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Risk of preterm birth with routine first-trimester combined screening for pre-eclampsia

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CONTRIBUTION

What are the novel findings of this work?

Women who are classified as high-risk of developing preterm preeclampsia in the first trimester are also at increased risk of both iatrogenic and spontaneous preterm birth (PTB). Our model for prediction of PTB before 33 weeks' gestation showed acceptable discrimination - similar to that obtained by an existing PTB prediction model.

What are the clinical implications of this work?

Iatrogenic and spontaneous PTB share signs of uteroplacental dysfunction in the first trimester that can be evaluated by Fetal Medicine Foundation screening for preterm preeclampsia. Women identified as high-risk of preterm preeclampsia in the first trimester may benefit from measures to assess and reduce the risk of spontaneous PTB.

ABSTRACT

Objectives: Preterm birth (PTB) is a major public health problem worldwide. It can occur spontaneously or be medically indicated for obstetric complications, such as pre-eclampsia (PE) or fetal growth restriction. The main objective of the study was to investigate the implication of uteroplacental dysfunction in the first trimester in subsequent PTB.

Methods: This retrospective cohort study on singleton pregnancies was conducted between March 2018 and December 2020. A total of 11,437 women underwent first-trimester screening for preterm PE using the Fetal Medicine Foundation algorithm, which includes maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and pregnancy-associated plasma protein (PAPP-A). Women with a risk of ≥1 in 50 for preterm PE were classified as high-risk and offered prophylactic aspirin 150mg and serial ultrasound assessments. The following outcomes at delivery were collected: PTB, iatrogenic PTB (iPTB) and spontaneous PTB (sPTB).

Results: 475 (4.2%) women had preterm births with 308 (64.8%) sPTB and 167 (35.2%) iPTB. Patients with PTB had a higher body mass index, were more likely to be Black or Asian and have a history of previous PTB. They also had higher MAP (87.70 vs 86.00, p<0.0001), higher UtA-PI MoM (0.99 vs 0.92, p<0.0001), lower PAPPA MoM (0.89 vs 1.08, p<0.0001). In women at high risk of PE, the odds ratio (OR) for iPTB was 6.0 (95% CI 4.29-8.43, p<0.0001) and for sPTB was 2.0 (95% CI 1.46-2.86, p<0.0001). A prediction model for PTB developed from this cohort performed as well as an existing first-trimester prediction model.

Conclusions: Increased first-trimester risk for uteroplacental dysfunction was associated with both iatrogenic and spontaneous PTB, implying a shared aetiological pathway. The same factors used to predict PE risk show acceptable discrimination to predict PTB before 33 weeks. Women at high risk of uteroplacental dysfunction may warrant additional monitoring and management for an increased risk of spontaneous PTB.

INTRODUCTION

Preterm birth (PTB) affects between 5% and 18% of pregnancies. The resulting complications are the leading cause of death in children under five years of age and a major public health problem worldwide.[1, 2] Maternal or fetal complications such as pre-eclampsia (PE), fetal growth restriction (FGR), placenta praevia or placental abruption are significant causes of iatrogenic PTB (iPTB), which accounts for 20-30% of all PTB.[3, 4] However, most PTB is initiated spontaneously (sPTB), with or without preterm prelabour rupture of membranes (PPROM).

There are multiple putative mechanisms proposed for sPTB.[2] Uteroplacental malperfusion associated with the development of PE and FGR is one of the proposed mechanisms for sPTB.[5-7] Indeed, placental lesions consistent with maternal vascular hypoperfusion were found in pregnancies complicated by preterm labour.[8, 9] Similarly, an imbalance in angiogenic factors with increased anti-angiogenic elements such as soluble endoglin (sEng) and soluble fms-like tyrosine kinase receptor-1 (sFlt-1) has also been associated with sPTB and early-term birth.[10, 11]

