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# Perinatal loss at term: role of uteroplacental and fetal Doppler assessment

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**KEYWORDS:** cerebroplacental ratio; perinatal death; perinatal mortality; term; uterine artery Doppler

## ABSTRACT

***Objective*** *To examine the associations of uterine artery (UtA) Doppler indices and cerebroplacental ratio (CPR) with perinatal outcome at term.*

***Methods*** *This was a retrospective cohort study conducted at a tertiary referral center that included all singleton pregnancies undergoing ultrasound assessment in the third trimester that subsequently delivered at term. Fetal biometry and Doppler assessment, including that of the umbilical artery (UA), fetal middle cerebral artery (MCA) and UtA, were recorded. Data were corrected for gestational age, and CPR was calculated as the ratio of MCA pulsatility index (PI) to UA-PI. Logistic regression analysis was conducted to examine for independent predictors of adverse perinatal outcome.*

***Results*** *The study included 7013 pregnancies, 12 of which were complicated by perinatal death. When compared with pregnancies resulting in perinatal survival, pregnancies complicated by perinatal death had a significantly higher proportion of small-for-gestational-age infants (25.0% vs 5%; $P = 0.001$) and a higher incidence of low ($< 5^{th}$ centile) CPR (16.7% vs 4.5%; $P = 0.041$). A subgroup analysis comparing 1527 low-risk pregnancies that resulted in fetal survival with pregnancies complicated by perinatal death demonstrated that UtA-PI multiples of the median (MoM), CPR $< 5^{th}$ centile and estimated fetal weight (EFW) centile were all associated significantly with the risk of perinatal death at term (all $P < 0.05$). After adjusting for confounding variables, only EFW centile (odds ratio (OR) 0.96 (95% CI, 0.93–0.99); $P = 0.003$) and UtA-PI MoM (OR 13.10 (95% CI, 1.95–87.89); $P = 0.008$) remained independent predictors of perinatal death in the low-risk cohort.*

***Conclusion*** *High UtA-PI at term is associated independently with an increased risk of adverse perinatal outcome, regardless of fetal size. These results suggest that perinatal mortality at term is related not only to EFW and fetal redistribution (CPR), but also to indices of uterine perfusion. Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.*

## INTRODUCTION

Growth-restricted fetuses are at increased risk of perinatal mortality, as well as immediate and long-term morbidity[1]. For cases of early-onset fetal growth restriction (FGR), the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) Study has set the standard for monitoring and determining the timing of delivery for these fetuses, in order to optimize perinatal outcome[2]. However, the identification and management of growth-restricted fetuses at term remains a major challenge.

Previous work in this field has focused almost exclusively on estimated fetal weight (EFW) and the identification of small-for-gestational-age (SGA) neonates as determinants of outcome; however, some recent work has challenged the idea of fetal size as defining those at high risk. Firstly, the majority of perinatal losses at term occur in babies born appropriately sized for gestational age (GA). More recently, Man *et al.*[3] investigated the effect of postmortem interval on the interpretation of body weight in cases of stillbirth. They reported a reduction in fetal weight between delivery and postmortem examination of more than 10%, and concluded that this phenomenon is likely to result in an overestimation of unexplained stillbirths being classified subsequently as SGA[3]. Markers for placental dysfunction, such as uterine perfusion (uterine artery (UtA) Doppler indices) and fetal redistribution (cerebroplacental ratio (CPR)), could arguably play a larger role in the identification of term pregnancies at high risk for adverse outcome.

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CPR, calculated as the ratio of the fetal middle cerebral artery pulsatility index (MCA-PI) to the umbilical artery (UA)-PI, has been suggested as a marker of fetal compromise secondary to placental insufficiency. In one study of a high-risk population, lower CPR was associated independently with admission to the neonatal intensive care unit at term[4]. In gestations after 26 weeks, CPR has been shown to be an independent predictor of stillbirth and perinatal mortality[5]. The application of UtA Doppler in the third trimester as a predictor of adverse neonatal outcome has been explored by some investigators, particularly with regard to suspected growth-restricted fetuses[6–8].

The aim of this study was to examine the importance of uterine perfusion (UtA-PI) and fetal redistribution (CPR) with regard specifically to perinatal outcome at term.

