**Biophysical and biochemical markers at 30–34 weeks' gestation in the prediction of adverse perinatal outcome**

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**Running head:** Third trimester biomarkers of adverse perinatal outcome

**Key words:** Third trimester screening, Perinatal outcome, Uterine artery Doppler, Umbilical artery Doppler, Middle cerebral artery Doppler, Mean arterial pressure, Placental growth factor, sFlt-1, Pyramid of antenatal care.

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**Abstract**

Objective: To investigate the potential value of biophysical and biochemical markers at 30-34 weeks' gestation in the prediction of adverse perinatal outcome.

Methods: Screening study in 8,268 singleton pregnancies at 30-34 weeks. Estimated fetal weight (EFW), uterine artery pulsatility index (PI), umbilical artery PI, fetal middle cerebral artery (MCA) PI, mean arterial pressure (MAP), serum placental growth factor (PLGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) were measured. The detection rate (DR) and false positive rate (FPR) of screening by each biomarker were estimated for stillbirth, preeclampsia, delivery of small for gestational age (SGA) neonate, cesarean section for fetal distress before or during labor, umbilical arterial cord blood pH <7.0 or umbilical venous blood pH <7.1, Apgar score <7 at 5 minutes and admission to the neonatal unit (NNU).

Results: Multivariable regression analysis demonstrated that significant prediction of PE was provided by PLGF, sFlt-1, MAP and MCA PI with DR of 98% of PE delivering at <37 weeks' gestation and 56% of those delivering at ≥37 weeks, at 10% FPR. Prediction of SGA was provided by EFW, PLGF, sFlt-1, uterine artery PI, umbilical artery PI, and MCA PI with DR of 88% of SGA at <37 and 51% at ≥37 weeks' gestation, at 10% FPR. Prediction of stillbirth was provided by EFW, uterine artery PI and MCA PI with DR of 30% at 10% FPR. Prediction of cesarean section for fetal distress before labor was provided by EFW, sFlt-1, uterine artery PI and umbilical artery PI with DR of 90%, at 10% FPR. Prediction of fetal distress in labor was provided by EFW and sFlt-1 with DR of 16%, at 10% FPR. There were no significant differences from the normal outcome group in any of the biomarkers for low cord blood pH, low Apgar score or NNU admission for cases other than those with PE and / or SGA.

Conclusion: At 30-34 weeks' gestation, biomarkers of impaired placentation and fetal hypoxemia provide good prediction of PE, SGA and fetal distress before labor, but poor or no prediction of stillbirth and adverse events in labor or after birth.

## Introduction

Impaired placentation, reflected in increased pulsatility index (PI) in the uterine arteries, reduced serum placental growth factor (PLGF) and increased soluble fms-like tyrosine kinase-1 (sFlt-1), is associated with subsequent development of preeclampsia (PE) and birth of small for gestational age (SGA) neonates [1,2]. Another marker of development of PE is increased mean arterial pressure (MAP) [1,2]. Impaired placentation is also associated with fetal hypoxemia and consequent redistribution in the fetal circulation, reflected in reduced fetal middle cerebral artery (MCA) PI and increased umbilical artery PI [3-10].

A screening study at 30-34 weeks' gestation, involving more than 30,000 singleton pregnancies, reported that the incidence of adverse perinatal outcome is higher in SGA than in non-SGA fetuses, but the majority of cases for each adverse event are in the non-SGA group, including about 70% of stillbirths and more than 80% of cases of cesarean section for fetal distress, low cord blood pH and low 5 minute Apgar score [11]. This is analogous to screening for Down syndrome where the risk in women aged $\geq$35 years is substantially higher than in younger women but the overall contribution of the latter group is more than twice as high as that of the older age group. It could therefore be argued that the objective of prenatal screening should be identification of pregnancies with impaired placentation and fetal hypoxemia, irrespective of fetal size.

The objective of this screening study is to investigate the potential value of uterine artery PI, umbilical artery PI, MCA PI, MAP and serum PLGF and sFlt-1, at 30-34 weeks' gestation, in the prediction of adverse perinatal outcome, including development of PE, birth of SGA neonate, stillbirth, cesarean section for fetal distress before or during labor, umbilical arterial cord blood pH $\leq$7.0 or umbilical venous blood pH $\leq$7.1, Apgar score <7 at 5 minutes and admission to the neonatal unit (NNU).

## Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the third trimester of pregnancy at King's College Hospital, London, University College London Hospital, London and Medway Maritime Hospital, Kent, between May 2011 and August 2014. This visit, which was held at $30^{+0}$-$34^{+6}$ weeks' gestation, included recording of maternal characteristics and medical history, estimation of fetal size from transabdominal ultrasound measurement of fetal head circumference, abdominal circumference and femur length. Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks [12,13]. Transabdominal color flow mapping was used to visualize the uterine arteries, umbilical arteries and fetal MCA [14-16]. Pulsed-wave Doppler was then used to obtain waveforms and when three similar consecutive waveforms were obtained the PI was measured.

Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the Ethics Committee of each participating hospital. The pregnancies included in the study were those with data on all eight biomarkers resulting in live birth or stillbirth of phenotypically normal babies at $\geq$24 weeks' gestation.

### Patient characteristics

Patient characteristics recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous, use of ovulation drugs or *in vitro* fertilization), cigarette smoking during pregnancy (yes or no),

medical history of chronic hypertension (yes or no), diabetes mellitus (yes or no), systemic lupus erythematosus (SLE) or anti-phospholipid syndrome (APS) and parity (parous or nulliparous if no previous pregnancies at $\geq$ 24 weeks). Maternal weight and height were measured.

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The outcome measures of the study were stillbirth, cesarean section for fetal distress in labor, umbilical arterial cord blood pH $\leq$7.0 or venous blood pH $\leq$7.1, Apgar score <7 at 5 minutes and admission to NNU. The newborn was considered to be SGA if the birth weight was less than the 10$^{th}$ percentile after correction for gestational age at delivery [17]. The birth weight Z-score was also derived from the normal range for gestational age [17]. The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [18].

