OBSTETRICS

First-trimester placental ultrasound and maternal serum markers as predictors of small-for-gestational-age infants

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OBJECTIVE: The objective of the study was to combine early, direct assessment of the placenta with indirect markers of placental development to identify pregnancies at greatest risk of delivering small-for-gestational age infants (SGA10).

STUDY DESIGN: We prospectively collected 3-dimensional ultrasound volume sets, uterine artery pulsatility index, and maternal serum of singleton pregnancies at 11-14 weeks. Placental volume (PV), quotient (placental quotient [PQ] = PV/gestational age), mean placental diameter (MPD) and chorionic diameters, and the placental morphology index (PMI = MPD/PQ and adjusts the lateral placental dimensions for quotient) were measured offline. Maternal serum was assayed for placental growth factor and placental protein-13. These variables were evaluated as predictors of SGA10.

RESULTS: Of the 578 pregnancies included in the study, 56 (9.7%) delivered SGA10. SGA10 pregnancies had a significantly smaller PV, PQ, MPD, and mean placental diameter and higher PMI compared with normal pregnancies ($P < .001$ for each). Each placental measure remained significantly associated with SGA10 after adjusting for confounders and significantly improved the performance of the model using clinical variables alone ($P < .04$ for each) with adjusted areas under the curve ranging from 0.71 to 0.74. Uterine artery pulsatility index did not remain significantly associated with SGA10 after adjusting for confounders ($P = .06$). Placental growth factor was significantly lower in SGA10 pregnancies ($P = .02$) and remained significant in adjusted models but failed to significantly improve the predictive performance of the models as measured by area under the curve ($P > .3$). Placental protein-13 was not associated with SGA10 ($P = .99$).

CONCLUSION: Direct assessment of placental size and shape with 3-dimensional ultrasound can serve as the foundation upon which to build a multivariable model for the early prediction of SGA.

Key words: 3-dimensional ultrasound, fetal growth restriction, placenta, placental growth factor, uterine artery Doppler

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Intrauterine growth restriction (IUGR) is a significant contributor to perinatal morbidity and mortality, including intrauterine fetal demise, newborn encephalopathy, and cerebral palsy[1,2] and may have an adverse impact on long-term health outcomes such as cardiovascular disease.[3-5] Several studies have indicated, however, that routine prenatal care fails to detect the vast majority of IUGR cases prior to delivery,[6,7] preventing clinicians from instituting appropriate fetal surveillance aimed at improving outcomes. In addition, although there are no effective interventions shown to prevent IUGR, any candidate intervention would likely be more effective if implemented earlier in pregnancy to those at greatest risk.

The placenta serves as the key to the transfer of oxygen and nutrition to the fetus. In addition, placental size and shape at delivery are strongly correlated with newborn birthweight.[8-11] Nevertheless, there are no standard, validated approaches to evaluating antenatal placental growth during pregnancy because the routine sonographic evaluation of the placenta focuses mainly on its location relative to the internal cervical os.[12,13]

Advances in 3-dimensional (3D) ultrasound technology have allowed for noninvasive measurement of the placental volume. In fact, early placental volume has been shown to be significantly associated with IUGR and preeclampsia in several studies.[14-19] Moreover, we have previously published pilot data that demonstrated how the relative contributions of both lateral placental growth and placental thickness to the placental volume may provide an enhanced assessment of early placental development and may even improve prediction of adverse pregnancy outcomes such as small-for-gestational-age (SGA).[17] Therefore, we set out to further explore the ability of 3D ultrasonographic evaluation of the early placenta to identify pregnancies at greatest risk of IUGR.

In addition, although 3D ultrasound can be used to directly evaluate gross

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placental size and shape, there are elements of early placental development for which indirect markers may be better suited to evaluate. For example, uterine artery Doppler (UtAD) velocimetry measures the resistance to flow into the uterus, which has had a significant impact from effective trophoblastic invasion and remodeling of the maternal vasculature into a low-resistance system.[20]

Investigational maternal serum markers may capture other critical components of early placental development such as placental angiogenesis and placental implantation. For example, placental growth factor (PlGF), a member of the vascular endothelial growth factor subfamily, is expressed by trophoblasts and exerts angiogenic effects on the developing placenta and its environment. Placental protein 13 (PP13), a galectin expressed by the placenta, binds to proteins in the extracellular matrix at the placenta-endometrium interface and assists in placental implantation and maternal artery remodeling. In fact, first-trimester serum concentrations of both of these serum markers are significantly decreased in pregnancies destined to develop complications such as preeclampsia.[21-27]

The objective of this study was to develop a multivariable screening model combining direct and indirect markers of early placental development that can accurately identify pregnancies at increased risk of developing SGA in pregnancy.