The ASPRE study introduced a first-trimester screening algorithm for preterm PE that combines maternal cardiovascular and placental factors to recognise women at higher risk of early uteroplacental dysfunction[12]. A subsequent clinical-effectiveness study demonstrated that the prophylactic treatment with low-dose aspirin in women at high risk of preterm PE could reduce the incidence of preterm PE by 80%.[12, 13] In addition to a reduction in iPTB, low-dose aspirin prophylaxis might also reduce sPTB in pregnant women at risk of PE by 7% before 37 weeks and 14% before 34 weeks.[14] These findings are consistent with previous studies where all types of PTB were associated with low pregnancy-associated plasma protein (PAPP-A) and increased uterine artery Doppler pulsatility index (UtA-PI) in the first trimester.[15, 16]

The main objective of this study was to detect a shared uteroplacental aetiology across different PTB subtypes in the first trimester of pregnancy. Therefore, we investigated the risk factors for PTB in a large cohort of patients who underwent a first-trimester screening program for preterm PE, and the risk of sPTB in the high-risk group for preterm PE. Moreover, we validated an existing first-trimester prediction model for PTB based on first-trimester biomarkers.

METHODS

Population

A retrospective cohort study was conducted at a tertiary centre in Southwest London. All singleton pregnancies booked at St George's Hospitals NHS Foundation Trust before 14 weeks gestation underwent first-trimester screening for preterm PE according to Fetal Medicine Foundation (FMF) algorithm from March 2018 to December 2020. The algorithm-based risk assessment includes maternal factors, mean arterial pressure (MAP), UtA-PI and PAPP-A. It has been previously demonstrated that PAPP-A performs similarly to placental growth factor (PlGF) in detecting preterm PE when applied in the same clinical setting of the current study.[17] At the routine 11-to-13-week ultrasound scan, the crown-rump length (CRL) dimension established gestational age, and the UtA-PI and MAP were measured according to established protocols.[18-20] Those with a risk of ≥1 in 50 for preterm PE were classified as high risk and offered prophylactic aspirin 150mg once a day, as described by previous studies.[13, 21] Moreover, they were scheduled for growth scans at 28 and 36 weeks gestation and offered labour induction from 40 weeks. All women who delivered at St George's University Hospitals NHS Foundation Trust who were managed with this protocol were included in the analysis. Exclusion criteria included pregnancies complicated by miscarriages, terminations and those lost to follow-up.

Study variables and outcomes

Maternal demographics, past medical history and prenatal data were obtained from the ultrasound database (ViewPoint version 5.6.26.148, ViewPoint Bildverarbeitung GMBH, Wessling, Germany) and delivery outcomes (gestational age, birthweight and type of labour and delivery) from the maternity birth registry (EuroKing, Wellbeing software, Mansfield, UK). Both databases are routinely used and checked for the provision of healthcare. The primary outcome was PTB, defined as being <37 weeks gestation. The secondary outcomes were iPTB, defined as PTB caused by indicated induction of labour or caesarean section because of fetal and/or maternal complications, and sPTB due to spontaneous preterm labour or PPROM.

This study was conducted as part of a local clinical audit, and patients' identifiable information was removed before merging the datasets. The local ethics committee advised that formal ethical approval was not required for this retrospective study.

Statistical analysis

Categorical data were presented as numbers (%) and compared using Fisher's exact or Chi-square test. Variables were assessed for normality by the Shapiro-Wilk test and by visualising their histograms. Continuous data were presented as median (interquartile range, IQR) because they were not normally distributed. Non-parametric analysis using Mann-Whitney U-test was then used to compare continuous data between the study groups. Logistic regression analyses were used to assess the association between PTB, iPTB and sPTB and an increased risk of preterm PE. Univariate and multivariate logistic regression analyses were performed, adjusting for risk factors for PTB.

Equations reported by Stout *et al.* of the full logistic regression model for preterm birth at less than 37 and less than 33 weeks were applied to our dataset to obtain predicted risk for each individual.[16] Moreover, a binomial logistic regression was performed to ascertain the effect of predictors from the pre-existing model (previous PTB, Black ethnicity, chronic hypertension, diabetes, PAPP-A MoM and UtA-PI MoM) on the likelihood that participants have PTB in our cohort[16]. Discrimination is the ability of a model to distinguish between delivering preterm and delivering at term and was assessed using the area under the curve (AUC) and 95% confidence interval (95% CI). An AUC of 0.50 indicates no discriminative ability, and the closer the AUC is to 1.0, the better the discriminative performance. Calibration was assessed graphically with a calibration plot. Perfect calibration implies that predictions are on a diagonal line.[22] P-values below 0.05 were considered statistically significant. The statistical analysis was performed using SPSS 27.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period, 11,437 women were screened for preterm PE in the first trimester according to the FMF algorithm, resulting in 475 (4.2%) preterm births with 308 sPTB and 167 iPTB (Figure 1). Maternal demographics, previous history of PTB and data from the first-trimester screening assessment recorded in this study are shown in Table 1. Women who delivered preterm had a higher BMI at booking, were more likely to be Black or Asian, be smokers, have pre-gestational hypertension/diabetes or have a history of PTB. Women who delivered preterm were also more likely to be assessed as high-risk for preterm PE (19.4% vs 6.6%, p<0.0001) with significantly higher MAP (87.70 vs 86.00, p<0.0001), higher UtA-PI MoM (0.99 vs 0.92, p<0.0001) and lower PAPPA MoM (0.89 vs 1.08, p<0.0001). The results of uni- and multivariate binary logistic regression analyses with PTB before 37 weeks as the main outcome is shown in Table S1.

Asian ethnicity, history of PTB, higher UtA-PI and lower PAPP-A MoM were significantly associated with sPTB (Table 2). They remained statistically significant in the multivariate logistic regression analysis: OR 2.92 (95% CI 2.12-4.02) for a history of PTB, OR 0.71 (95% CI 0.57-0.87) for PAPP-A MoM and OR 1.60 (95% CI 1.08-2.37) for UtA-PI MoM (Table S2). Women who had iPTB were older, heavier, Black and had more co-morbidities, including higher MAP at the first-trimester visit, compared to pregnancies complicated by sPTB (Table S3). The indications for elective birth in the iPTB group are shown in Table S4. In the women at high risk of placental dysfunction, there was a significant increase in the risk for both sPTB and iPTB (Table 3). The odds ratio (OR) in the high-risk group for PTB <37 weeks and <34 weeks was 3.4 (95% CI 2.66-4.30) and 2.3 (95% CI 1.47-3.67), respectively. Similarly, the OR for iPTB and sPTB in the high-risk group was 6.0 (95% CI 4.29-8.43) and 2.0 (95% CI 1.46-2.86), respectively.

The logistic regression model developed for PTB before 37 was statistically significant ($\chi^2(6) = 155.731$, p<0.0001). The model explained 5.0% (Nagelkerke R^2) of the variance in PTB and correctly classified 95.7% of cases (sensitivity: 3.2%, specificity: 99.6%, positive predictive value: 26.3% negative predictive value: 96.0%). Of the six predictors (previous PTB, Black ethnicity, chronic hypertension, diabetes, PAPP-A MoM and UtA-PI MoM), all were statistically significant in the model. The AUC (95% CI) of our PTB prediction model was 0.654 (0.627-0.681) for delivery

before 37 weeks and 0.704 (0.653-0.754) for delivery before 33 weeks which are similar to those obtained by the model by Stout *et al*. (AUC, 95% CI: 0.646, 0.619–0.673 for delivery <37 weeks and 0.694, 0.643–0.746, for delivery <33 weeks; Figure 2). In a sub-analysis of 6,274 nulliparous women excluding previous PTB as a predictor, both models gave similar results with AUC values of 0.638 (95% CI 0.602-0.674) and 0.625 (95% CI 0.588-0.662) for PTB before 37 weeks using our model and Stout's model, respectively. The corresponding AUCs for PTB before 33 weeks were 0.712 (95% CI 0.644-0.78) for our model and 0.684 (95% CI 0.613-0.756) for the model developed by Stout *et al.*

Figure S1 illustrates the calibration plot of the pre-existing model by Stout *et al.* for PTB before 37 weeks demonstrating overprediction of the risk.

