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Second-Trimester Placental Volume and Vascular Indices in the Prediction of Small-for-Gestational-Age Neonates

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Key Words
Placenta · Fetal growth restriction · Three-dimensional sonography · Color Doppler ultrasonography

Abstract
Objective: To evaluate the ability of second-trimester placental volume and vascular indices to predict small-for-gestational-age (SGA) birth weight pregnancies. ***Material and Methods:*** Women with singleton pregnancies were prospectively evaluated at 17–20 weeks of gestation. Second-trimester placental volume and vascular indices were obtained and calculated using volume organ computer-aided analysis and three-dimensional (3D) power Doppler ultrasound. Participants were followed until delivery and their medical records were reviewed, including maternal age, parity and pregestational body weight and body height, as well as the gestational age, birth weight and gender of the fetus. ***Results:*** Of the 163 women with complete follow-up, 20 gave birth to SGA and 143 to appropriate-for-gestational-age (AGA) neonates. The mean second-trimester placental volume was significantly lower in the SGA than in the AGA group (170.6 ± 49.8 vs. 213.5 ± 75.8 cm^3, $p = 0.015$). None of the vascular indices, including the vascularization index, flow index and vascularization flow index, differed significantly between the two groups. We also found that the optimum cutoff for placental volume at a gestational age of 17–18 weeks was 189.7 cm^3. ***Discussion:*** Second-trimester placental volume was positively correlated with neonatal birth weight. Second-trimester placental volume measured on 3D ultrasound may be predictive of SGA neonates.

Introduction

Small-for-gestational-age (SGA) neonates have a greater likelihood of experiencing clinical problems after birth and in their postnatal periods compared to appropriate-for-gestational-age (AGA) neonates. Approximately 10% of term infants in developed countries and 23% in developing countries are classified as SGA. Various maternal, neonatal and placental factors have been found to restrict fetal growth, resulting in the birth of SGA neonates. Among the placental factors, abnormal placental growth and impaired vascular development may cause mismatches between fetal nutritional requirements and placental supply, leading to impaired fetal growth.

Ultrasound is an important tool for prenatal examination and evaluation of the progress of fetal development.

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Advances in ultrasound, including the development of three-dimensional (3D) power Doppler ultrasound and virtual organ computer-aided analysis (VOCAL) have made possible the quantitative calculation of placental volume and placental blood circulation. Low placental volume during the second trimester has been shown to be associated with low birth weight [1–5]. Similarly, first-trimester placental volume has been found to be associated with fetal growth [6–8].

Placental blood circulation has been assessed by 3D power Doppler ultrasound and expressed as vascular indices, including the vascularization index (VI), flow index (FI) and vascularization flow index (VFI). VI is a measure of the percentage of color-coded voxels in the selected area and represents the number of blood vessels within a sample tissue. FI is a measure of the mean color value of all color-coded voxels and represents the average intensity of flow. VFI is a measure of the mean color value of all colored and gray voxels and represents both vascularization and blood flow [9, 10]. Placental vascular indices measured by 3D power Doppler ultrasound were shown to be constantly distributed throughout gestation [11]. Moreover, vascular indices for the entire volume of the placenta were found to differ significantly between normal pregnancies and those with intrauterine growth restriction (IUGR), with VI and VFI being the best parameters for the appropriate identification of IUGR pregnancies [2].

The present study prospectively assessed the ability of second-trimester placental volume and vascular indices (VI, FI and VFI) to predict SGA neonates. In addition, we sought to determine the optimal cutoff value for placental volume on 3D ultrasound that could predict SGA birth weight in clinical practice.

Material and Methods

This study prospectively screened 338 women with singleton pregnancies who visited our outpatient department from January 2001 to January 2002 and from January 2012 to January 2013. As part of their routine prenatal care, all of these women were offered an ultrasound examination during their second trimester to assess fetal growth and to calculate placental volume and vascular indices. All women in both cohorts were followed until delivery. Their medical records were reviewed for pre- and perinatal data, including maternal age, parity and pregestational body weight and body height, as well as the gestational age, neonatal birth weight and gender of the fetus.

The estimated date of conception was calculated from first-trimester crown–rump length in the participants. Since measurements of whole placental volume and vascular indices by 3D power Doppler ultrasound and VOCAL have been reported to be less reliable after a gestational age of 20 weeks because the placenta is larger in size than the ultrasound probe [12, 13], this study included only those patients who underwent assessments of placental volume and vascular indices at a gestational age of 17–20 weeks. Women with multiple fetuses or maternal systemic diseases, as well as those carrying fetuses with an anomaly or abnormal chromosomes, were excluded. In addition, patients carrying a fetus that died in utero with an unclear date of fetal death, those who delivered before a gestational age of 20 weeks and those lost to clinical follow-up were excluded. Because our main objective in this study was to compare the placental volume and vascular indices between the SGA and AGA groups, we excluded the large-for-gestational-age (LGA) pregnancies (neonatal birth weight over the 90th percentile) before final data analysis. Of the 338 women screened, 163 met our inclusion and exclusion criteria and were enrolled.

