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The cerebral-placental-uterine ratio as a novel predictor of late fetal growth restriction: a prospective cohort study

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ABSTRACT

Objectives

Fetal growth restriction (FGR) is a major risk factor for stillbirth and most commonly arises from uteroplacental insufficiency. Despite clinical examination and third trimester fetal biometry, cases of FGR often remain undetected antenatally. Placental insufficiency is known to be associated with altered blood flow resistance in maternal, placental, and fetal vessels. We evaluated the performance of individual, and combined Doppler blood flow resistance measurements for the prediction of term FGR.

Methods

This was a prospective study of fetal growth including Doppler measurements in 347 nulliparous women at 36 weeks' gestation. We analysed the pulsatility indices (PI) of the uterine arteries (UtA), umbilical artery (UA), and fetal vessels, individually and in combination, for prediction of birthweights <10th, <5th and <3rd centiles. We compared Doppler parameters' sensitivities, positive and negative predictive values, and odds ratios (OR) for these birthweights at ~90% specificity. We also analysed the correlations between Doppler measurements and other parameters of placental insufficiency – fetal growth velocity and neonatal body fat.

Results

The Doppler combination most strongly associated with placental insufficiency was a newly generated parameter which we have named the cerebral-placental-uterine ratio (CPUR). The CPUR is the cerebroplacental ratio (middle cerebral artery PI/UA PI) divided by the mean UtA PI. The CPUR detected FGR better than the mean UtA PI or the cerebroplacental ratio (CPR) alone. At ~90% specificity, a low CPUR had sensitivities of 50% for birthweight <10th centile, 68% for <5th centile, and 89% for <3rd centile. This was compared to respective sensitivities of 26%, 37% and 44% for a low CPR, and 34%, 47% and 67% for a high mean UtA PI. Low CPUR predicted birthweight <10th centile with an OR of 9.1, <5th centile with an OR of 17.3, and <3rd centile with an OR of 57 ($P<0.0001$ for all). The CPUR also correlated most strongly with fetal growth velocity and neonatal body fat measures.

Conclusions

In this cohort, our novel Doppler combination - the cerebral-placental-uterine ratio (CPUR; CPR/UtA PI) - had the strongest associations with placental insufficiency. The CPUR detected more FGR than any other Doppler parameter measured. If independently replicated, this new parameter may lead to better identification of fetuses at increased risk of stillbirth that may benefit from obstetric interventions.

INTRODUCTION

Fetal growth restriction (FGR) is associated with 50% of stillbirths – the majority of which occur after 34 weeks¹ – and commonly reflects uteroplacental insufficiency². Being small-for-

gestational-age (SGA; <10th centile), a common proxy for FGR, incurs a three to four-fold increased risk of stillbirth at all gestations^{1,3}. This includes term fetuses, for whom excellent outcomes would be expected if delivery were to be expedited. Around 30% of stillbirths at term occur among the SGA^{4,5}. Identifying SGA fetuses, and FGR among those appropriately grown, are therefore priorities to reduce late pregnancy stillbirth⁶.

Unfortunately, the accuracy of existing clinical tools to detect SGA fetuses is surprisingly modest. Currently, women with risk factors or clinically suspected FGR are referred for ultrasound – this approach detects 20% of SGA cases⁷. While universal ultrasound might be expected to detect most SGA fetuses, the reported sensitivity in high quality cohort studies is just 52-57%^{7,8}. In addition, methods assessing only fetal size, will be unable to detect fetuses that may be subject to placental insufficiency, but that are not small. We urgently need new methods to better detect FGR if we are to reduce term stillbirths.

Uteroplacental insufficiency is associated with altered blood flow resistance in the uterine, placental, and fetal vasculature. The maternal uterine arteries (UtA) and umbilical artery (UA) demonstrate increased resistance^{8,9}, and the fetus adapts by actively redistributing blood flow towards essential organs. Vasodilation of the fetal cerebral vessels can be identified as a reduced middle cerebral artery (MCA) pulsatility index (PI)⁹. To date, the cerebroplacental ratio (CPR; MCA PI/UA PI) shows the most promise for identifying at-risk fetuses in late pregnancy but its clinical use is not standardised. A low CPR is associated with stillbirth even after adjustment for fetal size¹⁰; and near term, cerebral vasodilation is a more sensitive indicator of

placental insufficiency than increasing UA PI^{11, 12}. High UtA PI at 36 weeks is also independently associated with perinatal death at term¹³, but this is not widely measured clinically.

Doppler assessments which combine information from the uterine, placental, and/or fetal vessels could improve detection of uteroplacental insufficiency near term. We examined which Doppler parameters (alone or in combination) best identified fetuses at risk of being SGA (birthweight <10th centile), or growth restricted (birthweight <5th or <3rd centile; reduced third trimester growth velocity; reduced neonatal body fat).

METHODS

Study design and participants

The Fetal Longitudinal Assessment of Growth (FLAG) study was a prospective study conducted at the Mercy Hospital for Women, a tertiary hospital in Melbourne, Australia. This study was approved by Mercy Health Research Ethics Committee, Approval Number R14/12, with written informed consent obtained from all participants.

Eligible women were invited to participate at the time of their glucose tolerance test –offered around 28 weeks' gestation. English-speaking women were eligible if they were nulliparous, over 18 years, with a singleton, well-dated pregnancy and normal mid-trimester ultrasound examination. Exclusion criteria were known fetal infection, low lying placenta, hypertension, antepartum haemorrhage, ruptured membranes, or estimated fetal weight (EFW) <10th centile at first study ultrasound. Inclusion was limited to nulliparous women as it is for these women that clinicians most need guidance. Parous women already have an established *a priori* risk for FGR on the basis of their previous pregnancy outcomes. In comparison, nulliparous women have no obstetric history from which to infer a risk profile for FGR, so their individual risk is harder to stratify.

Procedures

Each participant underwent two ultrasound examinations measuring fetal biometry, performed by one of two experienced operators. The first was performed between 27⁺⁰ and

29⁺⁰ weeks, and the second between 35⁺⁰ and 37⁺⁰ weeks' gestation inclusive. A General Electric Voluson 730 (GE Medical Systems, Zipf, Austria) device with 2-7-MHz linear curved-array transducer was used for all ultrasound examinations. Methods used to assign customised EFW and abdominal circumference (AC) centiles, and fetal growth velocity values have been previously described¹⁴.