Statistical analysis

Comparison between the outcome groups was by $\chi$2-test or Fisher's exact test for categorical variables and Mann Whitney-U test for continuous variables. Categorical data are presented as n (%) and continuous data as median and interquartile range (IQR).

The measured values of uterine artery PI, umbilical artery PI, MCA PI, MAP, PLGF and sFlt-1 were expressed as multiple of the median (MoM) after adjustment for variables from maternal characteristics and medical history that affect these measurements [9-23]. Univariable and multivariable logistic regression analysis was used to determine if $\log_{10}$ MoM of each biomarker had a significant contribution in predicting each adverse outcome. The detection rate (DR) and false positive rate (FPR) of screening were estimated for each adverse outcome. The performance of screening was determined by receiver operating characteristic (ROC) curves analysis.

The statistical software package SPSS 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp, 2013) was used for the data analyses.

## Results

Study population

The characteristics of the study population and the various subgroups according to outcome are given in Table 1.

Biomarkers in pregnancies with stillbirths, PE or birth of SGA neonates

The median MoM values of biomarkers and percentage of values above or below a percentile for pregnancies resulting in stillbirth, PE or birth of SGA neonates with birth weight <10$^{th}$ percentile are compared to the unaffected pregnancies by any one of these adverse outcomes are shown in Table 2.

Stillbirth occurred in 23 (0.28%) pregnancies and in 8 (34.8%) of these the birth weight was below the 10$^{th}$ percentile. In the pregnancies resulting in stillbirth, compared to the unaffected group, there were no significant differences in median MoM values of any of the seven biomarkers (Table 2). However, there was a non-significant tendency for lower PLGF, higher sFlt-1, higher uterine artery PI, lower MCA PI and lower EFW. Multivariable logistic regression analysis demonstrated that significant contributions for stillbirth were provided by

EFW, uterine artery PI and MCA PI (AUROC curve 0.683, 95% CI 0.568-0.797) (Table 3). The DR of stillbirth by combined screening, at FPR of 10%, was 30.4% (Figure 1).

Preeclampsia occurred in 223 (2.7%) pregnancies, including 40 (17.9%) in which delivery was at <37 weeks. In the pregnancies that developed PE, compared to the unaffected group, there was lower PLGF, higher sFlt-1, higher uterine artery PI and MAP and lower MCA PI and EFW; the differences from normal were nore marked in the group of PE delivering at <37 weeks' gestation than in those delivering at ≥37 weeks (Table 2). Multivariable logistic regression analysis demonstrated that significant contributions for PE <37 weeks were provided by PLGF, sFlt-1, uterine artery PI and MAP (AUROC curve 0.992, 95% CI 0.985-1.000) and contributions for PE ≥37 weeks were provided by PLGF, sFlt-1, MCA PI and MAP (AUROC curve 0.808, 95% CI 0.772-0.844) (Table 3). The DR of combined screening by all significant contributors, at FPR of 10%, was 97.5% for PE <37 weeks and 55.8% for PE ≥37 weeks (Figure 1).

In livebirths the birth weight was below the 10$^{th}$ percentile in 822 (9.9%) cases. In the pregnancies with SGA neonates, compared to the unaffected group, there was lower PLGF, MCA PI and EFW and higher sFlt-1, uterine artery PI, umbilical artery PI and MAP; the differences from normal were nore marked in the group of SGA delivering at <37 weeks' gestation than in those delivering at ≥37 weeks (Table 2). Multivariable logistic regression analysis demonstrated that significant contributions for SGA <37 weeks were provided by EFW, PLGF, sFlt-1 and uterine artery PI (AUROC curve 0.954, 95% CI 0.930-0.978) and contributions for SGA ≥37 weeks were provided by EFW, PLGF, sFlt-1, uterine artery PI, umbilical artery PI and MCA PI (AUROC curve 0.829, 95% CI 0.813-0.844) (Table 3). The DR of combined screening by all significant contributors, at FPR of 10%, was 88.3% for SGA <37 weeks and 51.0% for SGA ≥37 weeks (Figure 1).

Biomarkers in pregnancies delivered by cesarean section for fetal distress

In the 8,245 pregnancies with live births, there were 6,263 with vaginal delivery following spontaneous or induced labor, 873 with elective cesarean section for a variety of indications and 1,109 with cesarean section following spontaneous or induced labor; in the latter group the indication for cesarean section was fetal distress in 512 cases. In the elective cesarean section group (n=873) there were a variety of indications, including breech or transverse lie (n=191), placenta previa (n=41), previous cesarean section, traumatic birth or maternal request (n=567), maternal medical disorder (n=44) and SGA fetuses with fetal compromise diagnosed by abnormal fetal heart rate patterns or fetal Doppler indices (n=30).

The median MoM values of biomarkers and percentage of values above or below a percentile for pregnancies resulting in delivery by cesarean section for fetal distress before labor (n=30) or during labor (n=512) and those delivering vaginally are shown in Table 4.

In the group with cesarean section for fetal distress before labor, compared to those delivering vaginally, there was lower EFW, PLGF and MCA PI and higher sFlt-1, uterine artery PI, umbilical artery PI and MAP; the values were >90$^{th}$ or <10$^{th}$ percentile, depending on the biomarker, in 43-90% of the cases (Table 4). Multivariable logistic regression analysis demonstrated that significant contribution to elective cesarean section for fetal distress was provided by EFW, sFlt-1, uterine artery PI and umbilical artery PI (AUROC curve 0.972, 95% CI 0.944-0.999); the DR at 10% FPR, was 90.0% (Table 5, Figure 1).

In the group with cesarean section for fetal distress in labor, compared to those delivering vaginally, there was higher sFlt-1, but no significant differences in median value of the other biomarkers. Multivariable logistic regression analysis demonstrated that significant contribution to cesarean section for fetal distress was provided by EFW and sFlt-1 (AUROC curve 0.556, 95% CI 0.530-0.582); the DR at 10% FPR, was 16.2% (Table 5, Figure 1).