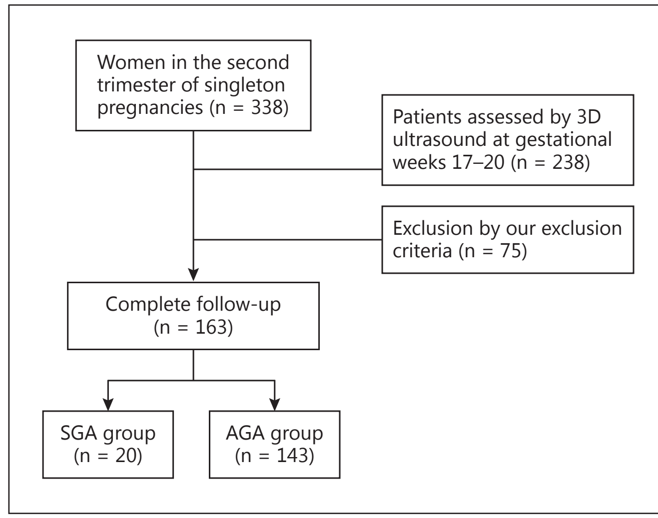

Fig. 1. Flow diagram for patient selection.

The 163 included patients were classified by their neonatal birth weight, gestational age at delivery and the gender of neonates, according to the 'Tenth percentile of birth weight for gestational age by gender: US 1991 Single Live Births to Resident Mothers'. They were divided into two groups, with 20 in the SGA birth weight group (estimated fetal weight below the 10th percentile) and 143 in the AGA birth weight group (fig. 1).

All ultrasound examinations were performed transabdominally using the same ultrasound machine (Voluson 730; GE Medical Systems) and a transabdominal 3D convex volume transducer (1.5–5.5 MHz) by a single trained ultrasound technician. The gain value was set individually for better image quality, since image quality was influenced by many factors, including the thickness of the maternal abdominal wall and the size and location of the placenta. A 2D ultrasound scan was performed first to evaluate fetal growth and identify the placental location. When the entire placenta could be visualized within the viewing area of the 3D probe, a 3D power Doppler ultrasound scan of the whole placenta was performed to obtain the placental vascular tree. In order to standardize the placental vascular indices evaluation, the unified power Doppler settings were used throughout the examination as follows: pulse repetition frequency, 0.9 kHz; frequency, low; wall

Fig. 2. a Analysis of placental area and volume by 3D power Doppler ultrasound and the VOCAL technique. **b** Calculation of vascular indices (VI, FI and VFI) of the entire placenta.

motion filter, low 1; quality, normal; flow response setting, mid 2; balance gain, >165; smooth, 4/5; ensemble, 15; line density, 6; power Doppler map, 5; artifact, on, and line filter, 2. Then the VOCAL technique was performed to determine placental volume. The VOCAL software was set as a manual trace with a rotation angle of 6, with 30 individual tracing planes to calculate placental volume calculation, followed by the automatic calculation of the placental vascular indices (VI, FI and VFI) throughout the entire placental area (fig. 2).

All statistical analyses were performed using IBM SPSS Statistics 17.0 software, with statistical significance defined as a p value <0.05. The baseline characteristics, placental volume and vascular indices (VI, FI and VFI) of the SGA and AGA groups were compared using independent t tests. Since 3D power Doppler ultrasound measurements of placental volume and vascular indices during the second trimester were reported to have fair-to-good intra- and interobserver reliability and reproducibility up to 18 weeks of gestational age [13, 14], we analyzed placental volume in women who underwent these examinations at a gestational age of 17–18 weeks using receiver operating characteristic (ROC) curves. The area under the ROC curve, asymptotic 95% confidence interval and optimum cutoff value were calculated.

Results

Of the 163 participants, 143 gave birth to AGA birth weight neonates and 20 to SGA neonates. The clinical characteristics of the two groups are compared in table 1. There were no significant between-group differences in maternal age, height or weight, nor were there differences in gestational age on ultrasound or in gestational weeks at delivery.

The mean ± standard deviation (SD) of second-trimester placental volume was significantly lower in the SGA than in the AGA birth weight group (170.6 ± 49.8 vs. 213.4 ± 75.8 cm³, p = 0.015). However, the values of VI (p = 0.749), FI (p = 0.968) and VFI (p = 0.825) were similar in the two groups (table 2).