At the 36 week ultrasound assessment, transabdominal colour and pulsed-wave Doppler were used to measure the mean UtA PI, and the UA PI. The PI of the fetal MCA, renal arteries, ductus venosus, and aortic isthmus were also recorded. Measurements were taken during periods of fetal apnoea and inactivity, with the angle of insonation close to zero. The UA PI was measured in a free loop of cord away from the cord insertion sites¹⁵. The MCA was recorded at 1-2cm from the circle of Willis¹⁶. For maternal UtA assessment the probe was placed in each of the iliac fossae, and the waveform recorded within 1cm of the UtA crossing the external iliac artery¹⁷. Aortic isthmus PI measurements were sampled from the longitudinal aortic arch, or 'three vessels and trachea', sonographic plane¹⁸. The ductus venosus was identified as the vessel with high blood flow velocities connecting the inferior vena cava and the umbilical vein¹⁹. The fetal renal artery PIs were measured in the coronal plane between the aortic origin of the vessel and the first emergent branch²⁰.

All PI values were measured in triplicate and the mean calculated. For the paired maternal uterine and fetal renal arteries, average PI values were obtained for both the right and left vessels, and these averaged to provide the overall mean PI. CPR was calculated as mean MCA

PI divided by mean UA PI. For each of the PI values, the gestation-dependent centile (if normally distributed) or multiples of the median (MoM) (if not normally distributed) were determined.

Treating clinicians were blinded to ultrasound results, notified only if the EFW was <10th centile, the UA PI was >95th centile¹⁵ or the MCA PI was <5th centile¹⁶, in which case management was at the discretion of the treating team. Aortic isthmus, ductus venosus, UTA, renal artery, CPR and fetal growth velocity values were never disclosed to clinicians.

Ultrasound EFW and AC centiles were not compared to Doppler measurements to predict SGA as (i) ultrasound operators were not blinded to the biometry; (ii) cases of EFW <10th centile required unblinding to clinicians, introducing the potential for bias; and (iii) the performance of ultrasound biometry has been well-established through larger, blinded prospective studies^{7,8}.

Outcomes

Following delivery, EFW and infant birthweights were customised using the GROW software²¹ (<https://www.gestation.net>). This generates a 'term optimal birthweight' standard, then adjusts for non-pathological factors affecting birthweight: maternal height, weight and nulliparity, infant sex, and exact gestational age. Coefficients for the Australian application of GROW were informed by a local dataset; the multiple regression model has a constant to which weight is added or subtracted for each of the variables: maternal height, weight, parity and fetal sex. We did not adjust for maternal ethnicity.

Ponderal index ($\text{birthweight(g)} \times 100 / \text{length(cm)}^3$) was calculated for all infants. Newborns also underwent estimation of body fat percentage by air displacement plethysmography using a PEA POD (COSMED, Concord, CA, USA) device within four days of birth, where possible.

Statistical analysis

Maternal characteristics and birth outcome data were compared between: participants delivering infants $<10^{\text{th}}$ centile, and those delivering infants $\geq 10^{\text{th}}$ centile; and between recruited participants and eligible women not recruited. This was performed using non-paired t-test (normally distributed) or Mann-Whitney test (not normally distributed) for continuous data, and Chi-square or Fisher's exact tests for categorical analyses.

Each Doppler parameter was tested for distribution per weeks' gestation. Aortic isthmus, ductus venosus, renal artery, and UA PI values were normally distributed and were converted to gestation-specific centiles. CPR, MCA PI and UtA PI values were not normally distributed so were converted to gestation-specific MoMs. The median value for each parameter or combination at each gestational week (35, 36 or 37 weeks) was identified, and then each Doppler value was divided by its relevant median value to represent the Doppler as a MoM. Univariate logistic regression was performed to determine which Doppler parameters, or combinations, were significantly associated with SGA (birthweight $<10^{\text{th}}$ centile). The performance of Doppler parameters' detection of SGA (birthweight $<10^{\text{th}}$ centile), and growth restriction (birthweight $<5^{\text{th}}$ and $<3^{\text{rd}}$ centile) was compared using area under the receiver operator characteristic curve (AUC) analysis. Also, after determining a cut-off most closely

corresponding to 90% specificity for detecting birthweight <10th centile, we calculated odds ratios (OR) for Doppler parameters for birthweights <10th, <5th and <3rd centile, as well as sensitivity, and positive and negative predictive values.

We tested the strength of correlation between our best performing Doppler parameters and indicators of placental function in the cohort. These measures included customised birthweight centile, fetal growth velocity and neonatal body fat measures. Fetal growth velocity in late pregnancy was assessed by calculating the change in EFW, and AC, centile over exactly eight weeks¹⁴. For neonatal body fat assessment, ponderal index and neonatal body fat percentage were calculated. The strengths of the linear correlations were quantified by Spearman r values, and compared.

Statistical analyses were performed using GraphPad Prism version 6.00 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com), and R version 3.3.2 (64-bit).

RESULTS

Study participants

Between February 2015 and February 2016, 361 (45.8%) of 788 eligible women were recruited to the study. Of the 361 participants enrolled, 347 attended for ultrasound Doppler examination between 35⁺⁰ and 37⁺⁰ weeks. Of these, 39 (11.2%) delivered SGA infants

(birthweight <10th centile) with 19 (5.5%) birthweight <5th centile infants, and 9 (2.6%) birthweight <3rd centile infants (Figure 1).

The characteristics of the 347 participants are shown in Table 1. When participants delivering SGA infants were compared to the remainder of the cohort there were no significant differences in maternal characteristics, the number that had their labour induced, or mode of delivery. SGA infants were significantly smaller, and delivered a median four days earlier.

Of the 427 women that were eligible but not recruited, 247 agreed to collection of their clinical outcome data. Their maternal and delivery characteristics were compared to the 361 recruited women to exclude potential recruitment or selection bias. No statistically significant differences were found, except that those recruited were slightly younger (by <one year) than the 247 non-participants (Table S1).