## PATIENTS AND METHODS

This was a retrospective cohort study conducted at the Fetal Medicine Unit at St George's Hospital, London, UK, a tertiary referral center. Cases were identified by performing an electronic database search (Viewpoint 5.6.8.428, Wessling, Germany) between January 2008 and June 2016.

Included were women with a singleton pregnancy who underwent third-trimester ultrasound examination, during which the UtA, UA and MCA were assessed using Doppler ultrasound, and who subsequently delivered after 36 weeks' gestation. A single ultrasound assessment was recorded per pregnancy. For pregnancies for which serial scanning was conducted, examination findings prior to delivery were recorded. The cohort constituted a mixed population of low- and high-risk pregnancies. The indications for ultrasound scan included reduced fetal movement, suspected or history of fetal growth disorders, follow-up for high mid-trimester UtA Doppler indices, maternal hypertension and metabolic disorders in pregnancy. Low-risk pregnancies were defined as those that underwent an ultrasound assessment after 36 weeks' gestation for indications such as routine postdates assessment, confirmation of fetal presentation or placental localization. Multiple pregnancies, pregnancies complicated by fetal abnormality, aneuploidy or genetic syndrome and pregnancies with missing outcome data were excluded from the analysis.

GA was determined according to first-trimester crown–rump length measurement[9]; pregnancies were dated according to head-circumference measurement when the first ultrasound examination was performed after 14 weeks' gestation[10]. For all ultrasound examinations, routine fetal biometry and Doppler assessment were performed by experienced operators. EFW was calculated from biparietal diameter, head and abdominal circumferences and femur length using the formula of Hadlock *et al.*[11]. Doppler recordings were performed during periods of fetal quiescence. All Doppler parameters were recorded automatically from consecutive waveforms with the angle of insonation below 30°. The UA Doppler waveform was produced by sampling a free-floating portion of the umbilical cord using color Doppler, and UA-PI was calculated according to a standard protocol[12]. A transverse section of the fetal head was obtained and the MCA was identified at the level of its origin from the circle of Willis using color Doppler. The MCA was sampled using pulsed Doppler with the vessel passing the sphenoid wing, and PI was calculated according to a standard protocol[13]. CPR was then calculated as the ratio of MCA-PI to UA-PI[14]. Color Doppler was also used to visualize the left and right UtAs at the level of the crossover with the external iliac artery. Pulsed-wave Doppler was applied to assess impedance to flow and PI was measured over three consecutive waveforms[15]. The mean value of the right and left UtA-PIs was subsequently calculated. All Doppler indices were converted into multiples of the median (MoM), correcting for GA[16]. EFW and birth-weight (BW) values were converted into centiles[17].

Maternal characteristics were recorded, including age, ethnicity (Asian, Afro-Caribbean, Caucasian, mixed or other), body mass index (BMI), method of conception, cigarette smoking during pregnancy and parity (parous or nulliparous if no previous pregnancy had gone beyond 24 weeks' gestation). Data on pregnancy outcomes were collected from hospital obstetric and neonatal records. These included onset of labor, mode of delivery, outcome (live birth, stillbirth, or neonatal death $<$ or $\geq 1$ week from delivery), GA at delivery, gender, BW and admission to the neonatal intensive care unit. Perinatal mortality included stillbirth and neonatal death within the first 28 days after delivery. Stillbirth was defined as fetal demise after 24 completed weeks of pregnancy. SGA was defined as EFW $< 10^{th}$ centile after correcting for GA.

### Statistical analysis

The Kolmogorov–Smirnov test was used to assess the distribution of the data for normality. Maternal baseline characteristics were compared using the chi-square test, and comparison between the two outcome groups (perinatal survival and perinatal death) was performed using the Mann–Whitney *U*-test for non-normally distributed data. Correlation between continuous variables was described using Pearson's coefficient or Spearman's rho.

Logistic regression analysis was performed in order to assess the relationship between EFW centile, UtA-PI MoM and CPR MoM and adverse perinatal outcome. Odds ratios (ORs) and their CIs were calculated. Statistical analysis was performed using SPSS v. 24.0 (SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was considered to indicate statistical significance.