Materials and Methods

In this prospective cohort study, women carrying singleton pregnancies who presented at 11-14 weeks' gestation for nuchal translucency screening at the Hospital of the University of Pennsylvania were recruited and consented during their genetic counseling session according to an institutional review board-approved protocol (no. 811129). Singleton gestations with available 3D volume sets, maternal serum, and obstetric outcome data were included in this analysis. Exclusion criteria included multiple gestations, patients presenting after 14 weeks, and patients delivering outside of our institution.

Ultrasound techniques

Enrolled subjects had a 3D volume sweep of the placenta obtained transabdominally (4-8 MHz probe; GE Voluson Expert; GE Healthcare, Milwaukee, WI) during their nuchal translucency examination. Sonographers were instructed to maximize their sweep angle and sector width and use the Max sweep quality setting (ie, slower sweep speed) to ensure the sweep included the entire placental mass at high resolution. The volume dataset was stored on external hard drives for offline analysis. The fetal crown-rump length was also recorded to confirm the gestational age. Pregnancies without a known last menstrual period (LMP) date or whose LMP was 7 or more days discrepant from the ultrasound dating were redated to reflect the crown-rump length. Finally, bilateral UtAD velocimetry was performed by identifying the sagittal view of the cervix, gradually moving the transducer laterally to each side, identifying the uterine artery with color Doppler as it crossed the iliac vessels, and then interrogating the vessel to obtain the pulsatility index (PI) as a measure of downstream vascular resistance. The mean PI was used for the analyses.

Each of the sonographers taking part in this study were previously trained and certified in the performance of UtAD techniques as part of a prior multicentered cohort study (Preterm birth in nulliparous women: an understudied population at great risk-U10, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; ClinicalTrials.gov [no. NCT01322529]).

The stored placenta volume sets were manipulated offline using 4DVIEW (GE Healthcare, Vienna, Austria) by a single investigator (N.S.), who was blinded to pregnancy outcome and using previously described techniques.[17] Briefly, placental volume (PV) was measured using virtual organ computer-aided analysis to trace the outline of the object of interest in successive planes obtained by rotating the object around the y-axis at 30° rotational intervals. The software then renders the structure and calculates the estimated volume (Figure 1, A). The placental quotient (PQ) was calculated to normalize the PV to gestational age (PQ = PV/days of gestation).

Next, to quantify the lateral placental dimensions, we obtained 4 measurements of the maternal placental surface evenly spaced around the circumference by: centering the placenta in all 3 orthogonal planes, measuring the traced length of the uterine-placental interface in the A and B planes to obtain yielding 2 orthogonal placental diameters, rotating the placenta 45° around the y-axis and repeating the 2 measurements (Figure 1, B). Thus, the mean placental diameter (MPD), the average of these 4 diameters, represents the lateral placental dimensions and approximates the gross surface area of the myometrial-placental interface.

We then calculated the placental morphology index (PMI = MPD/PQ), which quantifies the contribution of the lateral placental dimensions to the overall placental mass. Thus, the higher the PMI, the greater the relative contribution of the lateral placental dimensions compared with that of the placental thickness. On the other hand, a lower PMI signifies a more significant contribution of placental thickness to the overall placental mass.

Because there are data indicating the importance of the morphology and surface vasculature of the chorionic plate (the fetal surface of the placenta),[28,29] we also obtained 4 evenly spaced measurements of the diameter of the fetal surface of the placenta to obtain a mean chorionic diameter (MCD) using the same rotational approach mentioned above (Figure 1).

Serum markers

During the same patient encounter at 11-14 weeks' gestation, 5 mL of maternal blood was drawn and centrifuged ($1200 \times g$) at room temperature for 10 minutes. The collected serum was stored at −80°C until analysis. Thawed serum was then assayed for 2 serum markers involved in early trophoblastic development, PlGF and PP13. Serum concentrations of PlGF and PP13 were measured in duplicate using commercially available ELISA kits (PlGF: R&D Systems, Inc, Minneapolis, MN; PP13: