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The role of second trimester ultrasound in the diagnosis of placental hypoechoic lesions leading to poor pregnancy outcome

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Abstract

Objective. The purpose of the study was to quantify placental hypoechoic areas without blood flow by means of second trimester high-resolution ultrasound with power color Doppler and to evaluate its relationship to pregnancy outcome.

Methods. Patients referred for second trimester ultrasound from January 2001 to December 2003 were eligible for the study. Patients with placental parenchymal hypoechoic areas without blood flow constituted the study group (N = 65). The control group was comprised of 65 patients who had normal placental parenchyma. The groups were similar with regards to maternal age, gestational age, parity, race, and smoking. The mean of the two largest lesion diameters was used for severity classification.

Results. Fifty-two patients (80%) had aggregate lesions of ≤5 cm and 13 (20%) had lesions >5 cm. Mean ± standard deviation (SD) gestational age at delivery was 39.1 ± 1.8 weeks for the control group, 37.9 ± 2.8 weeks for those with lesions of ≤5 cm, and 35.2 ± 5.8 weeks for those with lesions > 5 cm (p = 0.0001). Mean birth weight ± SD was 3348 ± 492 g for the controls, 3134 ± 657 g for those with lesions of ≤5 cm, and 2524 ± 1339 g for those with lesions > 5 cm (p = 0.0005). The incidence of intrauterine growth restriction was 9.6% in the group with lesions of ≤5 cm and 38.4% in the group with lesions > 5 cm, compared to 3.1% in the control group (p = 0.0003; odds ratio (OR) = 5.7, p = 0.015). The incidence of preeclampsia in the control group was 0.0%, in the group with lesions of ≤5 cm was 7.7%, and in the group with lesions > 5 cm was 15.4% (p < 0.0214; OR = 14.3, p = 0.014).

Conclusions. Increased size of hypoechoic placental lesions is associated with increased risk for adverse perinatal outcome. Such lesions might be the result of intervillous space thrombosis, and ultrasound may be a useful tool in the identification of patients with pro-thrombotic abnormalities. The capability to identify patients with placental thrombosis will help us to identify those patients who will benefit most from anti-thrombotic treatment.

Keywords: Placenta, thrombosis, growth, preeclampsia, Doppler, ultrasound, hypoechoic, preterm

Introduction

Ultrasound has been useful in identifying placental thrombosis [1–5]. However, the types of lesions and their severity are variable. Sonography has not been used to quantify placental lesions and their impact on the pregnancy. The impact of early appearance of the lesions versus late appearance is not known. Unfortunately, detailed anatomical evaluation of the developing placenta during pregnancy is not part of the limited (level I) or the detailed (level II) ultrasound. Most ultrasound reports when referring to the placenta only contain information regarding placenta location and the presence or absence of calcifications (maturity grading).

Placental thrombosis has been associated with significant maternal and fetal morbidity and mortality such as, but not limited to, fetal growth restriction, preterm labor and delivery, premature rupture of membranes, cerebral palsy, abruptio placenta, and preeclampsia. In the majority of studies, evaluation of the relationship of placental thrombosis to perinatal outcome is based on the diagnosis of placental thrombotic lesions in pathology specimens after delivery [6–10]. Postnatal diagnosis of placental thrombosis precludes a timely prophylactic intervention.

Current ultrasound technology offers a variety of means for non-invasive assessment of the placenta in vivo. High-resolution imaging coupled with power color Doppler technology provides an important tool for the prenatal diagnosis of placental functional and structural abnormalities at all gestational ages [11–13].
This retrospective case–control cross-sectional study was designed to quantify placental hypoechoic lesions by means of high-resolution ultrasound and power color Doppler and to evaluate the relationship of such lesions to pregnancy outcome.