DISCUSSION

The findings of the study confirm that women assessed as being high-risk for placental dysfunction in the first trimester were at increased risk of sPTB in addition to the expected increase in iPTB for pregnancy complications (Figure 3). The placental function markers in our study were also able to replicate the performance and externally validate an existing first-trimester prediction model for PTB.

Interpretation of study findings and comparison with published literature

PTB is a significant cause of neonatal mortality and morbidity and, thus, a substantial public health problem that the World Health Organization and the UK Department of Health aim to reduce substantially in the near future.[23, 24] The manifestations of early uteroplacental dysfunction that include PE and FGR cause more than half of all iPTB.[25] Therefore, an effective screening program able to identify women at risk of placental dysfunction and reduce preterm PE by using low-dose aspirin will also be beneficial in reducing the rate of iPTB.[13] Consistent with this hypothesis, our data showed that women categorised as having a high risk of preterm PE have a 6-fold higher risk of iPTB, but also demonstrated a 2-fold higher risk of sPTB.

Women who delivered spontaneously preterm had lower PAPP-A MoM and higher UtA-PI in the first trimester, which are recognised markers of placental insufficiency, compared to those who did not. It is accepted that while the final common pathway may be the same, the aetiology of sPTB is multifactorial in nature, including factors such as infection/inflammation, placental ischemia, cervical weakness and uterine overdistension.[2] The role of uteroplacental ischemia in sPTB is supported by increasing evidence from placental histology and serum biomarkers. In sPTB, evidence of maternal vascular malperfusion was identified more often than inflammation/infection and was further associated with severe adverse neonatal outcomes, such as intraventricular haemorrhage.[3] Furthermore, about one-third of patients with sPTB have a failure of physiologic transformation of the myometrial segments of the spiral arteries, which is typically associated with PE and FGR.[8, 9, 26] Finally, preterm labour is associated with an anti-angiogenic profile of an elevated sFlt-1-to-PlGF ratio, in common with PE and FGR.[10, 11]

The ASPRE trial did not find a significant difference in sPTB in the aspirin vs the placebo group.[12] Nevertheless, the results of an individual participant data meta-

analysis including 17 RCT and 28,797 women showed a lower risk of sPTB at less than 37 weeks (RR 0.93, 95% CI 0.86–0.996) and less than 34 weeks (RR 0.86, 95% CI 0.76–0.99) in women assigned to antiplatelet treatment compared with placebo or no treatment.[14] On the basis of this finding, the authors suggested that prophylactic treatment with low-dose aspirin might be applied to a broader population of pregnant women other than those with a high risk of placental dysfunction.[14]

Five prediction models of sPTB, including only maternal factors before 16 weeks' gestation, were externally validated in a Dutch unselected cohort of 2,614 women. The AUC of these models ranged from 0.54 to 0.67 and from 0.56 to 0.70 for sPTB <37 weeks and <34 weeks of gestation, respectively. They performed better in multiparous than nulliparous women.[27] Signs of uteroplacental dysfunction, such as low PAPP-A and increased UtA-PI, in women who delivered preterm for iatrogenic or spontaneous reasons have been described by previous studies.[15, 16, 28] These factors could help improve prediction for women at risk of iatrogenic and spontaneous preterm birth, regardless of parity. Discrimination in our model for the prediction of PTB was similar, also in nulliparous women, to that when using an existing model by Odibo's research group,[16] but the performance was much lower than the AUC of 0.90 to 0.91 claimed by the authors at model development and internal validation.[16] The underperformance may have resulted from model overfitting or the systematic use of 150 mg aspirin in our high-risk group, which may have been protective against some iPTB and sPTB.