Biomarkers in pregnancies with adverse outcome after delivery

The median MoM values of biochemical and biophysical markers and percentage of values above or below a percentile in pregnancies with and without low cord blood pH, low Apgar score at 5 minutes and admission to the neonatal unit are shown in Table 6.

In the group with low cord blood pH compared to those with normal pH and in those with low 5 minute Apgar score compared to those with normal score, there were no significant differences in the median MoM values of any of the biomarkers. In the group with NNU admission, compared to those without admission, there was lower PLGF and higher sFlt-1 and uterine artery PI. Multivariable logistic regression analysis demonstrated that significant contribution to NNU admission was provided by all three biomarkers (AUROC curve 0.592, 95% CI 0.566-0.619); the DR at 10% FPR, was 24.8% (Table 7). However, when the cases of PE and those with SGA neonates were excluded, none of the biomarkers provided significant contribution in the prediction of NNU admission.

## Discussion

Main findings of the study

The findings of this study demonstrate that in pregnancies that develop PE and those that result in delivery of SGA neonates there is biophysical and biochemical evidence of impaired placentation reflected in increased uterine artery PI and serum sFlt-1 and reduced serum PLGF. In such cases of impaired placentation the EFW is reduced and there is also evidence of fetal hypoxemia reflected in low fetal MCA PI and high umbilical artery PI. The deviation from normal for the biophysical and biochemical markers is more marked in the most severe cases of PE and SGA requiring iatrogenic preterm delivery. Screening by a combination of biomarkers at 32 weeks' gestation predicted 98% of preterm PE and 56% of term PE, at FPR of 10%; the respective values for SGA in the absence of PE were 88% and 51%.

Impaired placentation and fetal hypoxemia are also observed in some of the pregnancies resulting in stillbirth, in those developing fetal distress in labor necessitating delivery by caesarean section and in those requiring admission to NNU. However, the performance of screening with biomarkers at 32 weeks' gestation for these complications is poor with respective DRs of 30%, 16% and 25%, at FPR of 10%. Biomarker testing at 32 weeks was not useful in prediction of low cord blood pH, low Apgar score, or NNU admission for cases other than those with PE and / or SGA.

Strengths and limitations of the study

The strengths of this third-trimester screening study are first, examination of a large population of pregnant women attending for routine care at a gestational age range which is widely used for the assessment of fetal growth and wellbeing, second, use of a specific methodology and appropriately trained doctors to measure MAP and carry out the Doppler studies, third, use of automated machines to prospectively obtain reproducible measurements of serum PLGF and sFlt-1, fourth, estimate MoM values for biophysical and biochemical markers after adjustment for factors that affect the measurements, and fifth, examine a wide range of well accepted indicators of adverse perinatal outcome.

The main limitation of the study is that the results of the 30-34 weeks' scan were made available to the obstetricians of the patients who would have taken specific actions on further monitoring and delivery for the cases of suspected SGA with abnormal Doppler findings. Consequently, the performance of screening for adverse perinatal outcomes by biomarkers of impaired placentation and fetal hypoxemia would have been negatively biased. It is likely

that at least some of the cases of SGA and fetal distress that were delivered by elective cesarean section would have resulted in stillbirth, fetal distress in labor and low cord blood pH had they not been detected by the routine assessment at 32 weeks. In our study there were 30 pregnancies with SGA fetuses that were delivered by elective cesarean section because of abnormal fetal heart rate patterns or fetal Doppler indices and this number is not negligible by comparison with the number of pregnancies with stillbirths and birth weight below the $10^{th}$ percentile (n=8).

Comparison with findings from previous studies

There are no previous third-trimester screening studies of a routine population for adverse perinatal events. In previous screening studies at 30-34 weeks' gestation we used Bayes theorem to combine maternal characteristics and medical history with biophysical and biochemical markers and reported that the DR, at 10% FPR, was 99% for preterm-PE, 89% for preterm-SGA, 75% for term-PE and 57% for term-SGA [21,22].

Implications for clinical practice

An integrated clinic at 32 weeks' gestation, which includes measurement of biomarkers, identifies nearly all cases that will develop PE and those delivering SGA neonates at <37 weeks' gestation and the majority of cases with these complications delivering at term. Performance of screening by combining biophysical and biochemical markers is superior to screening by either group of markers alone. The performance of screening for stillbirth is poor but this is likely to be underestimated because identification of cases with impaired placentation and fetal hypoxemia and their timely delivery would have prevented some of the stillbirths.

In pregnancies without SGA or PE, combined screening at 32 weeks is not useful in the prediction of adverse events during labor or after birth. The extent to which the performance of screening is improved by assessment at 36 rather than 32 weeks remains to be determined.

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## Figure legends

**Figure 1.** Receiver operating characterist curves for prediction of preeclampsia (PE) delivering at <37 and ≥37 weeks' gestation, small for gestational age (SGA) neonates delivering at <37 and ≥37 weeks' gestation, fetal distress resulting in delivery by cesarean section before and during labor, stillbirth and neonatal unit (NNU) admission.

**Table 1.** Maternal and pregnancy characteristics of the study population and subgroups of stillbirth, preeclampsia, small for gestational age neonates, fetal distress in labor leading to cesarean section, low umbilical arterial or venous cord blood pH, low 5-minute Apgar score and admission to the neonatal unit. In each group the data are compared to the cohort without the outcome measure.