## RESULTS

We identified 7100 women with a singleton pregnancy who had ultrasound assessment performed after

**Table 1** Maternal and pregnancy characteristics in 7013 singleton pregnancies, according to whether they resulted in perinatal survival or death

| *Parameter* | *Perinatal survival* *All* (n = 7001) | *Perinatal survival* *Low-risk subgroup* (n = 1527) | *Perinatal death* (n = 12) | P* | P† |
|---|---|---|---|---|---|
| Maternal age (years) | 32.0 (27.0–35.0) | 32.0 (29.0–35.0) | 31.0 (28.5–33.0) | 0.672 | 0.274 |
| BMI (kg/m$^2$) | 24.4 (21.7–28.5) | 24.5 (22.0–28.8) | 26.5 (23.0–29.7) | 0.302 | 0.379 |
| Ethnicity‡ | | | | 0.147 | 0.041 |
| Caucasian | 4023 (58.6) | 1001 (66.2) | 3 (25.0) | | |
| Afro-Caribbean | 1009 (14.7) | 213 (14.1) | 4 (33.3) | | |
| Asian | 1561 (22.7) | 249 (16.5) | 4 (33.3) | | |
| Mixed | 220 (3.2) | 37 (2.4) | 1 (8.3) | | |
| Other | 55 (0.8) | 11 (0.7) | 0 (0.0) | | |
| GA at US (weeks) | 36.4 (36.0–38.7) | 37.9 (36.3–41.4) | 37.0 (35.9–38.6) | 0.932 | 0.023 |
| US-to-delivery interval (weeks) | — | 1.3 (0.4–3.6) | 1.6 (0.9–2.9) | — | 0.445 |
| GA at delivery (weeks) | 40.1 (39.0–41.0) | 41.1 (39.7–41.9) | 39.0 (37.8–40.9) | 0.063 | 0.001 |
| Smoker‡ | 410 (6.4) | — | 0 (0.0) | 0.364 | — |
| Mode of conception‡ | | | | 0.790 | — |
| Spontaneous | 6398 (96.2) | — | 12 (100.0) | | |
| IVF/ICSI/IUI | 184 (2.8) | — | 0 (0.0) | | |
| Ovulation induction | 68 (1.0) | — | 0 (0.0) | | |

Data are given as median (interquartile range) or *n* (%). *Perinatal survival *vs* death. †Low risk *vs* perinatal death. ‡Data missing for < 10% of total cohort of survivors but for > 10% of low-risk subgroup, hence values not provided. BMI, body mass index; GA, gestational age; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, *in-vitro* fertilization; US, ultrasound.

36 weeks' gestation and for whom UtA and fetal Doppler assessments were undertaken and pregnancy outcome data were available. Of these, 87 (1.2%) were excluded owing to complications caused by either fetal structural abnormality or aneuploidy. A final cohort of 7013 pregnant women was available for analysis, with a SGA prevalence at birth of 4.4% and 12 perinatal deaths, comprising nine cases of stillbirth (1.3 per 1000 pregnancies) and three neonatal deaths (0.4 per 1000 pregnancies) (Table S1). Median GAs at the time of ultrasound assessment and delivery for the perinatal survival group were 36.4 weeks and 40.1 weeks, respectively.

A comparison of maternal and pregnancy characteristics between pregnancies that were complicated by perinatal death and those that were not is shown in Table 1. There were no significant differences between the two study groups. A subgroup analysis of 1527 low-risk pregnancies showed significant differences in ethnicity and GA at ultrasound and at delivery (Table 1).

Correlations between UtA-PI MoM, CPR MoM and EFW centile are displayed as scatterplots in Figures 1 and 2. Table 2 shows a comparison of ultrasound assessment and pregnancy outcome between cases resulting in perinatal survival and those complicated by perinatal death. When compared with the perinatal survival group, pregnancies complicated by perinatal death had a significantly higher proportion of SGA (25.0% *vs* 5%; $P = 0.001$) and a significantly higher incidence of CPR < 5$^{th}$ centile (16.7% *vs* 4.5%; $P = 0.041$). When compared with the low-risk subgroup of pregnancies resulting in perinatal survival, pregnancies complicated by perinatal death had a lower EFW (EFW centile 29.1 *vs* 59.6; $P = 0.020$), higher UtA-PI MoM ($P = 0.019$) and higher proportions of SGA ($P < 0.001$) and CPR < 5$^{th}$ centile ($P = 0.025$). There was a 40% difference between median EFW centile and actual BW centile in the perinatal death group compared with a 7% difference in the low-risk perinatal survival cohort. Logistic regression analysis revealed that EFW centile and UtA-PI MoM were independent predictors of perinatal death (OR 0.957 (95% CI, 0.93–0.99) and OR 13.10 (95% CI, 1.95–87.89), respectively) (Table 3).