Clinical and research implications

Our findings support the hypothesis that preterm labour might be initiated by early uteroplacental malperfusion in a discrete proportion of women. This finding has raised the possibility that high-risk women identified in the early pregnancy could be offered cervical length/fetal fibronectin monitoring and risk-reducing measures for sPTB.[29, 30] However, further studies are necessary to further study the mechanisms of the shared uteroplacental dysfunction in iPTB and sPTB and evaluate the best pathway to monitor and prevent sPTB in women at high risk of early uteroplacental insufficiency identified by the FMF algorithm.

Strengths and limitations

This study evaluates whether women screened and identified as high-risk for preterm PE are also at increased risk of sPTB. Comparing maternal demographic and medical characteristics in a significant cohort of patients is a strength of this study. Our model had moderate screening performance for PTB before 37 weeks obtaining similar results when an existing model's performance for PTB was tested; however, they should be ameliorated before clinical implementation. Another significant limitation is the retrospective design of the study and the potential for confounding factors, as patients at high risk of preterm PE are likely to change their behaviour to reduce this risk. These women were also on prophylactic low-dose aspirin up to 36 weeks gestation, which is known to minimise preterm PE. Moreover, the study did not include the most severe preterm births with PPROM <24 weeks, which resulted in second-trimester miscarriage.

Conclusions

Women identified as high-risk for preterm PE in the first trimester should be considered at increased risk of sPTB as well as iPTB. The demographic, biochemical and biophysical data used to assess preterm PE risk may also have utility in assessing the risk of PTB in the first trimester. Further studies are necessary to improve PTB prediction in the first trimester and to assess the best preventive strategy, such as cervical length screening in mid-gestation or other risk-reducing measures to reduce the risk of sPTB.

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FIGURE LEGENDS

Figure 1. Study diagram. PE: pre-eclampsia

Figure 2. Receiver operating characteristic curves for preterm birth before 33 weeks using our model and an existing prediction model (Stout's model).

Figure 3. Early uteroplacental dysfunction in the pathogenesis of iatrogenic and spontaneous preterm delivery. PTB: preterm birth.

Figure S1. Calibration plot of an existing prediction model for the prediction of preterm birth (37 weeks).

Table 1. Population description

	Term birth (n=10,962)	**Preterm birth (n=475)**	**p-value**
Maternal age	32 (29-35)	32 (29-36)	0.714
Weight	65.50 (58.60-75.00)	67.90 (59.10-78.70)	**0.015**
BMI	24.15 (21.76-27.61)	25.58 (22.11-29.32)	**<0.0001**
Ethnicity			
White	7313 (66.7)	249 (52.4)	**<0.0001**
Black	1167 (10.6)	91 (19.2)	**<0.0001**
Asian	2014 (18.4)	112 (23.6)	**0.002**
Mixed/other	468 (4.3)	23 (4.8)	0.787
Previous PTB	614 (5.6)	81 (17.1)	**<0.0001**
Smoking	439 (4.0)	32 (6.7)	**0.003**
ART Conception	395 (3.6)	24 (5.1)	0.100
Diabetes mellitus	93 (0.9)	16 (3.4)	**<0.0001**
Chronic hypertension	78 (0.7)	12 (2.5)	**<0.0001**
Preterm PE risk	391 (160-948)	212 (70- 552)	**<0.0001**
MAP	86.00 (81.20-91.20)	87.70 (82.30-92.50)	**<0.0001**
UtA-PI MoM	0.92 (0.74-1.12)	0.99 (0.77-1.24)	**<0.0001**
PAPP-A MoM	1.08 (0.75-1.52)	0.89 (0.61-1.32)	**<0.0001**

