spontaneous birth with no PE increased progressively across the categories of PE risk.

B, regression coefficient; *CI*, confidence interval; *DoF*, degrees of freedom; *HR*, hazard ratio; *PE*, preeclampsia; *SE*, standard error; *Wald*, Wald coefficient.

[a] Reference category.

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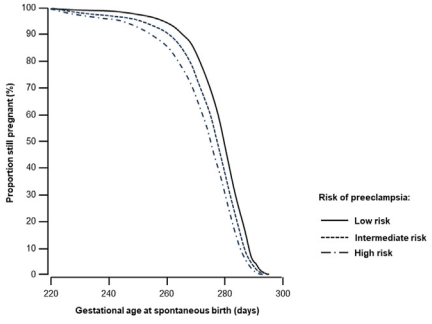
average risk increase of 41% across the entire gestation.

These findings imply that the risk increase for spontaneous birth with advancing gestational age is more pronounced when the risk for PE is greater and that risk separation among groups has a tendency to converge toward term. This explains the apparent discrepancy between the Kaplan-Meier estimate (actual survival estimates at given gestational age) and the Cox regression (risk across gestation).

FIGURE 1
Kaplan-Meier curves depicting spontaneous deliveries without PE in 3 risk categories, across gestational age



Group 1: low risk (<1:100); group 2: intermediate risk (1/50—1/100); group 3: high risk (>1:50). The greater the risk for PE, the earlier the gestational age at spontaneous birth with no PE.

PE, preeclampsia.

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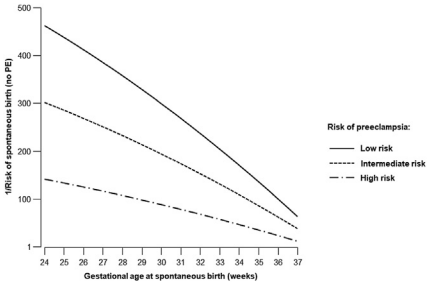
Interpretation in the context of what is known

Spontaneous onset of human parturition involves neuro-immune-endocrine interactions between the fetus, the placenta, and the chorionamniotic membranes and is coordinated by biologic clocks promoting myometrium contractility and cervical ripening.[22,30] There is a common denominator linking all processes of initiation of spontaneous birth, both at term and prematurely, defined by previous research on the PTB phenotype based on specific etiologic features.[31,32] The combined screening test for PE by the FMF algorithm captures clinical and subclinical forms of placental dysfunction, related to the inherent risk factors and biomarkers included in the risk calculation. Previous studies that examined the predictive power of first trimester screening tests for PTB reported heterogeneous results because of diversity in the study design, patients included, methods used, and thresholds of PTB definitions.[17—21] However, the overall thoughtful interpretation of previous literature available on this topic showed that iatrogenic and sPTB can be predicted by first-trimester screening for PE with a limited detection rate of about 30% for an false positive rate of about 10%.[18—21] Moreover, aspirin prophylaxis prevented 65% of PTB caused by PE but did not significantly prevent iatrogenic PTB without PE or sPTB.[17] Despite the suboptimal effectiveness of screening for PTB achieved with the FMF PE screening protocol, it should be emphasized the method was developed to achieve a different aim. Nevertheless, we believe that the application explored in this research may be used based on the results of the studies providing strong support for an association between dysfunctional placentation in the first trimester and sPTB or spontaneous birth at term. Placental dysfunction is believed to potentially precede sPTB, because there is also evidence that indicates the presence of disorders in deep placentation in a significant number of sPTB cases and failure of the physiological transformation of spiral arteries in patients with sPTB and intact membranes.[9,10]

FIGURE 2
Smoothed inverse-risk of spontaneous preterm delivery without PE in 3 risk groups at 24-37 weeks



Group 1: low risk (<1:100); group 2: intermediate risk (1/50—1/100); and group 3: high risk (>1:50). The smoothed risk for spontaneous birth without PE rises with a higher risk for PE and with the progression of gestational age. Furthermore, it tends to align and converge with advancing gestational age across different study groups.

PE, preeclampsia.

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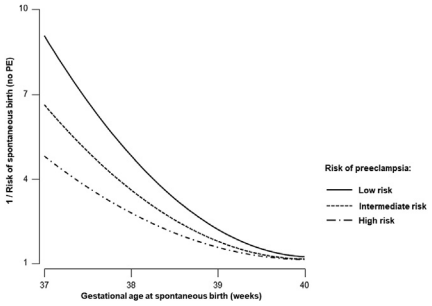
Strength and limitations

The major strength of this study is related to the high quality data that were derived from a major multicenter study in which data collection consistency was upheld through several measures throughout the study period (comprehensive training of investigators, standardized protocols, external validation, quality assurance of biomarker measurements, and continuous monitoring by an independent clinical trial unit). Further major

FIGURE 3
Smoothed inverse-risk of spontaneous term delivery without PE in 3 risk groups, at 37-40 weeks



Group 1: low risk (<1:100); group 2: intermediate risk (1/50—1/100); group 3: high risk (>1:50). The smoothed risk for spontaneous birth with no PE increases with increasing risk for PE. With advancing gestational age, the risk for spontaneous birth with no PE increases, whereas the risk difference among study groups reduces.

