Placental Pathology in Relation to Uterine Artery Doppler Findings in Pregnancies with Severe Intrauterine Growth Restriction and Abnormal Umbilical Artery Doppler Changes

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Abstract

Objectives Current guidelines for diagnosis and management of early-onset intrauterine growth restriction (IUGR) rely on umbilical artery Doppler (UAD), without including uterine artery Doppler (UtAD). We hypothesized that IUGR cases with abnormal UAD but normal UtAD has a different spectrum of placental pathology compared with those with abnormal UtAD.

Study Design Retrospective review of pregnancies with sonographic evidence of IUGR and abnormal UAD prior to delivery. Cases with ≥ 1 UtAD record(s) after 18^{+0} weeks' gestation and placental pathology were included. Cases were stratified according to initial UtAD pulsatility index (PI) values (n = 196): normal (n = 19; PI < 95th centile for gestational age/no notching), intermediate (n = 69; PI ≥ 95th centile/no/unilateral notching) and abnormal (n = 108; PI ≥ 95th centile/bilateral notching). Pregnancy outcomes and placental pathology were compared between groups.

Results Women in the normal group delivered later than those in the abnormal group (30.1 ± 3.5 vs. 28.0 ± 3.5 weeks; mean ± standard deviation; p = 0.03). Their placentas exhibited higher rates of chronic intervillositis (15.8 vs. 0.9%; p = 0.01), chorangiosis (15.8 vs. 0.9%; p < 0.0001), and massive perivillous fibrin deposition (21.1 vs. 7.4%; p = 0.05), but had lower rates of uteroplacental vascular insufficiency (26.3 vs. 79.6%; p < 0.0001).

Conclusion Approximately 10% of pregnancies with early-onset IUGR and abnormal UAD exhibited normal UtAD waveforms. They delivered later, and their placentas exhibited unusual placental pathologies.

Keywords

placental pathology - early-onset IUGR - uterine artery Doppler - umbilical artery Doppler

Intrauterine growth restriction (IUGR) of the normally formed fetus is most commonly attributed to disorders of placental function.[1] The more common “late-onset” type of growth restriction (> 34 weeks' gestation) may be difficult to recognize prenatally, since Doppler waveforms in both the uterine and the umbilical arteries are mostly normal.[2] On the contrary, the more rare “early-onset” IUGR (< 34 weeks' gestation) is characterized by abnormal umbilical artery Doppler (UAD) waveforms, with minimal, absent end-diastolic flow (AEDF), or even reversed end-diastolic flow (REDF) velocities.[3] [4] From a clinical perspective, the sonographic findings of an asymmetrically grown anatomically normal fetus, accompanied by low amniotic fluid and abnormal UAD, are considered sufficient to make a diagnosis of “placental insufficiency,” especially in the presence of preeclampsia (PE).[5] [6] As such, clinicians may not interrogate the uterine arteries during the evaluation of early-onset IUGR, since they may regard uterine artery Doppler (UtAD) as of limited utility[7] and, at present, it is not recommended in clinical management.[8] However, UtAD waveforms may be normal despite the presence of underlying placental pathologies, such as distal villous hypoplasia[9] and Breus' mole,[10] which are associated with high perinatal mortality rates.

Following delivery for severe preterm IUGR, the placenta is not consistently sent for pathologic analysis.[11] Possible explanations for this include cost (since, most likely, the analysis will demonstrate features of chronic maternal underperfusion[12]) or because the examination is not considered necessary to guide clinicians in future pregnancy management.[8] Our analysis of a large single-center cohort of placentas has revealed a wide spectrum of underlying pathologies in association with preterm IUGR.[5] In this study, we determined the proportion of pregnancies presenting with abnormal UAD while exhibiting normal UtAD waveforms, and hypothesized that in comparison to those with abnormal UtAD readings, these pregnancies will be associated with a different spectrum of underlying placental pathology and clinical prognosis.

Materials and Methods

We conducted a retrospective cohort study of suspected growth-restricted pregnancies with abnormal UAD waveforms delivering at Mount Sinai Hospital, Toronto, Canada, between 2005 and 2014. Research Ethics Board approval (REB# 11–0153-C) was obtained. Cases were initially identified by performing a search for “AEDF” or “REDF” in our hospital database system (Astraia Software, Munich, Germany). Only cases with UtAD waveforms recorded at one or more examinations from 18 weeks' gestation onward, which met the following criteria, were included: singleton pregnancy, ultrasound dating verified by crown rump length or biparietal diameter before 16 weeks' gestation, normal fetal anatomy, abnormal UAD waveforms recorded on one or more occasions after 18 weeks' gestation, and placental pathology performed at Mount Sinai Hospital following delivery. Exclusion criteria were a postnatal diagnosis of any major congenital abnormality or any nonplacental cause of fetal growth restriction. During the study period, a total of 196 cases met these criteria. Thirty-seven percent of the cohort is contained in our previous study which focused on sex-specific differences in placental pathology associated with extreme preterm delivery due to PE and/or IUGR.[5] Reflecting the nature of our tertiary referral center practice, the majority of women were clinically high-risk subjects attending Maternal-Fetal Medicine clinics or were transferred in the antenatal period for perinatal complications.

