Evaluation of Serial 2-D Sonographic Placental Volumetry and Umbilical Arterial Doppler and Their Correlation with Uterine Arterial Doppler in Predicting Adverse Fetomaternal Outcomes – An Observational Study from a Tertiary Care Centre in Pune, India

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ABSTRACT

BACKGROUND
An important part of human placental development is the extensive modification of maternal vasculature by trophoblasts. Fetal growth retardation (FGR) and pre-eclampsia (PE) are associated with deficient trophoblastic invasion and modification of the uterine spiral arteries leading to small-caliber vessels of high resistance which impairs placental blood flow, creating a hypoxic environment and subsequent oxidative stress. FGR and pre-eclampsia are important causes of maternal and perinatal morbidity and mortality and it is important to identify such 'at risk' pregnancies during routine antenatal care. Ultrasonography (USG) and colour-Doppler are readily available tools that may be used for identifying such 'at risk' pregnancies. The purpose of this study was to evaluate the accuracy of 2-D sonographic placental volumetry, umbilical arterial doppler and uterine arterial doppler in predicting adverse fetomaternal outcomes and compare the accuracy of these three tests with each other in terms of sensitivity and specificity.

METHODS
A total of 100 women were randomly selected from the antenatal clinics, and were subject to serial ultrasounds at 12 - 16 weeks, 20 - 24 weeks, and 28 - 32 weeks. The 2-D sonographic placental volume, umbilical and uterine arterial resistivity index (RI), and pulsatility index (PI) were measured. The pregnancies were followed up till delivery and the measurements were plotted against the actual placental weight and development of FGR and/or pre-eclampsia.

RESULTS
In pregnancies with FGR or pre-eclampsia, the placental volumes were low, and correspondingly the uterine and umbilical arterial RI and PI were high (increased impedance) as compared to the normal pregnancies. For the prediction of adverse outcomes, a receiver operating curve (ROC) analysis showed that placental volume and umbilical artery RI and PI had high sensitivity in the 1st-trimester, and high specificity in the 2nd-trimester.

CONCLUSIONS
2-D sonographic placental volumetry and umbilical arterial Doppler studies may be used as 1st-trimester screening tools to predict adverse fetomaternal outcomes. These patients may be subjected to more intensive follow-up to minimize maternal and perinatal morbidity and mortality.

KEYWORDS
Doppler Ultrasonography; Fetal Growth Retardation; Placenta; Pre-eclampsia; Umbilical Arteries; Uterine Artery

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BACKGROUND

The placenta is a multifunctional organ that is involved in the synthesis, metabolism, and transport of nutrients required by the fetus, and also a source of hormones that influence fetal, placental, and maternal metabolism and fetal development.[1,2]

An important part of human placental development is the extensive modification of maternal vasculature by trophoblasts. This event is integral to the pathogenesis of fetal growth retardation and pre-eclampsia, both being leading causes of maternal and perinatal morbidity and mortality. The accepted hypothesis is that reduced endovascular trophoblast invasion results in small-caliber vessels of high resistance, which impair placental blood flow, creating a hypoxic environment and subsequent oxidative stress. Since Zhang et al.[3] and Brosens et al.[4] described reduced trophoblast invasion with an absence of pregnancy-specific changes of uteroplacental arteries in pregnancies associated with FGR and PE, endovascular trophoblast invasion has been a major focus of research.

Doppler ultrasound permits the assessment of uteroplacental blood flow. Successful trophoblastic invasion of uterine spiral arteries causes reduced endovascular resistance and ensures continuous diastolic flow in the umbilical artery. A continuous decline in resistance over gestation has been found to correlate with normal birth weight and low risk of fetal distress. Conversely, rising umbilical arterial resistance with a progressive reduction in flow and eventual reversal of end-diastolic flow significantly correlates with worse fetomaternal outcomes. Uterine artery Doppler indices show a similar trend as the umbilical artery Doppler - decreasing impedance with gestational age in normal pregnancies and increasing impedance in established FGR and PE.

While this subject has been studied before, most of the placental volumetric studies were based on 3-D volumetry (which might not always be practicable in resource-limited settings) rather than 2-D volumetry and there is limited data on the subject from the subcontinent.

Aims & Objectives

To evaluate the accuracy of 2-D sonographic placental volumetry, umbilical arterial doppler and uterine arterial doppler in predicting adverse fetomaternal outcomes, and to compare the accuracy of these three tests with each other in terms of sensitivity and specificity.

METHODS

This observational study was carried out in a tertiary care teaching hospital from April 2019 to May 2020. The study population comprised of all women attending the antenatal clinic. A total of 100 women who visited the clinic before 16 weeks of gestation were randomly selected. The exclusion criteria included – gestation > 16 weeks at the first visit, history of chronic hypertension or PE or diabetes mellitus, multiple gestations, and Rh-negative isoimmunised status. After dating was confirmed, the patients underwent serial ultrasound scans at 12 - 16 weeks, 20 - 24 weeks, and 28 - 32 weeks, to record fetal biometry, placental volume, umbilical and uterine arterial RI and PI. Additional scans were done for fetal surveillance when warranted clinically. All women were followed up till delivery, and any adverse event was noted. The primary outcome was the development of pre-eclampsia, gestational hypertension, or intra uterine growth restriction (IUGR), leading to either term or preterm delivery. The secondary parameters measured were birth weight and placental weight in correlation to the antenatal ultrasound findings.

To minimize errors, sonography was performed by a single operator on a Logiq P5 unit (GE Systems, Milwaukee, USA) with a curvilinear low frequency (2 – 5 MHz) probe.

The expected placental volume on 2-D sonography was calculated using the following convex-concave shell formula, as described by Azpurua et al.[5]

$$V = (\pi T/6) * [4H (W - T) + W (W - 4T) + 4T^2]$$

(V = Volume; W = Maximal width; H = Height at maximal width; T = Thickness at maximal height)

Reference points were taken at the two edges of the placenta (in the plane of the insertion of the umbilical cord) to establish the width. Another reference point was taken at the apex of the placental curve at the interface of the placenta and myometrium. This point was connected to the width line perpendicularly to establish the height line. The placental thickness was measured along the height line to the point of the placenta-amniotic fluid interface (Fig 1).

The umbilical artery was identified using color Doppler, and flow measurements were taken after tracking the placental insertion of the cord. RI and PI were calculated both manually and automatically (machine software), and two successive similar readings were recorded. The uterine artery was identified as it ascended from the isthmus of the cervix, and RI and PI values were obtained.

In our study, gestational hypertension was diagnosed on a resting blood pressure reading ≥ 140/90 mmHg without proteinuria. Pre-eclampsia was diagnosed in patients, beyond 20 weeks gestation, having a resting blood pressure ≥ 140/90 mmHg with proteinuria of 1+ or more on the dipstick. IUGR was defined when the sonographic estimated fetal weight was < 10^{th} percentile for the gestational age.

The following obstetric data were also collected: age, parity, co-morbidities (previous pregnancy and current pregnancy), period of gestation at the first visit, period of gestation at the onset of an adverse event, length of gestation, and mode of delivery

The statistical analysis was done in the following manner:

1. Results were divided into the presence of any adverse outcome, presence of pre-eclampsia/gestational hypertension, presence of IUGR
2. Independent t-test was carried out for placental volumes in each trimester, umbilical arterial RI and PI, and uterine arterial RI and PI for the outcomes mentioned above
3. A receiver-operating curve was plotted to find out the positive predictive value of placental volume, umbilical arterial RI/PI, and uterine arterial RI/PI in each trimester for the development of pre-eclampsia or

IUGR.
4. Correlation between placental volume in each trimester with actual placental weight.

The statistical software packages Statistical Package for Social Sciences (SPSS 12.0) (SPSS Inc, Chicago, IL, USA) and MedCalc 14.10.2 (MedCalc Software BVBA, Belgium) were used for all data analysis.

RESULTS

A total of 100 women were recruited into this study and followed up till delivery. The participants were in the age range of 21 - 25 years. Fifty-nine women were primigravidas. Most of the patients had no past co-morbidities (94 %). Two women had hypothyroidism but were euthyroid on thyroid hormone replacement. One patient had a patent ductus arteriosus (corrected in childhood) and remained asymptomatic during her pregnancy. Ten were post-lower section caesarean section (LSCS) pregnancies. Overall, 25 % of the women underwent LSCS. One patient underwent vacuum delivery. Five patients had preterm deliveries. The demographic information is presented in Table 1

Adverse fetomaternal outcomes in terms of gestational hypertension or pre-eclampsia and IUGR were noted in 18 patients. Pre-eclampsia was detected in five, and IUGR in 16 patients. Of the patients having IUGR, five were associated with pre-eclampsia, 2 with gestational hypertension, and two with oligohydramnios. Of the five pre-term deliveries, three were due to pre-eclampsia and oligohydramnios. The pregnancy outcomes are depicted in Table 2.