Doppler parameters at 36 weeks' gestation associated with SGA infants

Each Doppler parameter was evaluated with logistic regression to determine its association with the subsequent delivery of a SGA infant. 36 week umbilical artery (UA) pulsatility index (PI) centile ($p=0.04$), middle cerebral artery (MCA) PI MoM ($p=0.009$), uterine artery (UtA) PI MoM ($p<0.001$), aortic isthmus PI centile ($P=0.04$) and cerebroplacental ratio (CPR; MCA PI/UA PI) MoM ($P <0.001$), were all significantly associated with SGA at birth; fetal renal artery and ductus venosus PI centiles were not. AUC analysis revealed mean UtA PI to have an AUC of 0.69 – the best of the five Doppler parameters significantly associated with SGA. The CPR

demonstrated an AUC of 0.67, performing better than either of its constituent parameters (UA PI AUC = 0.60; MCA PI AUC = 0.62). Aortic isthmus PI centile AUC was 0.60.

We next assessed whether combinations of the associated Doppler parameters could be used to further improve the detection of SGA fetuses. Given low CPR and high UtA PI values are associated with placental insufficiency and FGR²², we wondered whether a ratio incorporating both parameters may demonstrate a stronger relationship with SGA than either of its constituents. We therefore devised a ratio that has not been previously described, which we have named the cerebral-placental-uterine ratio (CPUR). The CPUR is the ratio of the CPR to the mean UtA PI (CPUR = CPR/UtA PI). CPUR MoM had an AUC of 0.76 in predicting SGA – better than any of the other Doppler parameters, including its constituent parameters. The CPUR also performed better than the UtA PI combined with either the MCA PI or UA PI alone (Figure 2A-E).

Having identified the CPUR as the best parameter for prediction of SGA, we compared the CPUR's performance for predicting other indicators of utero-placental insufficiency to that of the CPR and UtA PI. As well as being the CPUR's constituent parameters, these also represent established Doppler parameters with a body of literature behind them, in clinical use in some settings.

Doppler parameters at 36 weeks' gestation associated with FGR

The existence of a biological gradient and continuum of perinatal risk in FGR is well established. While being SGA is associated with a three to four-fold increased risk of stillbirth, this risk increases exponentially with decreasing birthweight centiles below the 10th centile^{4,5}. This is likely to be because the proportion of true FGR as a result of placental insufficiency rises with more severe decrements in birthweight. Therefore, we evaluated the ability of the CPUR to detect infants with birthweights <5th and <3rd centile, associated with six, and ten-fold increased risks of stillbirth^{5,23} respectively. The performance of the CPUR improved further for these lower birthweight centiles, with AUCs of 0.85 and 0.93 for <5th and <3rd centile respectively. CPUR again performed better than UtA PI and CPR alone to detect these birthweights indicative of FGR (Figure 3A-F).

We next calculated the odds of being SGA or growth restricted in the event of an abnormal Doppler parameter value at 36 weeks' gestation. We applied cut-off values for each parameter that most closely corresponded to 90% specificity for SGA in our cohort. These values were CPUR <0.71 MoM, CPR <0.78 MoM, and UtA PI >1.36 MoM. We used cut-offs for a standard specificity so that we could compare the detection rates for the different Doppler parameters at a fixed, similar false positive rate. We chose to approximate 90% specificity, as this is the reported specificity of universal blinded biometry⁷. Of all the Doppler parameters the CPUR produced the highest ORs to detect birthweights <10th centile (OR=9.1 [4.4-19.1], *P* <0.0001), <5th centile (OR=17.3 [6.2-48.3], *P* <0.0001) and <3rd centile (OR=57.0 [6.9-467.6], *P* <0.0001), higher than its constituent parameters (Table 2).

Using these same cut-offs, we next characterised the diagnostic performance of the CPUR in predicting infants destined to be delivered with birthweights <10th, <5th and <3rd centile. We compared the diagnostic performance characteristics to those of the CPR and UtA PI, and to ultrasound biometry EFW (Table 3). Low CPUR had higher sensitivity than either low CPR or high UtA PI for birthweight <10th centile (50%, compared to 26% and 34% respectively), birthweight <5th centile (68%, compared to 37% and 47%) and birthweight <3rd centile (89%, compared to 44% and 67%). Furthermore, the CPUR had consistently higher positive predictive value for these three birthweight cut-offs compared to the other two parameters (Table 3). In our cohort, our EFW values generated high specificity and positive predictive values for birthweights <10th, <5th and <3rd centile, but CPUR performed with greater sensitivity than biometry for these outcomes. When compared to EFW <28th centile – which was the cut-off of equivalent specificity (~90%) - ultrasound biometry was more sensitive than CPUR for prediction of SGA and <5th centile infants, but not for those most at risk – those with birthweight <3rd centile (Table 3). This comparison was performed to compare test sensitivities at the same false positive rate, but EFW <28th centile is not a parameter used clinically.

Doppler parameters associated with antenatal and neonatal measures of fetal growth potential

Infants with a birthweight between the 50th and 97th centiles have the lowest risks of stillbirth and perinatal mortality. A continuum of perinatal risk exists: stillbirth risk increases with decreasing birthweight centiles, rising even more sharply when the birthweight is below the 10th centile^{4, 5, 23}. Consistent with this, we found fetuses ≥50th centile had the lowest rates of

low CPUR, with a stepwise increase in the prevalence of low CPUR with decreasing birthweight centile (Table S2). Additionally, decreasing birthweight centile was associated with a stepwise increase in the OR of having a low CPUR, particularly at birthweight centile ranges <10th centile (Table S2).

We also evaluated the correlations between the Doppler parameters and clinical variables associated with FGR and placental insufficiency. As well as customised birthweight centile, we evaluated fetal growth velocity across the third trimester, and neonatal body composition measures – ponderal index and body fat percentage. We examined these variables, as reduced fetal growth velocity (evidenced by decreasing estimated fetal weight (EFW) and abdominal circumference (AC) centiles across pregnancy) occurs with placental insufficiency regardless of birthweight centile¹⁴. Similarly, neonatal body composition measures reflect *in utero* nutrient supply to the fetus, and predict neonatal morbidity better than birthweight centile²⁴. CPUR was associated with low EFW growth velocity (loss of >30 EFW centiles over eight weeks) with a higher AUC (0.72, $P<0.0001$) than CPR (AUC=0.69) or UtA PI (AUC=0.63) alone (Figures 4A-C). The CPUR was also associated with low third trimester EFW growth velocity with higher AUC and stronger significance than its constituent parameters when the analysis was confined only to infants born at $\geq 10^{\text{th}}$ centile (Figures 4D-F) – potentially better identifying the growth restricted among the seemingly appropriately grown. CPUR also showed the strongest linear correlation with every neonatal body composition variable measured, compared to CPR and UtA PI alone (Table S3).