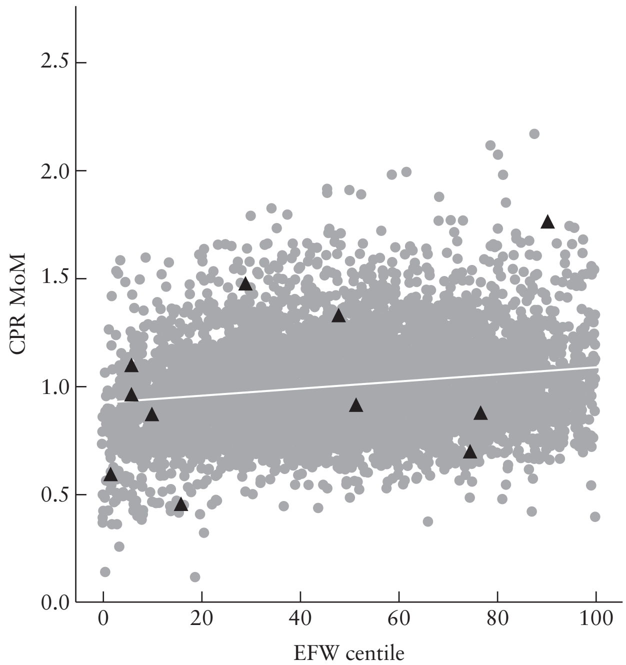


**Figure 1** Scatterplot of correlation between cerebroplacental ratio multiples of the median (CPR MoM) and estimated fetal weight (EFW) centile in 7013 singleton pregnancies, showing those that resulted in perinatal survival (●) and those complicated by perinatal death (▲).

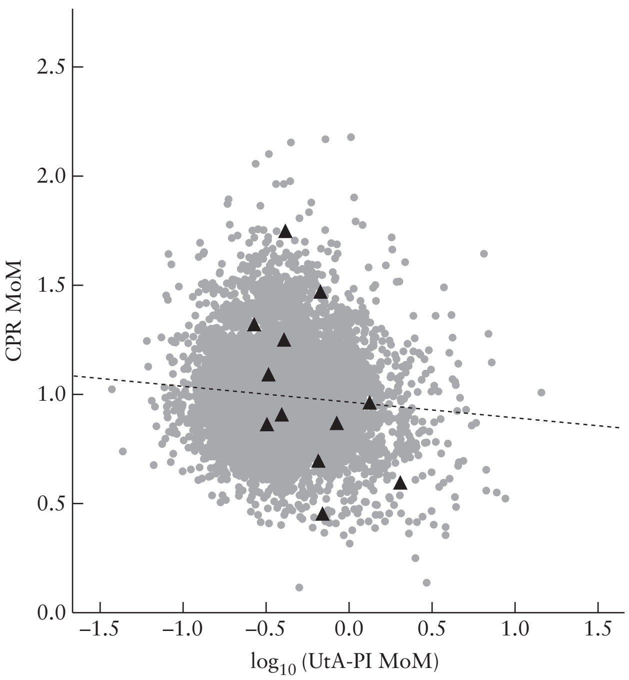


**Figure 2** Scatterplot showing relationship between cerebroplacental ratio multiples of the median (CPR MoM) and uterine artery pulsatility index (UtA-PI) MoM in 7013 singleton pregnancies, showing those that resulted in perinatal survival (●) and those complicated by perinatal death (▲).

**Table 3** Logistic regression analysis for prediction of perinatal death ($n = 12$) in singleton pregnancies

| *Variable* | *Odds ratio (95% CI)* | P |
|---|---|---|
| EFW centile | 0.957 (0.93–0.99) | 0.003 |
| CPR MoM | 1.969 (0.14–27.63) | 0.615 |
| UtA-PI MoM | 13.10 (1.95–87.89) | 0.008 |

CPR, cerebroplacental ratio; EFW, estimated fetal weight; MoM, multiples of the median; PI, pulsatility index; UtA, uterine artery.