| | All pregnancies (n=8,268) | Stillbirth (n=23) | Preeclampsia (n=223) | Small for gestation (n=822) | Fetal distress (n=512) | Low cord pH (n=84) | Low Apgar score (n=70) | NNU admission (n=524) |
|---|---|---|---|---|---|---|---|---|
| **Maternal characteristics** | | | | | | | | |
| Maternal age (years) | 31.0 (26.6-34.7) | 32.9 (23.2-37.2) | 31.5 (26.8-34.8) | 29.7 (25.2-34.2)** | 31.2 (27.0-35.9) | 32.1 (27.1-35.5) | 31.9 (26.5-35.6) | 30.9 (26.4-35.0) |
| Maternal weight (Kg) | 77.0 (68.7-87.8) | 89.0 (66.2-100.5) | 83.8 (72.0-97.5)** | 71.8 (64.0-81.0)** | 81.2 (72.0-93.0)** | 78.8 (73.3-88.7) | 81.9 (71.0-91.1) | 79.2 (70.8-92.0)** |
| Maternal height (m) | 1.65 (1.60-1.69) | 1.65 (1.61-1.68) | 1.64 (1.59-1.69) | 1.63 (1.58-1.67)** | 1.63 (1.59-1.68)** | 1.64 (1.59-1.68) | 1.62 (1.60-1.67) | 1.64 (1.60-1.69) |
| Cigarette smoker | 827 (10.0) | 3 (13.0) | 13 (5.8) | 148 (18.0)** | 46 (9.0) | 7 (8.3) | 8 (11.4) | 67 (12.8) |
| **Racial origin** | | | | | | | | |
| Caucasian | 6,185 (74.8) | 16 (69.6) | 138 (61.9) | 530 (64.5) | 337 (65.8) | 67 (79.8) | 41 (58.6) | 396 (75.6) |
| Afro-Caribbean | 1,437 (17.4) | 5 (21.7) | 69 (30.9)** | 191 (23.2)** | 130 (25.4)** | 11 (13.1) | 23 (32.9)* | 101 (19.3) |
| South Asian | 312 (3.8) | 1 (4.3) | 10 (4.5) | 56 (6.8)** | 27 (5.3) | 4 (4.8) | 2 (2.9) | 12 (2.3) |
| East Asian | 150 (1.8) | 1 (4.3) | 4 (1.8) | 13 (1.6) | 11 (2.1) | 0 (0.0) | 1 (1.4) | 6 (1.1) |
| Mixed | 184 (2.2) | 0 (0.0) | 2 (0.9) | 32 (3.9)* | 7 (1.4) | 2 (2.4) | 3 (4.3) | 9 (1.7) |
| **Conception** | | | | | | | | |
| Spontaneous | 7,996 (96.7) | 22 (95.7) | 215 (96.4) | 799 (97.2) | 485 (94.7) | 83 (98.8) | 68 (97.1) | 500 (95.4) |
| Assisted conception | 272 (3.3) | 1 (4.3) | 8 (3.6) | 23 (2.8) | 27 (5.3)* | 1 (1.2) | 2 (2.9) | 24 (4.6) |
| **Medical disorder** | | | | | | | | |
| Chronic hypertension | 121 (1.5) | 1 (4.3) | 30 (13.5)** | 10 (1.2) | 13 (2.5) | 1 (1.2) | 3 (4.3) | 13 (2.5) |
| SLE / APS | 15 (0.2) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 2 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Diabetes mellitus | 80 (1.0) | 0 (0.0) | 2 (0.9) | 7 (0.9) | 8 (1.6) | 0 (0.0) | 1 (1.4) | 19 (3.6)** |
| **Obstetric history** | | | | | | | | |
| Parous | 4,198 (50.8) | 10 (43.5) | 91 (40.8) | 324 (39.4) | 146 (28.5) | 39 (46.4) | 36 (51.4) | 216 (41.2) |
| Nulliparous | 4,070 (49.2) | 13 (56.5) | 132 (59.2)* | 498 (60.6)** | 366 (71.5)** | 45 (53.6) | 34 (48.6) | 308 (58.8)** |
| **Pregnancy complication** | | | | | | | | |
| Gestational diabetes | 215 (2.6) | 2 (8.7) | 13 (5.8)* | 19 (2.3) | 19 (3.7) | 7 (8.3)* | 3 (4.3) | 32 (6.1)** |
| SROM | 455 (5.5) | 0 (0.0) | 4 (1.8) | 52 (6.3) | 69 (13.5)** | 4 (4.8) | 3 (4.3) | 53 (10.1)** |
| **Labor and delivery** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Spontaneous labor, VD | 5,353 (64.7) | 8 (34.8) | 37 (16.6) | 514 (62.5) | 0 (0.0) | 41 (48.8) | 26 (37.1) | 246 (46.9) |
| Spontaneous labor, CS | 765 (9.3) | 0 (0.0) | 12 (5.4) | 65 (7.9) | 355 (64.5)** | 19 (22.6) | 12 (17.1) | 94 (17.9)** |
| Induced labor, VD | 931 (11.3) | 13 (56.5)** | 89 (39.9)** | 127 (15.5)** | 0 (0.0) | 9 (10.7) | 9 (12.9) | 60 (11.5) |
| Induced labor, CS | 344 (4.2) | 0 (0.0) | 38 (17.0)** | 46 (5.6)* | 177 (34.6)** | 9 (10.7) | 12 (17.1)** | 53 (10.1)** |
| Elective CS | 875 (10.6) | 2 (8.7) | 47 (21.1)** | 70 (8.5) | 0 (0.0) | 6 (7.1) | 11 (15.7) | 71 (13.5) |
| **Assessment** | | | | | | | | |
| GA at assessment (wks) | 32.2 (32.0-32.5) | 32.2 (32.0-32.4) | 32.1 (32.0-32.4) | 32.1 (32.0-32.5) | 32.2 (32.0-32.6) | 32.1 (32.0-32.4) | 32.2 (32.0-32.5) | 32.2 (32.0-32.5) |
| EFW (percentile) | 53.3 (28.9-77.6) | 42.5 (16.5-71.9) | 48.9 (20.9-75.7)** | 18.1 (6.9-37.0)** | 56.0 (31.7-80.4) | 55.1 (29.6-73.6) | 56.8 (23.5-86.5) | 54.9 (24.7-78.3) |
| **Outcome** | | | | | | | | |
| GA at delivery (wks) | 40.0 (39.0-40.9) | 38.3 (36.9-40.7)* | 38.6 (37.3-40.2)** | 39.9 (38.9-40.9) | 40.6 (39.4-41.4)** | 40.0 (38.5-40.9) | 39.9 (38.4-41.2) | 39.0 (36.8-40.6)** |
| BW (percentile) | 48.5 (23.7-74.4) | 32.7 (4.3-75.2)** | 35.0 (9.8-65.8)** | 5.3 (2.7-7.8)** | 41.9 (16.2-71.5)** | 49.8 (19.0-78.4) | 52.5 (15.4-83.0) | 44.5 (18.4-77.8) |