To evaluate the discriminatory ability of second-trimester placental volume, ROC curve analysis was performed in women who underwent ultrasound measurements at gestational ages of 17–18 weeks (fig. 3). The area under the ROC curve was 0.706 and the optimum cutoff value was 189.7 cm³, with a sensitivity of 57.6% and a specificity of 84.6%. Using this cutoff, we divided the patients into two new groups and compared their characteristics. Maternal age, height, weight, weeks at delivery, and parity were similar in the two groups. In contrast, neonatal birth weight differed significantly in women with second-trimester placental volume >189.7 and <189.7 cm³ (p = 0.004).

Table 1. Characteristics of the AGA and SGA birth weight groups

	AGA group (n = 143)	SGA group (n = 20)	p value
Maternal age, years	33.2±4.6	31.4±4.3	0.084
Maternal height, cm	159.2±4.4	157.7±2.9	0.119
Maternal weight, kg	58.58±10.04	55.95±5.51	0.089
Gestational week of ultrasound measurement	18.3±1.1	18.4±1.1	0.947
Weeks at delivery	37.3±4.2	37.4±3.8	0.982

Values are presented as means ± SD.

Table 2. Comparison of placental volume and placental vascular indices in the AGA and SGA birth weight groups

	AGA group (n = 143)	SGA group (n = 20)	p value
Placental volume, cm^3	213.5±75.8	170.6±49.8	0.015
VI, %	10.67 (0.15–61.93)	9.76 (1.55–20.96)	0.749
FI	40.30 (0.88–61.06)	40.20 (25.19–51.60)	0.968
VFI	4.08 (0.06–23.67)	3.85 (0.67–8.30)	0.825

Placental volume is presented as mean ± SD. Values in parentheses are ranges.

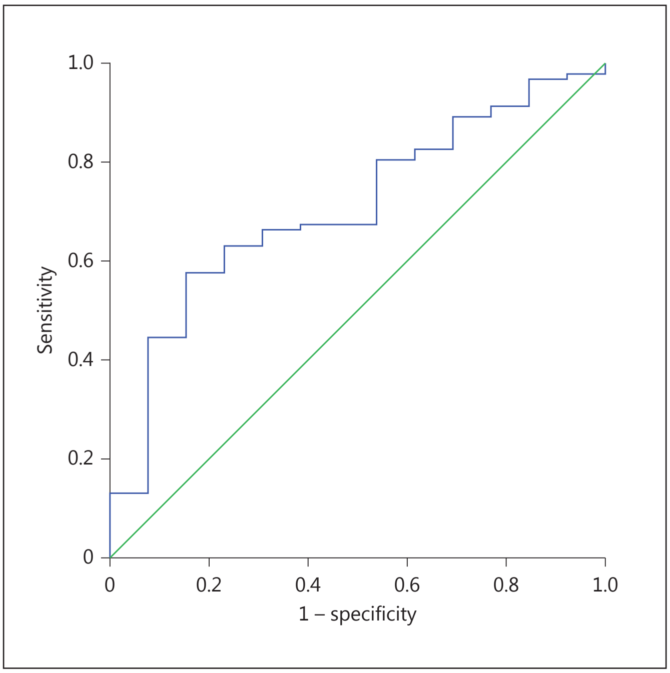

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Fig. 3. The ROC curve for ultrasound-determined placental volume at 17–18 weeks of gestation.

Discussion

The placenta has many important functions during pregnancy, including oxygen supplementation, transport of nutrients and fetal protection. Therefore, examining the placenta is important in evaluating normal and abnormal pregnancies [15]. Placental size and blood circulation may be associated with several maternal and fetal complications, including preeclampsia, pulmonary embolism and abnormal neonatal birth weight. The development of 3D power Doppler ultrasound has enabled the quantification of these placental characteristics and the possible earlier detection of at-risk pregnancies [15–17]. This may assist in deciding the necessity for early intervention and management, either before or at delivery, and may reduce the incidence of adverse neonatal outcomes.

In the study conducted by Hafner et al. [18], the link between neonatal birth weight and second-trimester placental volume measured by 3D ultrasound was investigated and it was found that placental volume alone could not accurately predict SGA birth weight. However, other following studies showed positive associations between first- or second-trimester placental volume and neonatal birth weight [1, 2, 4, 5, 8]. To determine whether second-trimester placental volume could predict SGA birth weight neonates, we measured placental volume before the gestational age of 20 weeks and found that it was significantly lower (by 42.8 cm^3) in the SGA group compared to the AGA group. This result confirmed our assumptions that early second-trimester placental volume measured by the VOCAL technique could serve as an effective parameter in predicting SGA pregnancies.