Data are shown as n (%) and median (IQR). BMI body mass index, PTB preterm birth, ART assisted reproductive technology, PE pre-eclampsia, MAP mean arterial pressure, UtA-PI uterine artery pulsatility index, PAPP-A pregnancy-associated plasma protein A, MoM multiple of median

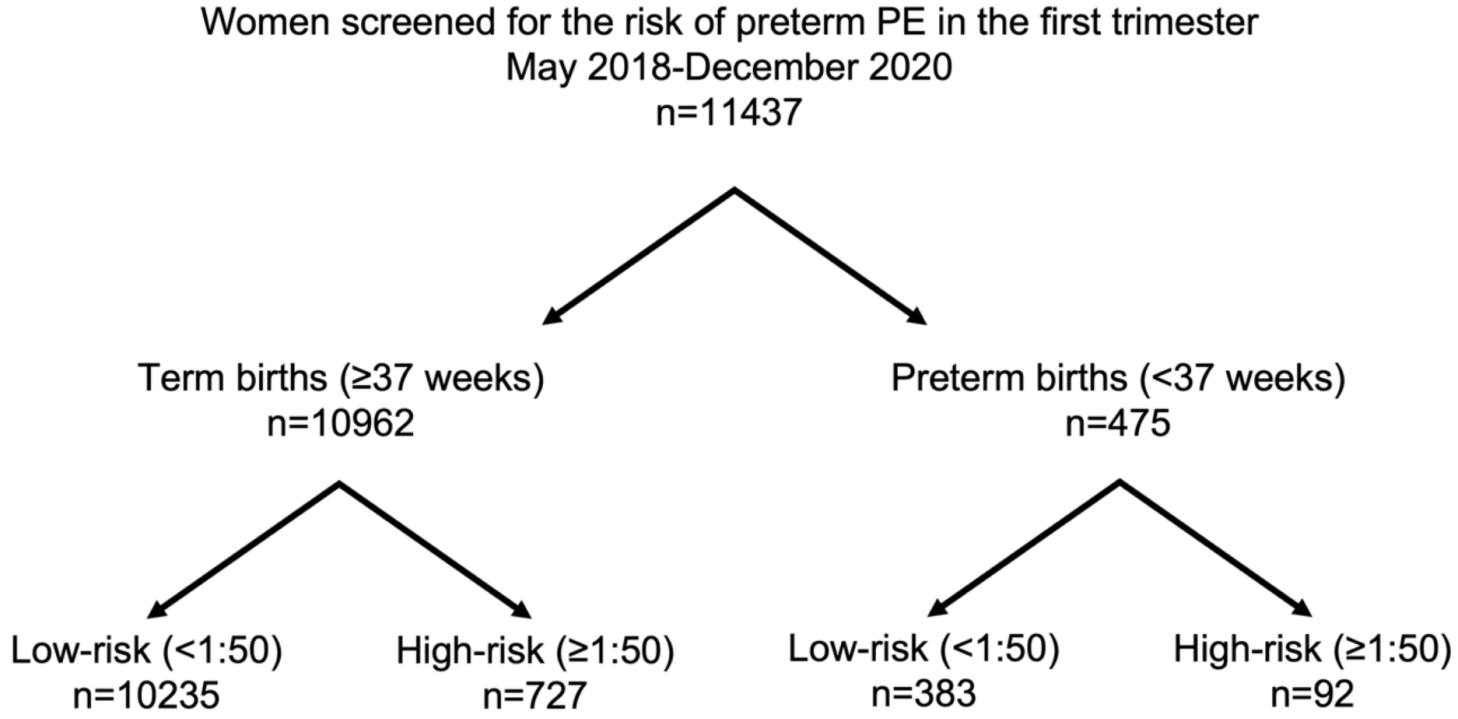
Table 2. Risk factors of spontaneous preterm birth (PTB).