SLE= systemic lupus erythematosus; APS = anti-phospholipid syndrome; SROM = Spontaneous rupture of membranes; VD = vaginal delivery; CS = cesarean section; GA = gestational age

Significance value adjusted for multiple comparisons with *post hoc* Bonferonni correction * = $p<0.01$; ** = $p<0.001$

**Table 2.** Biochemical and biophysical markers in pregnancies resulting in stillbirth, preeclampsia, birth of small for gestational age neonates and those unaffected by any of these adverse outcomes.

| | Unaffected (n=7,207) | Stillbirth (n=23) | PE < 37 wks (n=40) | PE ≥ 37 wks (n=183) | SGA < 37 wks (n=60) | SGA > 37 wks (n=762) |
|---|---|---|---|---|---|---|
| **Biochemical markers** | | | | | | |
| PlGF (MoM), median (IQR) | 1.01 (0.63-1.57) | 0.63 (0.45-1.31) | 0.13 (0.02-0.22)*** | 0.41 (0.28-0.78)*** | 0.33 (0.16-0.61)*** | 0.64 (0.38-1.06)*** |
| PlGF < 5$^{th}$ percentile, n (%) | 224 (3.1) | 1 (4.3) | 31 (77.5)*** | 41 (22.4)*** | 25 (41.7)*** | 93 (12.2)*** |
| PlGF < 10$^{th}$ percentile, n (%) | 534 (7.4) | 2 (8.7) | 36 (90.0)*** | 69 (37.7)*** | 31 (51.7)*** | 156 (20.5)*** |
| | | | | | | |
| sFlt -1 (MoM), median (IQR) | 0.99 (0.74-1.34) | 1.21 (0.64-1.95) | 4.54 (3.05-6.47)*** | 1.43 (0.94-2.20)*** | 1.43 (1.06-3.13)*** | 1.10 (0.78-1.52)*** |
| sFlt > 95$^{th}$ percentile, n (%) | 265 (3.7) | 2 (8.7) | 32 (80.0)*** | 45 (24.6)*** | 19 (31.7)*** | 52 (6.8)*** |
| sFlt > 90$^{th}$ percentile, n (%) | 602 (8.4) | 6 (26.1)** | 35 (87.5)*** | 62 (33.9)*** | 22 (36.7)*** | 102 (13.4)*** |
| **Biophysical markers** | | | | | | |
| Ut PI (MoM), median (IQR) | 0.99 (0.85-1.16) | 1.13 (1.00-1.31) | 1.60 (1.19-2.10)*** | 1.02 (0.85-1.28) | 1.08 (0.97-1.49)*** | 1.04 (0.91-1.28)*** |
| Ut PI > 95$^{th}$ percentile, n (%) | 294 (4.1) | 3 (13.0) | 20 (50.0)*** | 19 (10.4)*** | 12 (20.0)*** | 68 (8.9)** |
| Ut PI > 90$^{th}$ percentile, n (%) | 618 (8.6) | 4 (17.4) | 24 (60.0)*** | 33 (18.0)*** | 19 (31.7)*** | 131 (17.2)*** |
| | | | | | | |
| UA PI (MoM), median (IQR) | 1.01 (0.91-1.12) | 1.02 (0.86-1.13) | 1.08 (0.88-1.17) | 0.99 (0.92-1.10) | 1.16 (1.01-1.23)*** | 1.06 (0.95-1.17)*** |
| UA PI > 95$^{th}$ percentile, n (%) | 317 (4.4) | 1 (4.3) | 4 (10.0) | 6 (3.3) | 14 (23.3)*** | 72 (9.4)*** |
| UA PI > 90$^{th}$ percentile, n (%) | 664 (9.2) | 1 (4.3) | 5 (12.5) | 17 (9.3) | 15 (25.0)*** | 125 (16.4)*** |
| | | | | | | |
| MCA PI (MoM), median (IQR) | 1.02 (0.92-1.12) | 0.95 (0.86-1.01) | 1.01 (0.93-1.12) | 0.99 (0.87-1.09)** | 0.96 (0.87-1.06)** | 1.00 (0.90-1.10)** |
| MCA PI < 5$^{th}$ percentile, n (%) | 339 (4.7) | 2 (8.7) | 2 (5.0) | 18 (9.8)** | 5 (8.3) | 48 (6.3) |
| MCA PI < 10$^{th}$ percentile, n (%) | 668 (9.5) | 4 (17.4) | 4 (10.0) | 30 (16.4)** | 8 (13.3) | 95 (12.5) |
| | | | | | | |
| MAP (MoM), median (IQR) | 1.00 (0.94-1.05) | 1.01 (0.97-1.09) | 1.16 (1.10-1.26)*** | 1.08 (1.00-1.13)*** | 1.03 (0.97-1.11)*** | 1.01 (0.96-1.06)*** |
| MAP > 95$^{th}$ percentile, n (%) | 279 (3.9) | 1 (4.3) | 26 (65.0)*** | 40 (21.9)*** | 11 (18.3)*** | 46 (6.0)** |
| MAP > 90$^{th}$ percentile, n (%) | 606 (8.4) | 2 (8.7) | 29 (72.5)*** | 63 (34.4)*** | 14 (23.3)*** | 90 (11.8)** |
| | | | | | | |
| EFW centile, median (IQR) | 57.3 (33.5-79.4) | 42.5 (16.5-71.9) | 15.6 (1.0-52.2)*** | 55.0 (29.0-77.5) | 4.5 (0.2-18.2)*** | 19.1 (8.0-38.1)*** |
| EFW < 5$^{th}$ percentile, n (%) | 144 (2.0) | 2 (8.7) | 12 (30.0)*** | 7 (3.8) | 31 (51.7)*** | 135 (17.7) |
| EFW < 10$^{th}$ percentile, n (%) | 331 (4.6) | 4 (17.4) | 17 (42.5)*** | 13 (7.1) | 38 (63.3)*** | 228 (29.9)*** |