In addition, the ROC analysis showed that a placental volume cutoff of 189.7 cm^3 at 17–18 gestational weeks was predictive of SGA birth weight. A comparison of patients with placental volume above and below this cutoff showed that only fetal birth weight differed significantly, whereas other parameters did not, including maternal age, height, weight, and parity, as well as weeks at delivery. Although this cutoff value had a somewhat low sensitivity (57.6%), its specificity was higher (84.6%), making it a good reference value in our clinical practice. To our current knowledge, although many of the studies proved the association between placental volumes and neonatal birth weight, there are very few studies in the literature using ROC curves to convey the optimum cutoff value in specific gestational weeks. To integrate the previous available literature with the results of this study may provide clinicians with more complete clinical references to offer early counseling and relevant management for at-risk pregnancies.

A study using 3D power Doppler and the VOCAL technique to measure placental vascular indices in 45 patients (30 with IUGR and 15 with normal pregnancies) at 23–37 gestational weeks found that VI, VFI and FI were not dependent on placental position or gestational age, but were lower in the IUGR than in the normal group [19]. A subsequent prospective study comparing placental volume and blood circulation in 100 normal and 20 IUGR pregnancies at 22–44 gestational weeks by 3D power Doppler and VOCAL revealed significant differences between the groups in placental VI, FI and VFI, with cutoff values of 5.30, 36.0 and 2.30, respectively [2]. That study reported that VI and VFI were the optimal parameters for identifying IUGR pregnancies and for distinguishing IUGR from normal pregnancies. In contrast, we observed no significant differences in placental vascular indices (VI, FI and VFI) between the AGA and SGA birth weight groups, suggesting that placental circulation may not be predictive of fetal growth and neonatal birth weight. However, the study conducted by Raine-Fenning et al. [20] confirmed that the settings of power Doppler and the speed of acquisition could be significant factors affecting the measurement results of the vascular indices. They believed that signal power and gain had the greatest influence, followed by pulse repetition frequency. The power Doppler settings were different among the previous studies and our study, and some did not even describe the settings clearly. Moreover, intra- and interobserver reliability has been reported to decrease after 20 gestational weeks, which may have affected measurements of placental volume and vascular indices in some studies [12, 13]. Another possible explanation is that the sample size was insufficient to draw firm conclusions.

In recent years, many studies began to investigate the association between maternal biophysical and biochemical markers with placental function and neonatal birth weight. Karagiannis et al. [21] tried to develop a model based on maternal factors and biochemical and biophysical markers at 11–13 weeks of gestation to predict SGA neonates in the absence of preeclampsia. In their study, they found increased uterine artery pulsatility index and maternal MAP, and decreased fetal nuchal translucency (NT), free β-HCG, placental growth factor (PLGF), serum PAPP-A, A disintegrin and metalloprotease and placental protein 13 in the SGA group. They suggested that such additional markers could detect half of pregnancies with SGA neonates in the absence of preeclampsia at 11–13 weeks. Plasencia et al. [8] later combined maternal characteristics with PAPP-A or placental volume measured by 3D ultrasound at 11–13 weeks of gestation to predict SGA and LGA neonates. They showed a detection rate of about 30% at a false positive rate of 10%, and suggested this method could improve the prediction of SGA and LGA neonates compared to using maternal characteristics alone. This same team even set up specific risk algorithms for screening SGA neonates and preeclampsia by a combination of maternal characteristics and history with biochemical (PAPP-A, PLGF) and biophysical markers (uterine artery pulsatility index, MAP) [22, 23]. Similarly, the study conducted by Schwartz et al. [24] built a multivariable model of combining indirect markers of placental development (PLGF and placental protein 13) and direct assessment of the placenta at around 11–14 weeks of gestation for the early prediction of SGA. The changes of these biophysical and biochemical markers are thought to be related to placental insufficiency and were gradually utilized widely as predictive tools for SGA pregnancies and preeclampsia. Therefore, we believed that a combination of these markers with placental volume could indeed improve the results in our study and should be considered as a future objective of our research and as a reference for prenatal diagnosis.

In conclusion, the present study found that second-trimester placental volume was a reliable predictor of neonatal birth weight. The optimum cutoff value for placental volume, at 189.7 cm^3 at 17–18 gestational weeks, was highly specific, distinguishing between AGA and SGA neonatal birth weights. The above findings were based on data from a single hospital and a validation group may be needed. Our findings with regard to the relationships between placental vascular indices and neonatal birth weight differed from those of previous studies, suggesting the need for additional studies in larger numbers of patients, with unified power Doppler settings, to analyze the association between placental vascularization and neonatal birth weight. In addition, we had a very small number of severe SGA (below the 3rd or the 5th percentile) pregnancies and a lack of complete neonatal outcome information in this study. In future studies, we aim to collect larger case numbers and more complete data on the newborn outcome in order to provide more accurate clinical evidence and information.

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