## DISCUSSION

The findings of this study demonstrate that UtA-PI MoM, CPR < 5th centile and EFW and BW centiles were all associated significantly with perinatal death at term. After adjusting for interdependence of variables, only UtA-PI MoM and EFW centile remained associated significantly and independently with adverse perinatal outcome. Furthermore, when comparing median EFW and actual BW centiles, there was a 40% difference for pregnancies that resulted in perinatal death compared with a difference of only 7% for those in the low-risk perinatal survival group.

UtA Doppler indices have conventionally been the focus of studies in the first half of pregnancy. Low resistance in the UtA is thought to represent effective trophoblast invasion with adequate spiral artery remodeling and, therefore, normal placentation and placental function[18]. Conversely, in the presence of inadequate trophoblast invasion leading to placental dysfunction, high UtA Doppler indices have been associated with an increased risk of pre-eclampsia, FGR, placental abruption and stillbirth[19–23]. More recent evaluation of this ultrasound parameter in the third trimester has suggested that abnormal UtA Doppler indices are also associated with an increased risk of adverse pregnancy outcome[24,25]. In keeping with previous work by Khalil *et al.*[5], the findings of the current study confirm that significantly higher UtA resistance in the third trimester is associated with an increased risk of perinatal death. By performing regression analysis to determine the factors affecting the risk of perinatal death, we confirmed that UtA-PI, along with EFW, is associated significantly and independently with increased perinatal mortality. In this work, we assessed ultrasound parameters in the third trimester; it would seem to be important to determine if high third-trimester UtA resistances are already elevated in the second trimester or if they are a *de-novo* finding.

The association between low BW and perinatal mortality is also well established and presumed to be a consequence of placental insufficiency resulting in poor fetal growth and fetal hypoxia. The findings of the current study confirm that fetal size (EFW centile) is a significant

**Table 2** Ultrasound assessment and pregnancy outcome in 7013 singleton pregnancies, according to whether they resulted in perinatal survival or death

| | *Perinatal survival* | | | | |
|---|---|---|---|---|---|
| *Parameter* | *All* (n = 7001) | *Low-risk subgroup* (n = 1527) | *Perinatal death* (n = 12) | P* | P† |
| UtA-PI MoM | 0.66 (0.57–0.80) | 0.64 (0.55–0.76) | 0.76 (0.63–0.92) | 0.066 | 0.019 |
| UtA-PI > 90th centile | 701 (10.0) | 148 (9.7) | 3 (25.0) | 0.443 | 0.076 |
| UA-PI MoM | 1.07 (0.96–1.20) | 1.06 (0.95–1.19) | 1.18 (0.91–1.25) | 0.436 | 0.359 |
| MCA-PI MoM | 0.95 (0.85–1.07) | 0.97 (0.86–1.11) | 0.98 (0.76–1.09) | 0.856 | 0.614 |
| CPR MoM | 0.99 (0.85–1.14) | 0.99 (0.85–1.16) | 0.94 (0.74–1.31) | 0.902 | 0.880 |
| CPR < 10th centile | 698 (10.0) | 149 (9.8) | 3 (25.0) | 0.083 | 0.078 |
| CPR < 5th centile | 312 (4.5) | 60 (3.9) | 2 (16.7) | 0.041 | 0.025 |
| EFW centile | 49.56 (31.82–67.23) | 59.56 (42.36–76.10) | 29.10 (6.07–74.65) | 0.137 | 0.020 |
| BW centile | 40.52 (18.43–66.47) | 55.73 (30.69–79.52) | 20.51 (1.71–74.98) | 0.142 | 0.022 |
| SGA | 307 (5) | 14 (1.3) | 3 (25.0) | 0.001 | < 0.001 |

Data are given as median (interquartile range) or *n* (%). *Perinatal survival *vs* death. †Low risk *vs* perinatal death. BW, birth weight; CPR, cerebroplacental ratio; EFW, estimated fetal weight; MCA, middle cerebral artery; MoM, multiples of the median; PI, pulsatility index; SGA, small-for-gestational age; UA, umbilical artery; UtA, uterine artery.

 

independent predictor of perinatal death. There is ongoing debate about using fetal size exclusively as a screening tool to predict adverse perinatal outcome, and opposition to such use continues to be challenged[1]. Importantly, in the current study we noted a significant difference between EFW and BW centiles in the perinatal death group but not in the low-risk perinatal survival cohort. The reported accuracy of ultrasound estimation of fetal weight at term varies within the literature; however, a 40% difference cannot be explained by scan inaccuracy alone, especially given that EFW-to-BW discordance is not evident in the perinatal survival group[26,27]. The most likely contributor to this weight discrepancy is the time interval between intrauterine demise and determination of BW at the time of postmortem examination. Man *et al.*[3] recently showed that, following intrauterine death, fetuses lose weight *in utero* by maceration and continue to lose weight from dehydration after birth. Hence, it is likely that a significant proportion of stillbirths become SGA after their demise, and that autopsy-weight assessment may result in overestimation of the proportion of stillbirths defined as growth restricted[3].

As the debate regarding reference standards for assessing fetal size continues[28], the evaluation of additional ultrasound parameters as predictors of adverse pregnancy outcome becomes more relevant[2,4,5]. UA Doppler resistance is invariably normal at term[8] and fails to detect appropriately grown fetuses with hypoxemia. The oxygen requirements of the fetal brain increase with advancing gestation and one of the first hemodynamic alterations that occurs in the presence of fetal hypoxia is cerebral vasodilation and reduced MCA resistance, which has been associated with an increased risk of adverse perinatal outcome and subsequent abnormal neurodevelopment[29,30]. Fetal CPR has also been proposed as a predictor of adverse perinatal outcome and has been shown to be more sensitive than is UA or MCA Doppler assessment alone[31,32]. Fetal CPR measured in the third trimester is an independent and stronger predictor of stillbirth and perinatal mortality than is EFW[5]. In our study, CPR < $5^{th}$ centile was associated significantly with an increased risk of perinatal mortality, however, we did not find CPR MoM to be a significant independent predictor of adverse outcome. These findings are consistent with work by Akolekar *et al.*[33], who concluded that routine screening using CPR between 35 and 37 weeks' gestation provides poor prediction of indicators for adverse perinatal outcome. One of the possible explanations for this finding may be related to the time interval between CPR measurement on ultrasound scan and fetal demise. In the perinatal death group, the average interval between ultrasound assessment and delivery was 2.27 (range, 0.3–6.1) weeks. At term, the metabolic demands of the fetus increase exponentially, such that an inability of the placenta to meet these needs may result in sudden unpredictable fetal demise. Rather than focusing our attention on finding a sole ultrasound parameter to predict adverse outcome reliably, a combination of biophysical and biometric parameters, such as EFW, CPR and MCA and UtA Doppler assessment, together with maternal characteristics, may assist in the effective identification of pregnancies at risk.

The strengths of this study include the large number of pregnancies and outcomes examined within the cohort. On statistical analysis, we adjusted for confounding variables such as GA to ensure accurate analysis and interpretation of the data. In order to overcome the wide diversity of case mix within the perinatal survival cohort, we performed a subanalysis on what we considered to be a 'low-risk' population, and the findings remained significant.

The main limitation of this study is its retrospective design and therefore its risk of bias. In an attempt to ensure adequate numbers for comparison, we performed the search over an 8.5-year period. This may be a limitation, as clinical practice and protocols will have changed over this time period. There was also a relatively small number of cases in the perinatal death group (perinatal mortality rate of 1.7 per 1000 total births). The finding of significant relationships despite this low number indicates the strength of the associations and the potential utility in a clinical setting.

In conclusion, the study findings demonstrate that high UtA resistance at term is associated independently with an increased risk of severe adverse perinatal outcome, regardless of fetal size. Small fetuses also continue to be at increased risk of perinatal mortality. Further work to determine the optimum model of surveillance to identify those at increased risk of hypoxemia is required. In order to explore the underlying mechanism associated with increased third-trimester UtA Doppler indices and adverse perinatal outcome, we would advocate performing a prospective study to examine the trends in UtA Doppler indices throughout the second and third trimesters and their relationship with pregnancy outcome.

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## SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

**Table S1** Clinical details of 12 pregnancies complicated by perinatal death

 