A two-sample independent t-test was carried out for placental volume, umbilical arterial RI/PI, and uterine arterial RI/PI in each trimester with respect to the development of adverse outcomes (IUGR and pre-eclampsia).

It was found that, in the prediction of overall adverse outcomes, 1st-trimester placental volume had higher specificity (90.8 %) than sensitivity (57.9 %) (Fig 2). Both umbilical and uterine arterial 2nd-trimester RI values had good specificity (97.4 %) in the prediction of adverse outcomes.

A detailed analysis showed that 1st-trimester placental volume had good sensitivity and specificity (81.2 %, 88.6 %) in the prediction of IUGR. However, the best predictive value for the development of IUGR was found with 1st-trimester umbilical arterial RI (sensitivity 87.5%, specificity 96.2 %) (Fig 3). For the prediction of the development of pre-eclampsia, placental volumetry was neither sensitive nor specific in any trimester. Umbilical arterial PI had higher sensitivity (85.7 %) in the 1st-trimester compared to other trimesters, while uterine arterial PI had the highest sensitivity (100 %) in the 1st-trimester for the prediction of pre-eclampsia (Fig 4).

Since there was no consensus in the literature on the absolute cut-off values of placental volume, umbilical arterial and uterine arterial Doppler values, a 'receiver operating curve' analysis was done, and the 'area under the curve' (AUC) was calculated for each of the parameters studied for development of pre-eclampsia and IUGR.

The placental volume was found to be significantly lower only in the 1st-trimester in patients who developed pre-eclampsia, compared to the normal population. The umbilical and uterine arterial RI were found to be significantly raised only in the 3rd-trimester. Umbilical arterial PI had a significantly higher cut-off value in the 2nd-trimester, while the uterine arterial PI had a higher cut-off value in the 1st-trimester.

A similar analysis for IUGR showed a significant decrease in placental volume in all trimesters in the affected group as compared to the normal group. The umbilical and uterine arterial Doppler values, similarly, revealed a higher cut-off value in all the three trimesters for patients developing IUGR.

Uterine arterial PI had a higher sensitivity in the prediction of pre-eclampsia in the 1st-trimester (Fig 4), while RI had higher specificity in the prediction of IUGR (Fig 5).

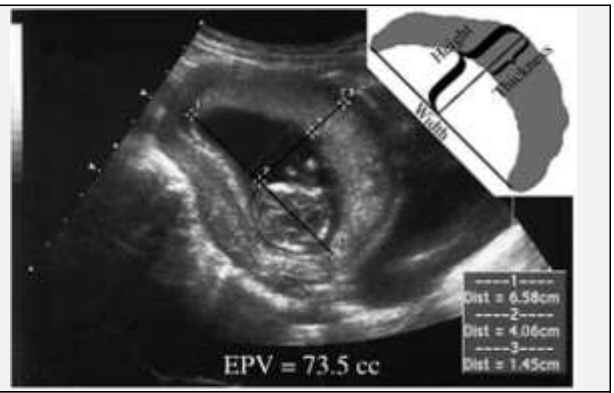
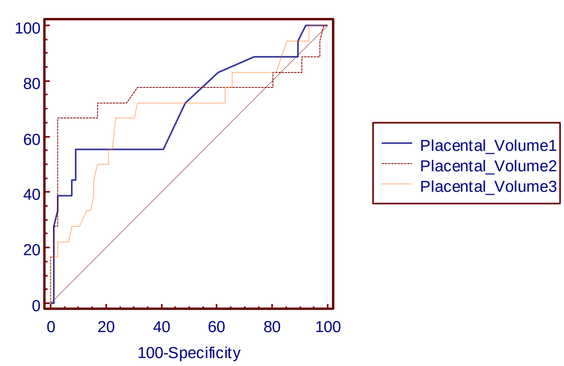
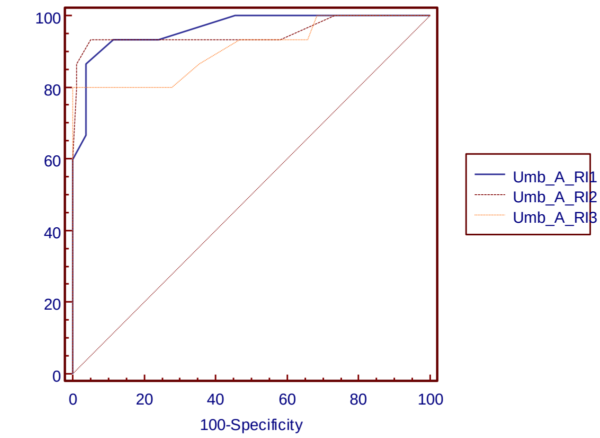