Methods

All patients referred for second trimester ultrasound (between 18 and 22 weeks of gestation) for the following indications: fetal anatomical evaluation, gestational age assessment (poor menstrual history), and small for age or large for age (discrepancy of menstrual dating (LMP) and clinical assessment), between January 1, 2001 and December 31, 2003 at Kofinas Perinatal, New York Methodist Hospital, Brooklyn, NY, USA, were eligible for the study. All patients with placental lesions at the first ultrasound (between 18 and 22 weeks) were selected for the study group. Each patient was seen only once (cross-sectional design). Gestational age was confirmed by accurate menstrual history and/or corroborating ultrasonic measurements. The following conditions, if present, constituted the exclusion criteria: pregnancies with an abnormal fetus, multiple gestations, history of drug abuse, vaginal bleeding prior to the exam at any time during the index pregnancy, placenta previa, chronic hypertension, diabetes, preterm labor, premature rupture of membranes, incompetent cervix, and growth restriction (ultrasoundically estimated fetal weight <10th percentile at the time of exam). All patients with otherwise normal pregnancies and evidence of placental parenchyma with any hypoechoic lesions >5 mm at the time of the ultrasound examination constituted the study group (N = 65). The control group was comprised of 65 patients with normal placental parenchyma at midtrimester ultrasound (no evidence of lesions >5 mm) and was selected from our ultrasound database. The selection of the control group was based on the absence of hypoechoic lesions >5 mm in their largest diameter. In our experience most if not all patients have a few small anechoic lesions that are clinically insignificant. Our goal was to establish a lesion size that would be easily recognizable and clinically significant. The two groups were not different regarding maternal age, gestational age, parity, race, and smoking habits (Table I). Both groups of patients were seen in the same time period as noted above.

Placental integrity was assessed with high-resolution ultrasound and power color Doppler. Power color Doppler is angle independent and the only one able to evaluate small tortuous vessels with slow flow patterns. The color scale was set always at the lowest level (0.6 KHz) and the filter at a level to eliminate wall motion artifacts. Patients were included in the study only if the placenta could be visualized in its entirety regardless of its position (anterior, posterior, or lateral). In patients with parenchymal thrombosis there is a loss of normal homogeneous appearance of the placenta due to the presence of hypoechoic areas in the placental parenchyma. The anechoic areas represent regions of chorionic villous degeneration and necrosis. The absence of maternal flow within the anechoic areas was confirmed with power color Doppler (Figures 1–3). Sequential transverse and longitudinal scans in real-time were used to evaluate the degree and severity of the lesions. If no placental hypoechoic areas >5 mm were identified, the placenta was classified as normal. All lesions >5 mm were evaluated and their two largest diameters measured. The aggregate mean of the two diameters was used for severity classification. All patients with placental hypoechoic areas exceeding >5 mm were classified into two groups according to the aggregate of the measured lesions: those with ≤5 cm in aggregate size and those with >5 cm in aggregate size. In no case did we make any recommendations for treatment in patients with placental hypoechoic lesions.

The following pregnancy and fetal characteristics and outcomes were investigated in association with placental health: gestational age at time of delivery, birth weight, the presence of intrauterine growth restriction (IUGR; birth weight <10th percentile), preterm delivery (delivery prior to 37 completed weeks), pregnancy-induced hypertension (BP ≥150/90 mmHg, with or without proteinuria), and fetal or neonatal death. All neonates were evaluated at the time of birth by a pediatric attending or neonatologist (if premature). The study was approved by the Research Committee and the Institutional Review Board of the New York Methodist Hospital.

Statistical analysis was performed by means of JMP statistical program for Windows (SAS institute,
Cary, NC, USA) and SPSS (11.5). Continuous outcome variables were analyzed by parametric methods (t-test, analysis of variance) and frequency data by non-parametric methods (Chi-square, odds ratio (OR)). Statistical significance was set at $p = 0.05$. 

Figure 1. High resolution magnified simultaneous recording of the same placental region with gray-scale imaging next to power color imaging. Note the early partial fetal thrombotic vasculopathy (FTV) with low density of chorionic villi in panel B and evidence of active persistent intervillous space flow in panel A. The yellow arrow points to parenchyma with normal chorionic villus density and no evidence of chorionic degeneration for comparison.