	Non-spontaneous PTB (n=11,129)	**Spontaneous PTB (n=308)**	**p-value**
Maternal age	32 (29-35)	32 (28-35)	0.122
BMI at screening	24.17 (21.77-27.65)	24.96 (21.42-28.76)	0.157
Ethnicity			
White	7387 (66.4)	175 (56.8)	**0.001**
Black	1214 (10.9)	44 (14.3)	0.062
Asian	2050 (18.4)	76 (24.7)	**0.005**
Mixed/other	478 (4.3)	13 (4.2)	0.950
History of PTB	644 (5.8)	51 (16.6)	**<0.0001**
Smoking	455 (4.1)	16 (5.2)	0.335
ART Conception	403 (3.6)	16 (5.2)	0.195
Diabetes mellitus	103 (0.9)	6 (2.0)	0.068
Chronic hypertension	86 (0.8)	4 (1.3)	0.309
UtA-PI MoM	0.92 (0.74-1.13)	0.97 (0.76-1.23)	**0.002**
PAPP-A MoM	1.08 (0.75-1.53)	0.90 (0.64-1.34)	**<0.0001**

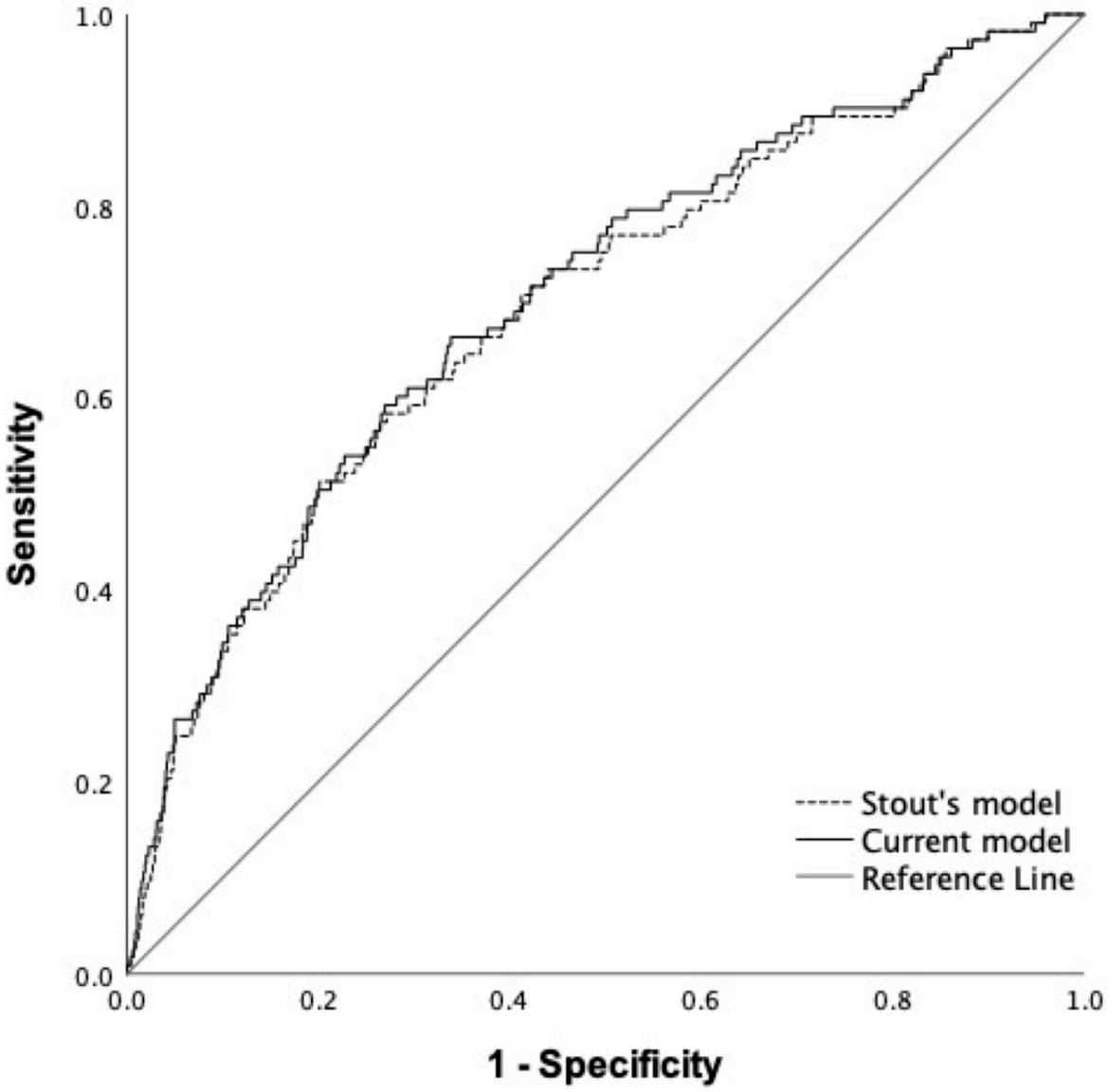
ART assisted reproductive technology, MAP mean arterial pressure, UtA-PI uterine artery pulsatility index, PAPP-A pregnancy-associated plasma protein A, MoM multiple of median.