PE, preeclampsia.

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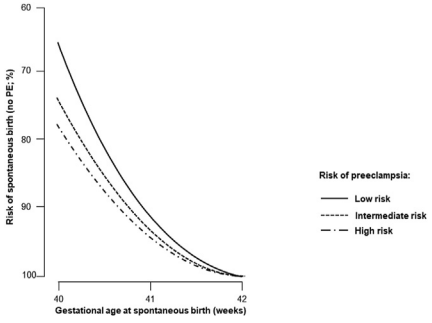
FIGURE 4
Smoothed risk of spontaneous post-term delivery without PE in 3 risk groups at 40-42 weeks



Group 1: low risk (<1:100); group 2: intermediate risk (1/50—1/100); group 3: high risk (>1:50). Again, the smoothed risk for spontaneous birth with no PE increases with increasing risk of PE. With advancing gestational age, the risk for spontaneous birth with no PE increases, whereas the risk difference among study groups reduces. Beyond 41 weeks, there the risk difference among the study groups was minimal.

PE, preeclampsia.

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strengths are that the risk for PE is based on a combination of several covariates showing biologic correlation with placental dysfunction. Finally, the results are likely to be broadly generalizable because the study included a wide array of demographic and racial backgrounds.

Limitations are related to the retrospective design of this analysis and the relatively small sample size of the subgroup with early PTB, especially in the range between 24 and 28 weeks' gestation, which may yield approximate risk estimations, an unavoidable issue with secondary analyses of studies designed to address different research questions. A further limitation relates to the paucity of preventive interventions for sPTB to date. However, this knowledge should stimulate future research on the interplay between onset of labor and placental function. Meanwhile, cervical length screening and timely progesterone administration should be recommended, particularly in the group at higher risk. Finally, 2.7% of women were taking aspirin based on clinician's suggestions (and not based on PE risk), however, the subgroup analysis matched for PE risk failed to show a significant effect of aspirin on the risk for spontaneous birth. Despite these limitations, the correlation between placental dysfunction and spontaneous birth at term or prematurely is clear.

Clinical implications and future research

The SPREE study showed the benefits of first-trimester screening with the use of the FMF algorithm with a DR of preterm PE of 82%, at 10% FPR, compared with a DR of 41% when using screening based on the NICE guidelines.[2] Following these and the major findings of the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention trial, different scientific societies currently endorse early screening for PE using the FMF algorithm,[4,33,34] and a growing number of research groups produced similar results.[35]

This study showed a further potential benefit of PE screening by the FMF method, namely predicting sPTB. Patients at high risk for PE were more likely to deliver earlier and may benefit from additional monitoring for PTB, including monitoring of cervical length. Future large-scale studies with big data mining would untangle the controversies in this research area if centers involved adopt the rigorous research and clinical standard promoted by the FMF. Research tailored to specific clinical phenotypes of PTB related to clinical or subclinical placental dysfunction may deliver specific interventions specific for the PTB etiology.

Conclusion

This study contributes to a better understanding of the natural onset of human parturition. In general, an increased risk for PE during the first trimester as determined by the FMF protocol, is linked to an earlier onset of spontaneous birth, either prematurely or near term. Future research could explore both the prediction of sPTB and the determination of the optimal gestational age for delivery based on the individual PE risk and taking into consideration the shared factors among PE risk, placental dysfunction, and the initiation of labor in a broader framework.[36] ■

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Informed consent was not deemed necessary for the patients recruited retrospectively because anonymous data collection was respected. The patients of the primary study (SPREE study) provided a signed consent form for publishing the anonymized data of the clinical case including all additional analyses on the stored data set.

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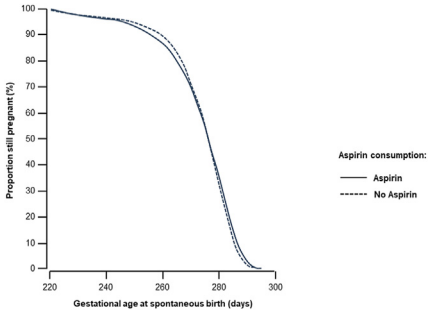
SUPPLEMENTAL FIGURE

Kaplan-Meier curve for spontaneous deliveries without PE, by gestational age, comparing aspirin consumers and non-consumers



The 2 curves are not statistically different.

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