PE = preeclampsia; SGA = small for gestational age neonate with birth weight below the 10$^{th}$ percentile. PLGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; Ut PI = uterine artery pulsatility index; UA PI = umbilical artery pulsatility index; MCA PI = middle cerebral artery pulsatility index; MAP = mean arterial pressure; EFW = estimated fetal weight. Significance value adjusted for multiple comparisons with *post hoc* Bonferonni correction ** $p<0.01$; *** $p<0.0001$

**Table 3.** Univariable and multivariable logistic regression analysis in prediction of stillbirth, preeclampsia and birth of small for gestational age fetuses from biochemical and biophysical markers

| | Stillbirth | | | | Preeclampsia | | | | Small for gestation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariable analysis | | Multivariable analysis | | Univariable analysis | | Multivariable analysis | | Univariable analysis | | Multivariable analysis | |
| | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
| EFW Z-score | 0.63 (0.42-0.95) | 0.028 | 0.66 (0.44-0.99) | 0.037 | 0.70 (0.61-0.81) | <0.0001 | | | 0.28 (0.25-0.30) | <0.0001 | 0.29 (0.26-0.32) | <0.0001 |
| PlGF ($Log_{10}$ MoM) | 0.32 (0.09-1.15) | 0.080 | | | 0.02 (0.01-0.03) | <0.0001 | 0.10 (0.06-0.15) | <0.0001 | 0.13 (0.10-0.16) | <0.0001 | 0.20 (0.15-0.26) | <0.0001 |
| sFlt -1 ($Log_{10}$ MoM) | 3.04 (0.43-21.68) | 0.267 | | | 123.8 (70.1-218.8) | <0.0001 | 17.42 (9.0-33.72) | <0.0001 | 3.80 (2.70-5.36) | <0.0001 | 1.73 (1.18-2.56) | 0.005 |
| Ut PI ($Log_{10}$ MoM) | 75.41 ($2.79-2.0e^{03}$) | 0.010 | 51.89 ($2.10-12.8e^{02}$) | 0.016 | 40.8 (13.6-122.4) | <0.0001 | | | 18.48 (9.88-34.56) | <0.0001 | 8.39 (4.17-16.91) | <0.0001 |
| UA PI ($Log_{10}$ MoM) | 0.13 (0.00-67.44) | 0.520 | | | 0.85 (0.11-6.81) | 0.880 | | | 160.1 (49.3-520.2) | <0.0001 | 24.28 (6.51-90.60) | <0.0001 |
| MCA PI ($Log_{10}$ MoM) | $3.1e^{-04}$ ($4.4e^{-07}$-0.21) | 0.015 | 0.001 ($9.6e^{-07}$-0.29) | 0.019 | 0.05 (0.01-0.41) | 0.006 | 0.05 (0.01-0.58) | 0.017 | 0.11 (0.03-0.36) | <0.0001 | 0.11 (0.03-0.43) | 0.001 |
| MAP ($Log_{10}$ MoM) | $4.29e^{03}$ ($0.03-73.5e^{07}$) | 0.174 | | | $8.6e^{12}$ ($1.7e^{11}$-$4.5e^{14}$) | <0.0001 | $2.1e^{08}$ ($2.7e^{06}$-$1.6e^{10}$) | <0.0001 | 160.1 (18.7-1367.9) | <0.0001 | | |

EFW = estimated fetal weight; PLGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; Ut PI = uterine artery pulsatility index; UA PI = umbilical artery pulsatility index; MCA PI = middle cerebral artery pulsatility index; MAP = mean arterial pressure.

**Table 4.** Biochemical and biophysical markers in pregnancies delivering by cesarean section for fetal distress and those delivering vaginally.

| Biomarker | Vaginal delivery (n=6,263) | Cesarean section for fetal distress | |
|---|---|---|---|
| | | In labor (n=512) | Before labor (n=30) |
| **Biochemical markers** | | | |
| PlGF (MoM), median (IQR) | 0.95 (0.58-1.51) | 0.94 (0.52-1.58) | 0.24 (0.11-0.42)*** |
| PlGF < 5$^{th}$ percentile, n (%) | 348 (4.6) | 29 (5.7) | 15 (50.0)*** |
| PlGF < 10$^{th}$ percentile, n (%) | 711 (9.4) | 60 (11.7) | 19 (63.3)*** |
| | | | |
| sFlt -1 (MoM), median (IQR) | 1.01 (0.74-1.39) | 1.05 (0.79-1.52)** | 3.55 (1.47-5.43)*** |
| sFlt > 95$^{th}$ percentile, n (%) | 328 (4.3) | 42 (8.2)*** | 18 (60.0)*** |
| sFlt > 90$^{th}$ percentile, n (%) | 693 (9.1) | 77 (15.0)*** | 21 (70.0)*** |
| **Biophysical markers** | | | |
| Ut PI (MoM), median (IQR) | 1.00 (0.85-1.17) | 1.00 (0.86-1.18) | 1.44 (1.01-2.14)*** |
| Ut PI > 95$^{th}$ percentile, n (%) | 355 (4.7) | 33 (6.4) | 12 (40.0)*** |
| Ut PI > 90$^{th}$ percentile, n (%) | 726 (9.0) | 66 (12.9) | 16 (53.3)*** |
| | | | |
| UA PI (MoM), median (IQR) | 1.02 (0.92-1.12) | 1.03 (0.92-1.13) | 1.14 (1.06-1.43)*** |
| UA PI > 95$^{th}$ percentile, n (%) | 370 (4.9) | 26 (5.1) | 10 (33.3)*** |
| UA PI > 90$^{th}$ percentile, n (%) | 746 (9.8) | 56 (10.9) | 12 (40.0)*** |
| | | | |
| MCA PI (MoM), median (IQR) | 1.02 (0.91-1.12) | 1.04 (0.92-1.13) | 0.96 (0.89-1.03)* |
| MCA PI < 5$^{th}$ percentile, n (%) | 379 (5.0) | 27 (5.3) | 3 (10.0) |
| MCA PI < 10$^{th}$ percentile, n (%) | 761 (10.0) | 49 (9.6) | 4 (13.3) |
| | | | |
| MAP (MoM), median (IQR) | 1.00 (0.95-1.05) | 1.01 (0.95-1.06) | 1.10 (0.99-1.21)*** |
| MAP > 95$^{th}$ percentile, n (%) | 331 (4.5) | 34 (6.8) | 14 (46.7)*** |
| MAP > 90$^{th}$ percentile, n (%) | 692 (9.4) | 65 (13.0)* | 14 (46.7)*** |
| | | | |
| EFW percentile, median (IQR) | 51.9 (28.3-75.8) | 56.0 (31.7-80.4) | 4.16 (0.16-8.96)*** |
| EFW < 5$^{th}$ percentile, n (%) | 279 (3.7) | 19 (3.7) | 15 (50.0)*** |
| EFW < 10$^{th}$ percentile, n (%) | 541 (7.1) | 40 (7.8) | 24 (80.0)*** |

PLGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; Ut PI = uterine artery pulsatility index; UA PI = umbilical artery pulsatility index; MCA PI = middle cerebral artery pulsatility index; MAP = mean arterial pressure; EFW = estimated fetal weight. Significance value adjusted for multiple comparisons with *post hoc* Bonferonni correction ** p<0.01; *** p<0.0001

**Table 5.** Univariable and multivariable logistic regression analysis in prediction of caesarean section for fetal distress before and during labor.

| Variable | Cesarean section for fetal distress in labor | | | | Cesarean section for fetal distress before labor | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable analysis | | Multivariable analysis | | Univariable analysis | | Multivariable analysis | |
| | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
| EFW Z-score | 1.12 (1.02-1.22) | 0.022 | 1.21 (1.02-1.23) | 0.015 | 0.21 (0.16-0.29) | <0.0001 | 0.26 (0.17-0.39) | <0.0001 |
| PlGF ($Log_{10}$ MoM) | 0.83 (0.63-1.10) | 0.201 | | | 0.01 (0.003-0.02) | <0.0001 | | |
| sFlt -1 ($Log_{10}$ MoM) | 2.31 (1.52-3.51) | <0.0001 | 2.36 (1.55-3.60) | <0.0001 | $13.0e^{02}$ ($3.3e^{02}$-$51.5e^{02}$) | <0.0001 | $2.1e^{02}$ ($40.5$-$1.07e^{03}$) | <0.0001 |
| Ut PI ($Log_{10}$ MoM) | 1.60 (0.72-3.57) | 0.252 | | | $19.5e^{03}$ ($16.2e^{02}$-$23.4e^{04}$) | <0.0001 | $1.2e^{03}$ ($43.7$-$3.0e^{04}$) | <0.0001 |
| UA PI ($Log_{10}$ MoM) | 1.57 (0.38-6.44) | 0.534 | | | $11.6e^{08}$ ($2.4e^{06}$-$5.5e^{11}$) | <0.0001 | $1.2e^{04}$ ($14.3$-$10.5e^{06}$) | 0.006 |
| MCA PI ($Log_{10}$ MoM) | 3.00 (0.66-13.72) | 0.156 | | | 0.001 ($4.0e^{-06}$-0.40) | 0.023 | | |
| MAP ($Log_{10}$ MoM) | 20.13 (1.44-282.4) | 0.026 | | | $1.05e^{15}$ ($6.49e^{10}$-$1.69e^{19}$) | <0.0001 | | |

EFW = estimated fetal weight; PLGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; Ut PI = uterine artery pulsatility index; UA PI = umbilical artery pulsatility index; MCA PI = middle cerebral artery pulsatility index; MAP = mean arterial pressure.

**Table 6.** Biochemical and biophysical markers in pregnancies with and without low cord blood pH, low Apgar score at 5 minutes and admission to the neonatal unit.

| Biomarker | Cord blood pH | | Apgar score at 5 minutes | | Neonatal unit admission | |
|---|---|---|---|---|---|---|
| | Normal (n=3,244) | Low (n=84) | Normal (n=7,054) | Low (n=70) | No (n=7,721) | Yes (n=524) |
| **Biochemical markers** | | | | | | |
| PlGF (MoM), median (IQR) | 0.94 (0.57-1.52) | 1.01 (0.49-1.49) | 0.94 (0.57-1.50) | 1.13 (0.56-1.71) | 0.95 (0.58-1.51) | 0.83 (0.40-1.47)*** |
| PlGF < 5$^{th}$ percentile, n (%) | 172 (5.3) | 9 (10.7) | 363 (5.1) | 3 (4.3) | 341 (4.4) | 72 (13.7)*** |
| PlGF < 10$^{th}$ percentile, n (%) | 338 (10.4) | 13 (15.5) | 720 (10.2) | 6 (8.6) | 717 (9.3) | 108 (20.6)*** |
| | | | | | | |
| sFlt -1 (MoM), median (IQR) | 1.03 (0.75-1.44) | 0.97 (0.73-1.27) | 1.02 (0.75-1.40) | 1.16 (0.78-1.57) | 1.00 (0.74-1.38) | 1.16 (0.85-1.71)*** |
| sFlt > 95$^{th}$ percentile, n (%) | 195 (6.0) | 4 (4.8) | 356 (5.0) | 5 (7.1) | 340 (4.4) | 72 (13.7)*** |
| sFlt > 90$^{th}$ percentile, n (%) | 367 (11.3) | 9 (10.7) | 698 (9.9) | 12 (17.1) | 709 (9.2) | 112 (21.4)*** |
| **Biophysical markers** | | | | | | |
| Ut PI (MoM), median (IQR) | 1.00 (0.86-1.18) | 1.01 (0.87-1.20) | 1.00 (0.85-1.18) | 0.98 (0.86-1.09) | 1.00 (0.85-1.17) | 1.02 (0.87-1.23)** |
| Ut PI > 95$^{th}$ percentile, n (%) | 187 (5.8) | 6 (7.1) | 370 (5.2) | 2 (2.9) | 361 (4.7) | 50 (9.5)*** |
| Ut PI > 90$^{th}$ percentile, n (%) | 348 (10.7) | 9 (10.7) | 733 (10.4) | 2 (2.9) | 748 (9.7) | 75 (14.3)** |
| | | | | | | |
| UA PI (MoM), median (IQR) | 1.02 (0.91-1.13) | 0.99 (0.90-1.11) | 1.02 (0.91-1.12) | 1.01 (0.89-1.12) | 1.02 (0.91-1.12) | 1.03 (0.92-1.15) |
| UA PI > 95$^{th}$ percentile, n (%) | 165 (5.1) | 7 (8.3) | 346 (4.9) | 0 (0.0) | 378 (4.9) | 35 (6.7) |
| UA PI > 90$^{th}$ percentile, n (%) | 327 (10.1) | 10 (11.9) | 700 (9.9) | 3 (4.3) | 762 (9.9) | 64 (12.2) |
| | | | | | | |
| MCA PI (MoM), median (IQR) | 1.02 (0.92-1.12) | 1.00 (0.92-1.09) | 1.02 (0.91-1.12) | 1.03 (0.90-1.13) | 1.02 (0.91-1.12) | 1.01 (0.91-1.11) |
| MCA PI < 5$^{th}$ percentile, n (%) | 170 (5.2) | 5 (6.0) | 356 (5.0) | 3 (4.3) | 388 (5.0) | 23 (4.4) |
| MCA PI < 10$^{th}$ percentile, n (%) | 326 (10.0) | 8 (9.5) | 718 (10.2) | 6 (8.6) | 777 (10.1) | 46 (8.8) |
| | | | | | | |
| MAP (MoM), median (IQR) | 1.00 (0.95-1.06) | 1.01 (0.94-1.06) | 1.00 (0.95-1.06) | 1.00 (0.92-1.04) | 1.00 (0.95-1.05) | 1.01 (0.95-1.07)* |
| MAP > 95$^{th}$ percentile, n (%) | 172 (5.5) | 2 (2.4) | 339 (4.9) | 3 (4.4) | 350 (4.7) | 51 (10.0)*** |
| MAP > 90$^{th}$ percentile, n (%) | 328 (10.4) | 8 (9.6) | 685 (10.0) | 6 (8.8) | 725 (9.7) | 75 (14.9)*** |
| | | | | | | |
| EFW percentile, median (IQR) | 55.3 (30.5-78.6) | 55.1 (29.6-73.6) | 53.3 (29.0-77.6) | 56.7 (23.5-86.5) | 53.3 (29.1-77.5) | 54.9 (24.7-78.3) |
| EFW < 5$^{th}$ percentile, n (%) | 127 (3.9) | 3 (3.6) | 272 (3.9) | 3 (4.3) | 284 (3.7) | 43 (8.2)*** |
| EFW < 10$^{th}$ percentile, n (%) | 224 (6.9) | 9 (10.7) | 514 (7.3) | 8 (11.4) | 567 (7.3) | 56 (10.7)** |

PLGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; Ut PI = uterine artery pulsatility index; UA PI = umbilical artery pulsatility index; MCA PI = middle cerebral artery pulsatility index; MAP = mean arterial pressure; EFW = estimated fetal weight. Significance value adjusted for multiple comparisons with *post hoc* Bonferonni correction ** p<0.01; *** p<0.0001

**Table 7.** Univariable logistic regression analysis in prediction of umbilical cord blood pH, low 5 minute Apgar score and univariable and multivariable logistic regression analysis in prediction of admission to neonatal unit.

| Variable | Low cord blood pH | | Low 5 minute Apgar score | | Neonatal unit admission | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable analysis | | Univariable analysis | | Univariable analysis | | Multivariable analysis | |
| | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
| EFW Z-score | 0.92 (0.75-1.14) | 0.450 | 1.09 (0.86-1.38) | 0.481 | 0.96 (0.88-1.04) | 0.316 | | |
| PlGF ($Log_{10}$ MoM) | 0.69 (0.37-1.32) | 0.265 | 1.33 (0.63-2.80) | 0.457 | 0.39 (0.30-0.51) | <0.0001 | 0.58 (0.44-0.76) | <0.0001 |
| sFlt -1 ($Log_{10}$ MoM) | 0.60 (0.22-1.64) | 0.322 | 2.22 (0.77-6.40) | 0.142 | 6.37 (4.32-9.39) | <0.0001 | 4.77 (3.19-7.14) | <0.0001 |
| Ut PI ($Log_{10}$ MoM) | 1.95 (0.30-12.49) | 0.482 | 0.33 (0.04-2.79) | 0.308 | 5.25 (2.46-11.22) | <0.0001 | 3.37 (1.58-7.18) | 0.002 |
| UA PI ($Log_{10}$ MoM) | 0.82 (0.03-22.72) | 0.909 | 0.09 (0.003-3.36) | 0.194 | 4.69 (1.17-18.82) | 0.029 | | |
| MCA PI ($Log_{10}$ MoM) | 0.16 (0.01-5.39) | 0.306 | 4.10 (0.08-219.22) | 0.487 | 0.61 (0.14-2.66) | 0.513 | | |
| MAP ($Log_{10}$ MoM) | 2.68 (0.01-13.26) | 0.755 | 0.01 (0.00-9.63) | 0.190 | 103.8 (8.02-13.43$e^{03}$) | <0.0001 | | |

EFW = estimated fetal weight; PLGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1; Ut PI = uterine artery pulsatility index; UA PI = umbilical artery pulsatility index; MCA PI = middle cerebral artery pulsatility index; MAP = mean arterial pressure.