Table 3. Risk of preterm birth (PTB) in the high-risk and low-risk groups for placental dysfunction.

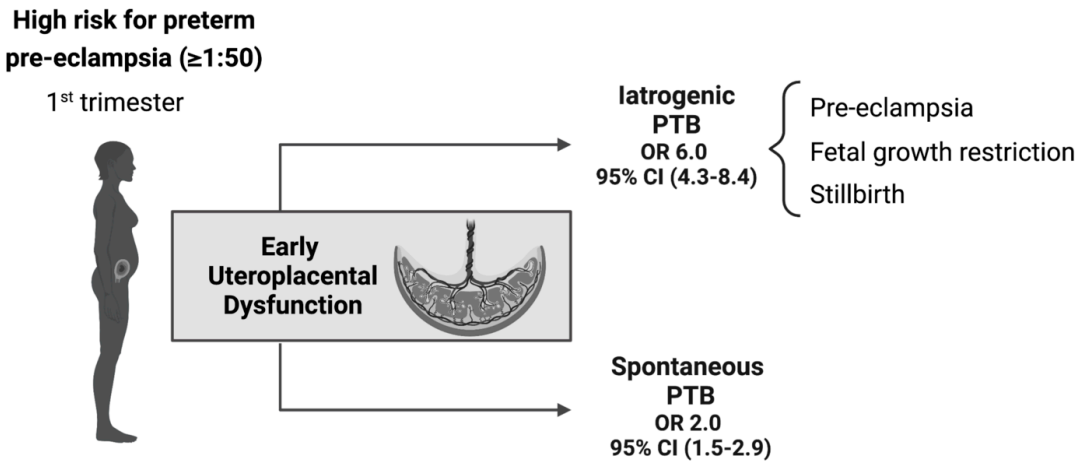
	Low risk (<1:50)	**High risk (≥1:50)**	**OR (95%, CI)**	**p-value**
All PTB <37weeks	383 (3.61%)	92 (11.23%)	3.4 (2.66-4.30)	**<0.0001**
All PTB <34weeks	125 (1.18%)	22 (2.69%)	2.3 (1.47-3.67)	**<0.0001**
Spontaneous PTB	267 (2.51%)	41 (5.01%)	2.0 (1.46-2.86)	**<0.0001**
Iatrogenic PTB	116 (1.09%)	51 (6.23%)	6.0 (4.29-8.43)	**<0.0001**



UOG_24915_Figure 1.tiff



UOG_24915_Figure2.tiff



UOG_24915_Figure 3.tiff