Assessment of the validity of a ratio approach

The CPUR was compared to an alternative model using the individual additive covariates (MCA PI MoM, UA PI centile and mean UtA PI MoM) in a linear predictor. The test performance characteristics of the additive model were essentially the same as for the CPUR for prediction of SGA infants, and those with birthweight <5th centile (S4 – Assessment of the validity of a ratio approach). Given our small cohort and low numbers with a birthweight <3rd centile, it was not statistically valid to compare CPUR with a model using individually additive covariates for this outcome.

DISCUSSION

In this prospective cohort study, we found that a novel combination of Doppler parameters, the CPUR (CPR/UtA PI), was the best Doppler predictor of SGA infants and FGR in late pregnancy. At 36 weeks, the CPUR performed better than either of its constituent parameters to predict infants with birthweights <10th, <5th and, <3rd centile. Furthermore, the CPUR demonstrated a strong biological gradient across all birthweights below the 50th centile, with an exponential increase in the rate of low CPUR at birthweight centiles <10th. This gradient mirrors the continuum of adverse perinatal outcome associated with placental insufficiency in large epidemiological studies, particularly term stillbirth^{4, 5, 23}. In addition, the CPUR showed the strongest correlations with other important indicators of placental insufficiency. These indicators include third trimester fetal growth velocity, and neonatal fat measures which reflect *in utero* substrate supply.

This finding is important given detection of FGR in late pregnancy remains poor, yet is recognised to be a priority to reduce term stillbirth²⁵. When SGA fetuses are identified during pregnancy, they are delivered earlier, and the stillbirth risk is halved¹. There is no increase in the rate of caesarean section when women with SGA fetuses have labour induced at term²⁶. Therefore, a safe and acceptable intervention to reduce stillbirth does exist, should FGR be identified in late pregnancy. Yet, a population study of 460,000 term births found that of all stillbirths that occurred among SGA fetuses, antenatal care providers only suspected the fetus was small in one quarter of cases²⁷. The traditional approach – measuring the uterine fundus using a tape measure and sending women measuring small, or with risk factors, for an ultrasound – only detects 20% of SGA fetuses⁷. Even universal third trimester ultrasound to estimate the fetal weight has a reported sensitivity of 52-57%^{7,8}. If our findings are replicated independently, the CPUR could be applied to better identify SGA fetuses and FGR. Importantly, the CPUR could feasibly be introduced into clinical practice rapidly. Experience with the relevant Doppler parameters is well established, such that measurement of the CPUR is not difficult to perform.

Notably, low CPUR in our study performed particularly well in identifying fetuses not just small, but growth restricted. Infants with birthweight <3rd centile are a particularly high-risk group. They are at the highest risk of stillbirth^{4,5}, and carry a four-fold increased risk of fetal distress and acidosis in labour compared to 3rd-10th centile fetuses²⁸. Potentially, CPUR may perform with better sensitivity to detect this at-risk group than ultrasound biometry. In a study of

almost 4,000 participants, blinded universal ultrasound biometry detected 77% of infants with birthweight <3rd centile, at 87% specificity, with 12% positive predictive value⁷. In comparison, in our much smaller study, CPUR <0.71 MoM demonstrated 89% sensitivity and 16% positive predictive value at comparable specificity. Our study was limited in that we did not blind the ultrasound operators to biometry, and our study was too small to assess for additive algorithms. However, for prediction of birthweight <3rd centile the CPUR performed with greater sensitivity than biometry in this cohort also. However, it is possible that the CPUR could potentially be added to biometry in a combined model to improve ultrasound detection of FGR.

As a functional measurement, the CPUR is able to distinguish between the pathologically small and the healthy or constitutionally small fetus, which biometry alone is unable to achieve. Likewise, the CPUR may aid the detection of the growth restricted fetus among the appropriate-for-gestational-age ($\geq 10^{\text{th}}$ centile) cohort. The CPUR more strongly associated with low third trimester EFW growth velocity than its constituent parameters, even among fetuses born at what is considered a normal birthweight. The CPUR also linearly correlated most strongly with these other measures of placental function including fetal growth velocity and neonatal body composition. Slowing fetal growth velocity is an important measure of placental insufficiency¹⁴, and low body fat percentage is a better predictor of neonatal morbidity than a classification of SGA²⁴. Both of these outcome measures are indicators of placental insufficiency regardless of birthweight centile.

To our knowledge, this is the first study to combine the CPR and UtA PI into an individualised ratio to predict FGR in a prospective cohort. These associations are biologically credible, since the CPUR combines Doppler parameters that each represent unique biological manifestations of placental insufficiency. Raised UtA resistance may indicate maternal uterine malperfusion to the placental bed²⁹; increased UA PI indicates increased placental resistance to fetal blood flow³⁰, and therefore reduced oxygen and nutrient transfer; and lowered cerebral vascular resistance is a fetal adaptation maximising oxygenation of the brain⁹. Lower CPR and higher UtA PI measurements have each been associated with SGA infants⁸, fetal decompensation in labour and neonatal acidosis^{12, 22, 31}, neonatal nursery admission^{12, 31}, and perinatal mortality^{10, 13}. While the use of a ratio may not always be an optimal approach³², its use does not preclude clinical assessment of any of the parameters in isolation. In addition, when compared to an alternative model using the individual Doppler parameters as covariates, the CPUR showed equivalent, if not better performance.

Strengths of this study include its prospective design, and that clinicians providing clinical care were blinded to Doppler values, minimising intervention bias. Another strength is that we did not rely on birthweight centile alone to define the presence of FGR and placental insufficiency. We included indicators of placental insufficiency independent of birthweight, namely slowing of growth *in utero* and neonatal body fat percentage.