Figure 2. This image shows a mixture of placental regions with thrombosed and intact intervillous space (IVS) flow. Black areas represent complete villous degeneration and IVS thrombosis. Orange areas represent villous degeneration but intact persistent IVS flow.
Results

Fifty-two patients (80%) exhibited lesions ≤5 cm and 13 (20%) had lesions >5 cm. Mean ± SD gestational age at delivery was 39.1 ± 1.8 weeks for the control group, 37.9 ± 2.8 weeks for those with lesions ≤5 cm, and 35.2 ± 5.8 weeks for those with >5 cm lesions (p < 0.0001). Mean ± SD birth weight was 3348 ± 492 g for the control group, 3134 ± 657 g for those with lesions ≤5 cm, and 2524 ± 1339 g for those with lesions >5 cm (p = 0.0005). Preterm delivery (<37 weeks) was not more frequent in patients with lesions, despite the lower mean gestational age at delivery for the group with lesions >5 cm; most probably this is the result of small numbers (type II error). However, the incidence of IUGR was more frequent in patients with placental hypoechoic areas without blood flow: 9.6% in the group with ≤5 cm lesions and 38.4% in the group with >5 cm lesions, in comparison to 3.1% in the control group (p = 0.0003).

The probability of a pregnancy resulting in IUGR with an ultrasound diagnosis of placental lesions during the second trimester was 5.7 times greater than for patients without evidence of placental lesions (OR = 5.7; p = 0.015). Preeclampsia was also more frequent in the patients with placental lesions: control group 0.0%, ≤5 cm lesions group 7.7%, and >5 cm lesions group 15.4% (p < 0.0214). The probability of a pregnancy complicated by preeclampsia was 14.3 times greater in patients with placental lesions than in the controls (OR = 14.3; p = 0.014) (Tables II and III).

There were no pregnancy losses in the control group. There was one neonatal death (1.9%) at 26 weeks in the ≤5 cm lesion group. The neonate was severely growth-restricted. There were two losses in the >5 cm lesions group: one intrauterine demise at...
24 weeks with severe growth restriction and one loss at 22 weeks with preterm premature rupture of membranes. The 24 week demise with growth restriction was normal at the time of the study at 18 weeks. At the time of delivery, the placenta was grossly thrombotic.

**Discussion**

The present study shows an association between placental thrombosis as seen by real-time ultrasound and some of the most significant pregnancy complications. We have also demonstrated that there is increased incidence of adverse outcomes studied in the presence of larger placental lesions. The absence of visible placental hypoechoic areas is associated with the best outcomes. The frequency of the complications studied was less than average in such patients. Patients with lesions ≤5 cm experienced higher numbers of adverse outcomes in comparison to the patients without lesions. The frequency of adverse outcomes in patients with lesions ≤5 cm is slightly higher but in the vicinity of the frequency of such outcomes in the unselected population as reported in the obstetrical textbooks [14,15]. Furthermore, if one were to combine the control patients with the study group with lesions ≤5 cm, the overall incidence of complications in this combined group would not be different to that of the unselected population. Worst outcomes were present in patients with significant hypoechoic placental lesions without blood flow. We have no explanation for the decreased incidence of adverse outcomes in the patients without lesions. We can only speculate that such patients maintained their normal placentas for the duration of the pregnancy and thus presented with better outcomes. Most pregnancy complications are one way or another related to placental quality. It should not then be surprising that patients with the least placental damage achieve the best outcomes. Although there is a possibility of selection bias of the control group, we believe this is not the case here because we selected the patients based on placental quality and the outcomes were then extracted from the chart.

Lesions that are larger than 3 cm in pathology specimens of placentas with thrombotic lesions after delivery are associated with poor perinatal outcomes [8]. It appears that there is a ‘dose-dependent’ effect. The more placental damage the more severe the outcomes. Using ultrasound we defined placental hypoechoic areas without blood flow as significant when the mean of two diameters was larger than 5 cm, because placentas in vivo are larger than placental specimens that have been treated with formaldehyde. However, this difference in size is arbitrary due to lack of any previous estimates.

Placental thrombosis has been primarily studied in placental specimens, where gross and microscopic anatomical descriptions have been used to explain the pathophysiology. Opinions are contradictory as to whether the origin of the defect that leads to thrombosis originates in the maternal or fetal circulation [16]. The human placenta is of the hemochorial type with a dual circulation. The maternal part perfuses the intervillous space (IVS) and the fetal is contained within the chorionic villi. Infarcts involving the maternal circulation are the result of uteroplacental vascular insufficiency and spiral arteriolar thrombosis. Infarcts involving the fetal circulation are less well understood and are the result of fetal thrombotic vasculopathy [17,18]. It makes teleological sense that if the maternal spiral artery is thrombosed, the corresponding fetal vessels will eventually regress due to lack of perfusion and the chorionic villi will degenerate. Based on previous evidence [19] we speculate that the same may be true for the maternal circulation in the case of fetal arterial thrombosis. The coexistence of partial and complete chorionic degeneration in the same lesions (Figures 3–5) suggests the progressiveness of the etiologic pathology. We speculate that in some cases with isolated thrombotic lesions and normal outcomes the pathology might be a random one-time event while in pregnancies with poor outcomes, the pathology might be chronic and progressive. Longitudinal prospective studies are needed to test this hypothesis.

The placenta must maintain a delicate balance between excessive clotting and hemorrhage. Any condition that disturbs this balance may lead to either hemorrhagic or thrombotic damage. Because of the hypercoagulable bias of the hemostatic mechanism during pregnancy, it is more likely that the placenta will sustain thrombotic injury in the course of the pregnancy. A number of prothrombotic states have been associated with placental thrombosis and adverse perinatal outcomes [20–25]. Such prothrombotic imbalances between the maternal and fetal circulations may be responsible for

<table>
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<th>Table III. Odds ratio analysis: Control group compared to the entire placental lesions group (≤5 cm and &gt; 5 cm lesions combined).</th>
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<td>Control</td>
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IUGR: intrauterine growth restriction; OR: odds ratio; CI: confidence interval.
Figure 4. The boxed area demonstrates low power appearance of hypoechoic lesion with partial and complete chorionic villous degeneration. The region outside the box has chorionic villi of normal appearance and density.

Figure 5. High-resolution magnified appearance of the boxed area from Figure 4 demonstrating partial and complete chorionic villous degeneration coexisting in the same lesion.
progressive placental thrombosis and degeneration of the chorionic villi that may in turn cause variable degrees of placental insufficiency and poor pregnancy outcomes as shown in the current study. The large variety of prothrombotic factors in pregnant women makes it difficult to assess outcomes reliably and thus identify patients at risk based on maternal testing alone. Controversial outcomes from similar maternal prothrombotic conditions may be the result of inconsistent definitions of what constitutes thrombophilia but also may be the result of variable effects by such factors depending on co-existing fetal prothrombotic abnormalities. By focusing on placental ultrasonic pathology, we may be able to identify the common link that will help us identify patients with prothrombotic imbalances who are more likely to experience adverse outcomes.

Although it is important to identify a degree of thrombosis that would be clinically significant and would prompt us to intervene with some form of antithrombotic treatment, it is equally important to view such pathology as a continuum and not as a dichotomous state. Severe lesions may cause extreme outcomes, such as early pregnancy loss or fetal loss after 20 weeks of gestation, but milder degrees of thrombosis may be associated with preeclampsia, growth failure, placental inflammation, and preterm labor. The degree of severity may define the gestational age at which the complications arise, a very significant factor in the quality of outcomes.

Future prospective studies may be able to refine the quantification process and increase the diagnostic accuracy and thus improve our ability to better define abnormal conditions. Furthermore, longitudinal studies may help us elucidate the impact of isolated random lesions versus the impact of chronic and expansive lesions. Gray-scale imaging alone cannot differentiate between intact maternal intervillous circulation and thrombosis of the intervillous space. The use of power color Doppler is indispensable for making such distinctions. In our experience, fetal vascular thrombosis (chorionic vessel thrombosis) is far more common in the presence of intact maternal intervillous space circulation. Maternal intervillous circulation remains active for up to three weeks from the time fetal vascular thrombosis is diagnosed. In the end, maternal circulation ceases and a clot is formed (unpublished data). Identification of such lesions earlier in pregnancy may become an indication for maternal and paternal testing for prothrombotic abnormalities. Antithrombotic treatment of such coagulation abnormalities may improve placental development and function and thus reduce the incidence of related complications.

In summary, we have presented evidence for an association between the presence of placental hypoechoic lesions and adverse perinatal outcomes. We have shown that increased size of lesions is associated with higher incidence of adverse perinatal outcomes. High-resolution ultrasound with power color Doppler is a useful tool for identifying placental lesions that may be the result of prothrombotic abnormalities. The placenta is the ‘battlefield’ of potentially abnormal prothrombotic conditions during pregnancy given the vascular nature of the organ. In addition, future studies may prove ultrasound with power color Doppler to be useful for the long term monitoring of such conditions especially if antithrombotic treatment is to be implemented.

References