Figure 1. Measurement of Placental Volume as Described by Azpuruo et al.



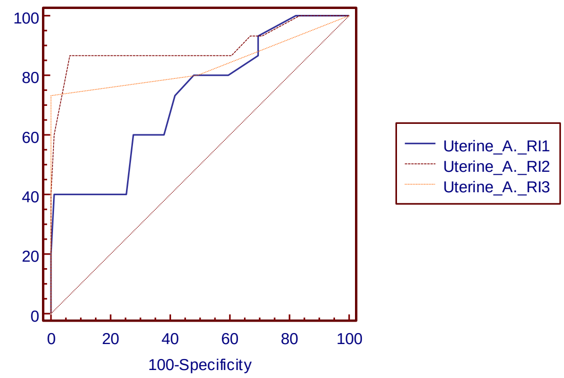
ROC Findings						
Placental Volume	Cut Off Point	Sensitivity	Specificity	Area Under the Curve (AUC)	Lower C.I AUC	Upper C.I AUC
1st trimester	≤ 123	57.90 %	90.80 %	0.719	0.618	0.807
2nd trimester	≤ 157	63.20 %	97.40 %	0.742	0.642	0.826
3rd trimester	≤ 319	66.70 %	76.30 %	0.691	0.587	0.782

Figure 2. ROC Curve of Placental Volume with Respect to Adverse Outcome



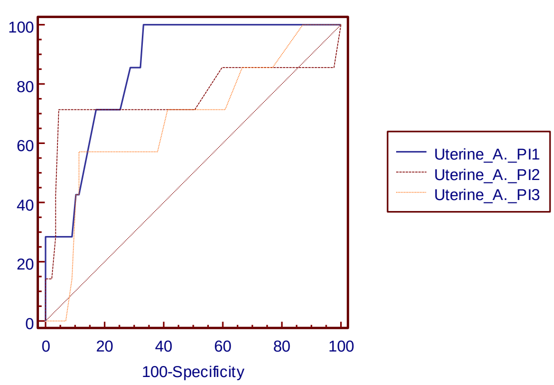
ROC Findings		Cut Off Point	Sensitivity	Specificity	Area Under the Curve (AUC)	Lower C.I AUC	Upper C.I AUC
Umbilical RI	1st trimester	> 0.86	87.5 %	96.20 %	0.964	0.904	0.991
	2nd trimester	> 0.78	63.20 %	97.40 %	0.773	0.675	0.852
	3rd trimester	> 0.7	80.00 %	100.00 %	0.907	0.829	0.957

Figure 3. ROC Curve of Umbilical Artery RI with Respect to IUGR



ROC Findings		Cut Off Point	Sensitivity	Specificity	Area Under the Curve (AUC)	Lower C.I AUC	Upper C.I AUC
Uterine RI	1st trimester	> 0.81	37.50 %	98.70 %	0.712	0.61	0.8
	2nd trimester	> 0.56	81.20 %	93.70 %	0.841	0.752	0.908
	3rd trimester	> 0.50	73.30 %	100.00 %	0.834	0.743	0.903

Figure 5. ROC Curve of Uterine Artery RI with Respect to IUGR



ROC Findings		Cut Off Point	Sensitivity	Specificity	Area Under the Curve (AUC)	Lower C.I AUC	Upper C.I AUC
Uterine PI	1st trimester	> 1.73	100.00 %	68.80 %	0.869	0.786	0.928
	2nd trimester	> 1.31	71.40 %	95.70 %	0.77	0.676	0.849
	3rd trimester	> 0.86	57.10 %	88.50 %	0.679	0.575	0.772

Figure 4. ROC Curve of Umbilical Artery PI with Respect to Pre-eclampsia

	Characteristic	Distribution
Age (years)	Mean age	23
	< 20 years	26
	21 - 25 years	63
	26 - 30 years	10
	➢ 30 years	1
Parity	Primigravida	59
	Multigravida	41
Co-morbidities	Hypothyroidism	2
	Rh-negative non-isoimmunised	1
	Thalassemia minor	1
	Congenital cardiac anomaly (operated)	1
	Post-Lower section caesarean section (LSCS)	10
Mode of delivery	Spontaneous vertex delivery	74
	LSCS	25
	Instrumental (Vacuum)	1
Time of delivery	Term (> 37 weeks)	95
	Pre-term (< 37 weeks)	5

Table 1. Demographic Characteristics of the Patients

Outcome	Frequency
GDM	1
Gestational HTN + IUGR	2
IFG	1
IUGR	5
Oligohydramnios	2
Oligohydramnios + IUGR	2
Pre-eclampsia	4
Severe Pre-eclampsia, Ascites, Deranged liver enzymes	1

Table 2. Patients with Adverse Pregnancy Outcomes

GDM: Gestational diabetes mellitus HTN: Hypertension
IUGR: Intra-uterine growth retardation IFG: Impaired fasting glucose

DISCUSSION

From the 2nd-trimester onwards, various studies have highlighted the correlation between the placental volume and the expected birth weight, and consequent identification of the neonate 'at risk'. However, most of these volumetric studies used 3-D ultrasound techniques, which might not be easily and widely available in low-resource settings, unlike 2-D sonography.

The placental volumetry technique proposed by Azpuruo et al. using widely available 2-D sonography is simple and rapid.[5] Their study showed a significant positive correlation between expected placental volume (EPV) and actual placental weight (APW) at all gestational ages (Spearman's rho = 0.80, P < 0.001). ROC analysis of the EPV for adverse fetomaternal outcomes showed high specificity of prediction especially in the 1st- and 2nd-trimester, more significantly so in the 2nd-trimester.

Studies by Odibo et al. Afrakhteh et al. Moran et al. and Schwartz et al. have also mentioned the role of 2nd-trimester placental volumetry in predicting adverse outcomes.[6,7,8,9] The studies by Odibo et al. Afrakhteh et al. and Schwartz et al. are also interesting since they mention the use of placental thickness and diameter in place of volumetry, to predict adverse outcomes. However, our study did not have a high discriminatory ability with regard to adverse outcomes as shown by AUC of 71% in the 1st-trimester and 74 % in the 2nd-trimester (Fig. 2).

A subgroup analysis of placental volumetry for the prediction of pre-eclampsia did not show any statistical significance in our study. Odibo et al. even with the use of 3D ultrasound, did not find any statistical difference between 1st-trimester placental volumes in pregnancies complicated by pre-eclampsia and normal pregnancies.[6] Plasencia et al. also mentioned a lower sensitivity for the prediction of pre-eclampsia by 1st-trimester placental volumetry alone.[10] However, overall consensus does say that pre-eclampsia is associated with lower placental volumes beginning with the 1st-trimester, as compared to normal pregnancies.

The relation of placental volumetry with IUGR was found to be significant, especially in the 2nd-trimester. Concerning IUGR, the discriminatory ability of placental volumetry was 87.5 % and 84.7 % for the 1st- and 2nd-second trimesters, respectively. The findings from our study are similar to the findings of the studies carried out using 3-D ultrasound.[6,7,8,10]

The importance of umbilical arterial PI as a negative predictive tool for IUGR and pre-eclampsia has been much studied. Moran et al.[8] Schwartz et al.[9] Chen et al.[11] Eastwood et al.[12] and Odeh et al.[13] found abnormal values in the 1st- and 2nd-trimester Doppler screening of pregnancies with pre-eclampsia and IUGR. Our study did not find a difference in the values between normal pregnancies and those with pre-eclampsia. On the other hand, in accordance with the studies quoted above, the Doppler indices were significantly negatively predictive of the development of IUGR.

A ROC analysis of the umbilical arterial Doppler values clarifies the issue further. With respect to overall adverse outcomes, umbilical arterial RI and PI have a modest negative predictive ability in all three trimesters, ranging from 75 – 78 %. Further sub-group analysis also revealed a similar picture. The umbilical arterial PI values have shown greater specificity, approaching 100 %, in the 2nd- and 3rd-trimester, for prediction of IUGR. However, the umbilical artery RI was a highly sensitive parameter in the 1st-trimester, in the prediction of IUGR. Analysis of the pre-eclampsia group differed from the above analysis. Both umbilical arterial PI and RI values showed a good negative predictive value in the 2nd-trimester, with AUC of 79 % and 81 %, respectively. The corresponding specificities were also 94 % and 91%, respectively. The study by Odibo et al.[6] mentions independent umbilical arterial Doppler studies to be of modest negative predictive value in the development of pre-eclampsia. Our study also conforms to the same finding.

Compared to the umbilical artery, the uterine artery has been much more extensively studied for its role in the prediction of pre-eclampsia or IUGR. In our study, uterine arterial RI and PI have shown a statistically significant relation in all three trimesters, for overall adverse outcomes and development of IUGR. As with umbilical artery Doppler, only the 1st-trimester uterine arterial PI was significantly different in patients with pre-eclampsia, compared to normal patients. Studies on uterine artery by Hafner et al.[14] Yücel et al.[15] and Chhabra et al.[16] have mentioned the role of 1st-trimester uterine artery Doppler studies in the prediction of adverse fetomaternal outcomes and pre-eclampsia. On comparing the negative predictive value of uterine arterial RI/PI on ROC analysis, uterine arterial PI was found to have higher specificity (92 %), with a negative predictive value of almost 80 %. In comparison, the uterine arterial RI had higher sensitivity in the 1st-trimester (84 %), but not very good negative predictive ability. These findings also do not match the findings of Chhabra et al.[16] which mentioned a positive correlation between uterine arterial RI > 95th percentile in 1st-trimester and development of adverse fetomaternal outcomes, especially hypertensive disorders.

The findings of this study point towards a better sensitivity of prediction in the 1st-trimester, and higher specificity in the 2nd-trimester. Neither placental volumetry nor umbilical/uterine artery Doppler individually had a good predictive ability to detect pre-eclampsia/IUGR. However, a combination of both volumetry and Doppler studies might improve the negative predictive value of detecting any adverse fetomaternal outcome, especially in the 1st-trimester.

CONCLUSIONS

This study adds to the current body of evidence, in which both umbilical and uterine arterial RI and PI have been shown to have a good negative predictive value in identifying women at high risk of pre-eclampsia and IUGR. It also highlights the possible role of 2-D sonographic placental volumetry in resource-limited settings.

The following conclusions may be drawn:

1. 1st-trimester placental volumetry would not be a good modality to screen for the development of pre-

eclampsia. However, it may be used to screen for the development of IUGR.

2. Both umbilical arterial RI and PI are extremely sensitive in the 1st-trimester for the prediction of adverse outcomes, especially IUGR. However, umbilical arterial RI is a better tool. In the 2nd-trimester, both RI/PI values have higher specificity in the prediction of adverse fetomaternal outcomes.
3. Uterine arterial PI value had a higher sensitivity in the prediction of pre-eclampsia in the 1st-trimester, while RI value had higher specificity in the prediction of IUGR (Fig 5). Uterine arterial PI/RI values had better specificity in the 2nd-trimester for the prediction of adverse outcomes, especially IUGR.

   A larger-scale study needs to be carried out to confirm these findings.

Limitations of This Study

The current study has its limitations. The first being limited sample size. There were no standard cut-off values for the placental volumes and the Doppler indices measured. Previous studies have mostly used the 95th percentile value, obtained from their respective results, as a cut-off. Although the results from our study have shown a significant correlation between 1st-trimester and 2nd-trimester volumetry and adverse outcomes, our study is limited by the fact that 2-D ultrasound was used for calculation of placental volume, based on mathematic modelling, which is less accurate than 3D volumetry. Placental volumetry was also technically difficult in the 3rd-trimester wherein the fetus tends to obscure the placenta.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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