The main limitation of our study is that it was not powered to detect important but uncommon perinatal outcomes such as stillbirth or significant neonatal morbidity. The CPUR warrants

validation in larger independent cohorts – ideally adequately powered for clinically relevant, adverse perinatal outcomes. It is also possible that combining the CPUR with biometry and/or biomarkers may detect FGR, and predict adverse outcome, with better accuracy than any single method³³; yet our study was also not designed to assess for this. In addition, we have not evaluated the reproducibility of the CPUR, which should also be considered in future validation studies.

Overall, the CPUR is a novel Doppler ratio with a strong association with placental insufficiency and superior sensitivity for fetal growth restriction compared to existing Doppler parameters. If our findings are replicated in independent cohorts, the CPUR may lead to better identification of term fetuses at increased risk of stillbirth that may benefit from obstetric interventions.

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FIGURE LEGENDS

Figure 1: Study Profile

Figure 2: Area under the receiver operator characteristic curve analysis for Doppler parameters' prediction of SGA infants.

A. CPR MoM; B. Mean UtA PI MoM; C. CPUR MoM; D. MCA PI/UtA PI MoM; E. UA PI x UtA PI MoM.

AUC=area under the curve; CPR=cerebroplacental ratio (MCA PI/UA PI); CPUR=cerebral-placental-uterine ratio (CPR/UtA PI); MCA=middle cerebral artery; MoM=multiples of the median; PI=Pulsatility Index; SGA=small-for-gestational-age (birthweight <10th centile); UA=Umbilical artery; UtA=uterine artery.

Figure 3: Area under the receiver operator characteristic curve analysis for Doppler parameters' prediction of FGR.

A. CPR MoM prediction of birthweight <5th centile; B. Mean UtA PI MoM prediction of birthweight <5th centile; C. CPUR MoM prediction of birthweight <5th centile; D. CPR MoM prediction of birthweight <3rd centile; E. Mean UtA PI MoM prediction of birthweight <3rd centile; F. CPUR MoM prediction of birthweight <3rd centile

AUC=area under the curve; CPR=cerebroplacental ratio; CPUR=cerebral-placental-uterine ratio (CPR/UtA PI); FGR=fetal growth restriction; MoM= multiples of the median; PI=Pulsatility Index; UtA=uterine artery.

Figures 4A-C: Area under the receiver operator characteristic curve analysis for Doppler parameters' association with low third trimester EFW growth velocity (>30 EFW centiles loss over eight weeks)

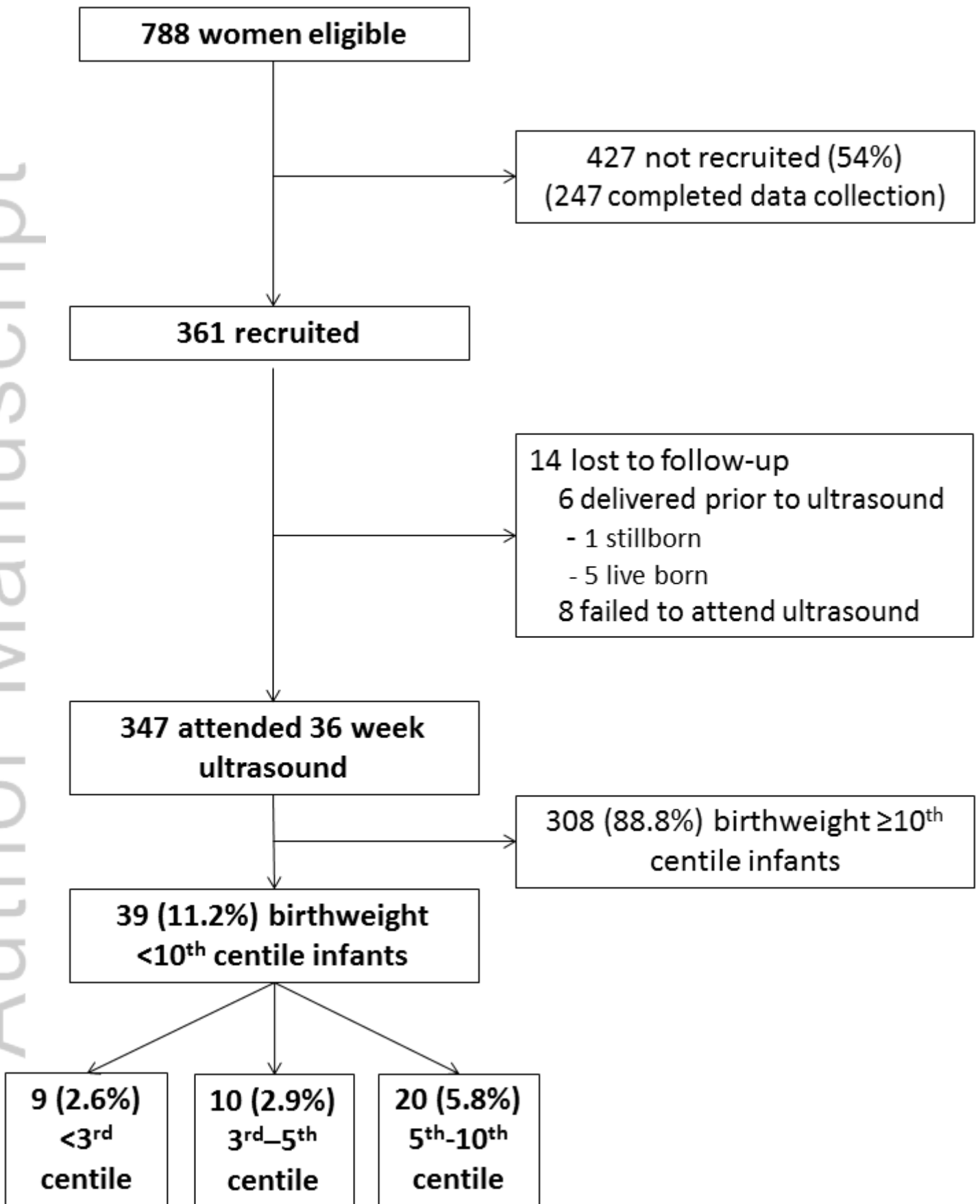
A-C - among the whole cohort:

A. CPR MoM; B. Mean UtA PI MoM; C. CPUR MoM

D-F - among AGA fetuses:

D. CPR MoM; E. Mean UtA PI MoM; F. CPUR MoM

AGA=appropriate-for-gestational-age ($\geq 10^{\text{th}}$ centile); AUC=area under the curve; CPR=cerebroplacental ratio; CPUR=cerebral-placental-uterine ratio (CPR/UtA PI); EFW=estimated fetal weight; MoM= multiples of the median; PI=Pulsatility Index; UtA=uterine artery.



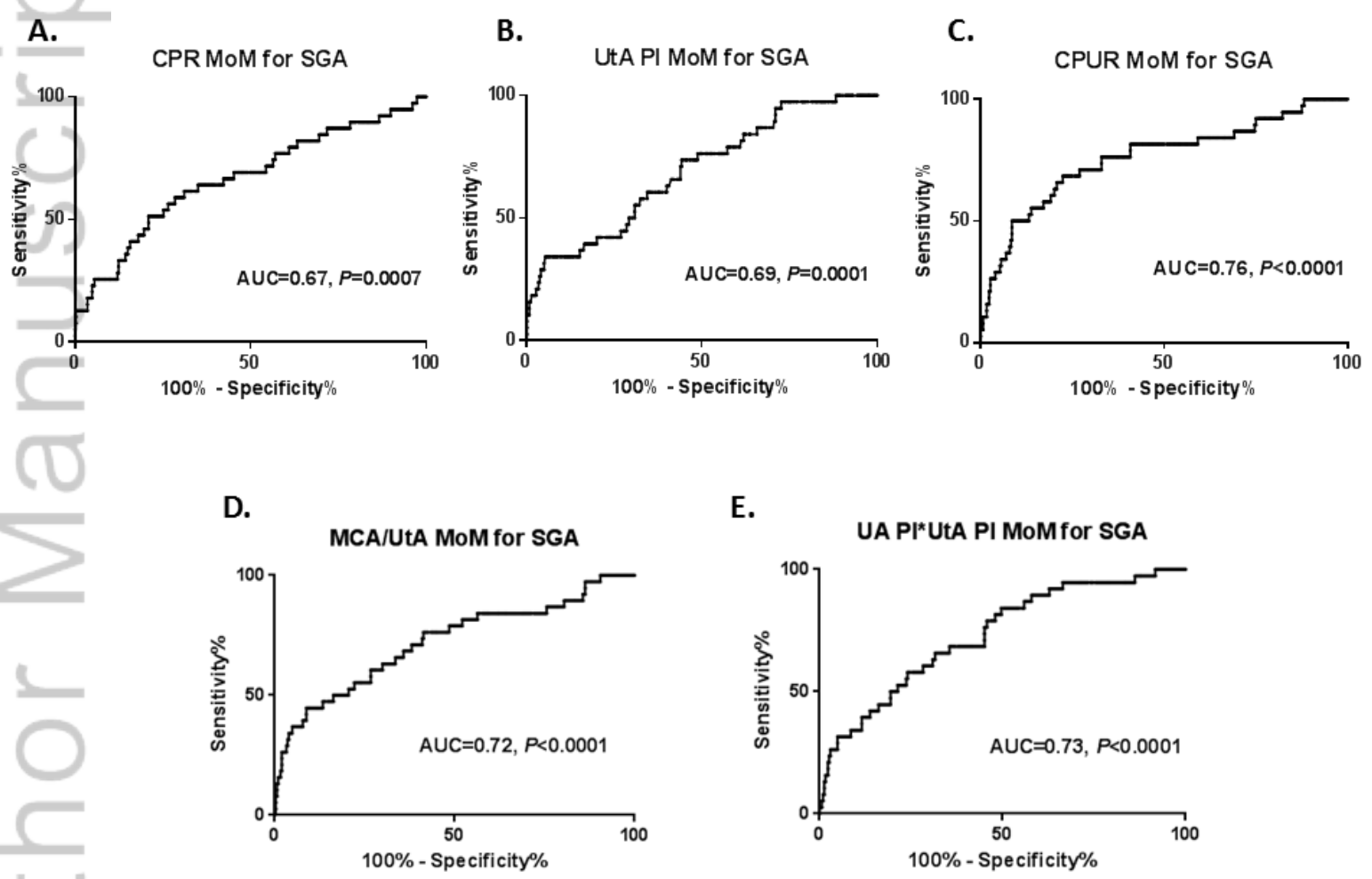


Figure 2A-E R1.tif

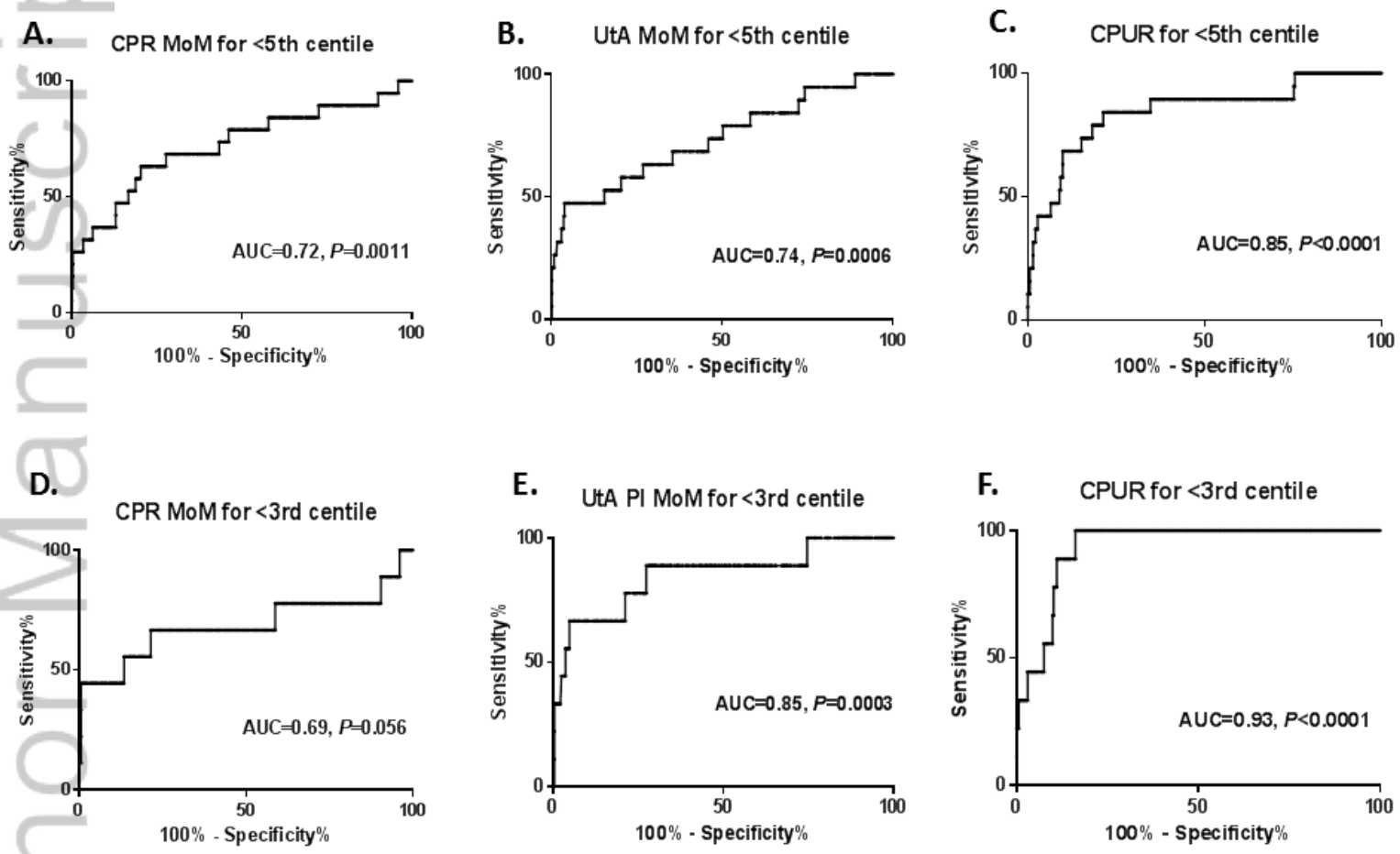


Figure 3A-F R1.tif

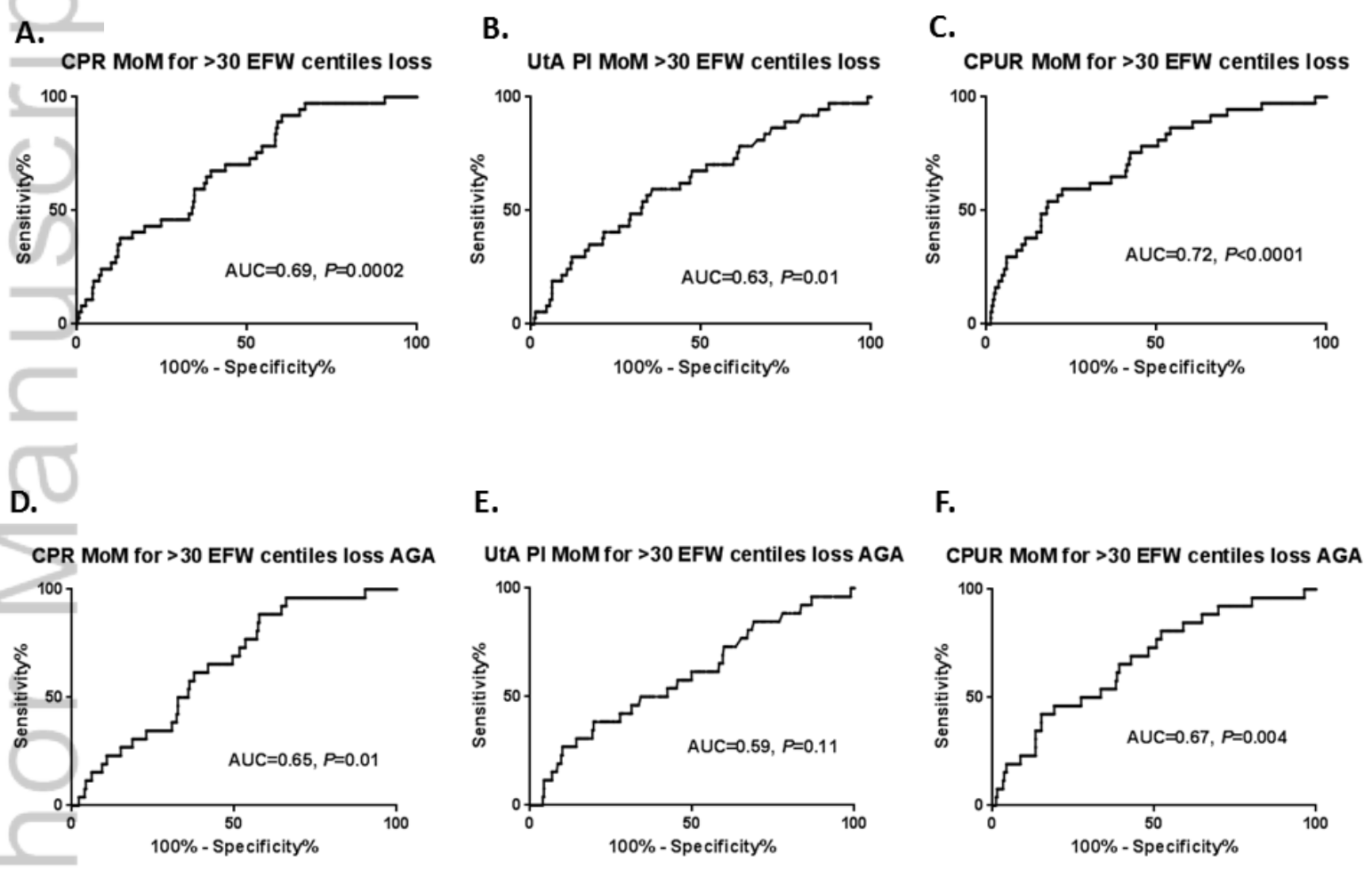


Figure 4A-F R1.tif

Table 1: Maternal characteristics and delivery outcomes

	Total cohort (n=347)	Infant birthweight <10th centile (n=39)	Infant birthweight ≥10th centile (n=308)	P
Age (years)	30.9 (4.1)	30.0 (3.2)	31.0 (4.2)	0.07
Booking BMI (kg/m²)	23.7 [21.5-26.9]	24.0 [20.7-26.8]	23.6 [21.5-26.9]	0.84
Smoking status				
Ever smoked	99 (28.6%)	10 (25.6%)	89 (29.0%)	0.85
Never smoked	247 (71.4%)	29 (74.4%)	218 (71.0%)	
Preeclampsia	21 (6.1%)	3 (7.7%)	18 (5.8%)	0.72
GDM	43 (12.4%)	5 (12.8%)	38 (12.3%)	1.00
Onset of delivery				
Induction of labour	170 (49.0%)	23 (59.0%)	147 (47.7%)	0.10
Spontaneous labour	150 (43.2%)	11 (28.2%)	139 (45.1%)	
No labour	27 (7.8%)	5 (12.8%)	22 (7.1%)	
Mode of delivery				
Normal vaginal delivery	131 (37.8%)	14 (35.9%)	117 (38.0%)	0.75
Instrumental delivery	115 (33.1%)	14 (35.9%)	101 (32.8%)	
Emergency caesarean	77 (22.2%)	7 (17.9%)	70 (22.7%)	
Elective caesarean	24 (6.9%)	4 (10.3%)	20 (6.5%)	
Birthweight (g)	3366 (486.0)	2680 (325.8)	3453 (431.0)	<0.0001
Birthweight centile	40.1 [18.7-70.5]	5.2 [3.5-7.4]	49.9 [26.7-72.6]	<0.0001
GA at birth (weeks)	39.9 [38.9-40.6]	39.3 [37.6-40.4]	39.9 [38.9-40.6]	0.04

Data presented as mean (standard deviation) if normally distributed data, as median

[interquartile range] if not normally distributed data, and as number (%) if categorical. BMI =

Body Mass Index; GA = gestational age; GDM = Gestational Diabetes Mellitus. Note: some

percentages do not sum to 100% due to rounding to one decimal place.

Table 2: Odds ratios for fetal growth restriction with an abnormal Doppler finding

Doppler & cut-off	OR for birthweight <10 th centile (SGA)		OR for birthweight <5 th centile		OR for birthweight <3 rd centile	
		<i>P</i>		<i>P</i>		<i>P</i>
CPR <0.78 MoM	3.7 [1.6-8.4]	0.003	6.0 [2.2-16.3]	0.002	7.6 [1.9-29.7]	0.009
UtA >1.36 MoM	4.8 [2.2-10.4]	0.0002	7.7 [2.9-20.4]	0.0001	16.2 [3.9-67.4]	0.0002
CPUR <0.71 MoM	9.1 [4.4-19.1]	<0.0001	17.3 [6.2-48.3]	<0.0001	57.0 [6.9-467.6]	<0.0001

95% Confidence interval provided for each odds ratio (OR). CPR = cerebroplacental ratio; CPUR

= cerebral-placental-uterine ratio (CPR/UtA PI); MoM = multiple of the median; SGA = small-

for-gestational-age; UtA = uterine artery

Table 3: Predictive performance of CPR, UtA PI, CPUR and EFW at 36 weeks for detecting FGR

Birthweight cut-off	Parameter	Sensitivity	Specificity	PPV	NPV
<10 th centile (SGA)	CPR <0.78MoM	25.6 [13.0-42.1]	91.5 [87.8-94.4]	27.8 [16.7-42.4]	90.6 [88.9-92.1]
	UtA PI >1.36MoM	34.2 [19.6-51.4]	90.2 [86.3-93.3]	30.2 [19.9-43.1]	91.7 [89.8-93.3]
	CPUR <0.71MoM	50.0 [33.4-66.6]	90.1 [86.2-93.2]	38.8 [28.5-50.2]	93.5 [91.3-95.2]
	EFW <10 th centile	20.5 [9.3-36.5]	98.7 [96.7-99.7]	66.7 [38.7-86.4]	90.8 [89.3-92.0]
	EFW <28 th centile	59.0 [42.1-74.4]	90.3 [86.4-93.3]	43.3 [33.3-54.1]	94.6 [92.3-96.2]
<5 th centile	CPR <0.78MoM	36.8 [16.3-61.6]	91.1 [87.4-93.9]	19.4 [10.9-32.4]	96.1 [94.6-97.2]
	UtA PI >1.36MoM	47.4 [24.5-71.1]	89.6 [85.7-92.7]	20.9 [13.0-31.9]	96.7 [95.0-97.8]
	CPUR <0.71MoM	68.4 [43.5-87.4]	88.9 [84.9-92.1]	26.5 [19.0-35.8]	98.0 [96.1-98.9]
	EFW <5 th centile	26.3 [9.2-51.2]	100 [98.9-100]	100%	95.9 [94.7-96.8]
	EFW <28 th centile	73.7 [48.8-90.9]	88.1 [84.1-91.4]	26.4 [19.4-34.9]	98.3 [96.5-99.2]
<3 rd centile	CPR <0.78MoM	44.4 [13.7-78.8]	90.5 [86.8-93.4]	11.1 [5.3-21.8]	98.4 [97.1-99.1]
	UtA PI >1.36MoM	66.7 [29.9-92.5]	89.0 [85.1-92.1]	14.0 [8.5-22.0]	99.0 [97.5-99.6]
	CPUR <0.71MoM	89.0 [51.8-99.7]	87.7 [83.7-91.0]	16.3 [11.9-22.0]	99.7 [97.9-100.0]
	EFW <3 rd centile	11.1 [0.3-48.3]	99.4 [97.9-99.9]	33.3 [4.7-83.4]	97.7 [97.1-98.2]
	EFW <28 th centile	66.7 [29.9-92.5]	86.1 [81.9-89.6]	11.3 [7.0-17.9]	99.0 [97.5-99.6]

95% Confidence interval provided for each value.

CPR = cerebroplacental ratio; CPUR = cerebral-placental-uterine ratio; EFW = estimated fetal weight; FGR= fetal growth restriction; MoM = multiples of the median; NPV = Negative Predictive Value; PI = Pulsatility Index; PPV = Positive Predictive Value; SGA = small-for-gestational-age; UtA = uterine artery