Doppler recordings were obtained using Philips iU22x MATRIX ultrasound systems (Philips Healthcare, Andover, MA) as an integrated part of the care of pregnancies with suspected early-onset IUGR.[1] The proximal uterine arteries were located in a standard manner using color flow imaging at the crossover point with the external iliac artery; a pulsed Doppler gate was placed just above this crossover point to obtain the pulsatility index (PI).[13] The presence/absence of an obvious early diastolic notch was also recorded. UtAD assessment is used in our center as part of a placental health screening strategy to stratify subsequent care according to the estimated risk of early delivery necessitating Level 3 perinatal center care.[14] UAD waveforms were obtained in free loops of cord by pulsed Doppler to derive PI values and record AEDF or REDF velocities. All archived image sets for each case were reviewed blinded to clinical and placental pathology outcomes. When serial umbilical artery and UtAD measurements were performed, the first and last sets of observations were recorded. Archived placental images were reviewed for placental dimensions (maximum length [as a single linear measurement, or as two linear segments combined, if curved] and maximum placental thickness); these measurements were recorded in 117 cases (median gestational age: 23 weeks [range 18–31]).[15]

Clinical outcomes, including maternal complications, mode of delivery, and infant outcomes were recorded from electronic records. Birth weight was categorized by sex-specific Canadian-derived centiles.[16] The diagnosis of IUGR was assigned where the sex-specific birth weight was < 10th centile, since all had abnormal UAD. PE and the hemolysis, elevated liver enzymes, and low platelets syndrome were diagnosed according to the current American College of Obstetricians and Gynaecologists guideline.[17]

Placental pathologic assessment following delivery was performed by a pathologist specializing in perinatal pathology at Mount Sinai Hospital, according to guidelines[18] [19] described in previous publications.[5] [9] In brief, placentas were fixed in formalin for 2 to 3 days, following which the gross features of the placenta and cord were recorded. Following removal of the placental cord and membranes, the weight was recorded in grams and expressed as a centile using a standard reference,[20] with values < 10th centile considered abnormal. Cord coiling was categorized as normal (1–3 turns/10 cm), hypocoiling (< 1 turn/10 cm), or hypercoiling (> 3 turns/10 cm), approximating values obtained in healthy term deliveries.[21] The fixed organ was then cut into 1 to 2 cm slices to identify grossly visible lesions. Samples containing specific lesions, together with samples of full-thickness apparently normal parenchyma, a membrane roll, and umbilical cord were embedded in paraffin to generate hematoxylin & eosin-stained sections for microscopic review. The location (marginal vs. central) of lesions was recorded. At least three samples of placental disc were obtained from each specimen. The percentage of grossly affected tissue was recorded. Placental findings were categorized by the gross and histologic observations, being either focal (observed in one–two blocks) or diffuse (observed throughout three blocks). An abnormal placental pathology diagnosis was defined by the following criteria: (1) chorion regression syndrome (CRS; placental weight < 10th centile for gestational age accompanied by eccentric/marginal/velamentous cord insertion and/or diffuse distal villous hypoplasia)[22]; (2) uteroplacental vascular insufficiency (UPVI; two or more of the following: placental weight < 10th centile for gestational age; decidual vasculopathy [atherosis and/or eosinophilic necrosis of decidual arterial walls]; central [> 1 cm], full-thickness or multifocal infarction; accelerated villous maturation with syncytial knot formation)[23] (combination of 1 and/or 2 has been classified as maternal vascular malperfusion (MVM) under recently-published guidelines[24]); (3) chronic maternal inflammation (chronic villitis of unknown etiology,[25] plasma cell deciduitis,[26] or chronic intervillositis[27]); (4) hemorrhage (large hemorrhage in a marginal, subchorionic, or retroplacental location, or small hemorrhage associated with basal villous infarction); (5) fetal vascular disease (large vessel thrombosis or fetal thrombotic vasculopathy)[28]; (6) other disorders of villous development: chorangiosis, distal villous immaturity[29]; and (7) massive perivillous fibrin deposition (maternal floor infarction).[30]

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistical Software, Version 22 (Armonk, NY). Descriptive data were described using percentages, mean and standard deviation, or median and range, as appropriate. UtAD PI centile values were derived using the reference by Bahlmann et al,[13] obtained in 921 healthy women. Prior to analysis, and blinded to placental pathology, the cohort was separated into three predefined groups based on their earliest recorded UtAD PI findings after 18^{+0} weeks: normal (UtAD PI < 95th centile and no early diastolic notches; *n* = 19, 9.7%); intermediate (UtAD PI ≥ 95th centile and no notching or

unilateral early diastolic notching; *n* = 69, 35.2%); and abnormal (UtAD PI ≥ 95th centile and bilateral early diastolic notches; *n* = 108, 55.1%). Continuous data were compared using Student *t*-test. Categorical data were compared using the chi-squared test for difference of proportions. One-way analysis of variance followed by the Bonferroni post hoc was used to define differences between three groups. Statistical significance was defined as $p < 0.05$.

Results

Maternal characteristics, mode of delivery, hypertensive complications, and pregnancy outcomes are summarized in [Table 1], stratified by UtAD category (normal, intermediate, and abnormal). Irrespective of UtAD category, only 10 women (5.1%) delivered infants > 10th centile birth weight without hypertensive complications; these were distributed equally across the categories. Pregnancies with normal UtAD delivered at a significantly later gestational age, on average 2 weeks, compared with those with abnormal UtAD ($p = 0.03$). This difference did not significantly influence birth weight centile distributions between the groups. Perinatal mortality was high (80/196, 40.8%) but did not differ significantly between the groups. Most perinatal deaths were stillbirths with previable weights, including unmonitored vaginal deliveries using misoprostol for severe PE with a guarded intact survival prognosis.[31] No significant sex differences were observed. Despite trends toward more hypertensive complications and earlier deliveries in the group with abnormal UtAD, no significant differences were observed.

Discussion

Our study demonstrates three key findings relevant to perinatologists evaluating and managing women with a sonographic diagnosis of early-onset IUGR that is presumed to be due to underlying placental dysfunction identified by abnormal UAD waveforms. First, a subset of approximately 10% of such pregnancies are associated with normal UtAD waveforms and this group is both likely to deliver infants at higher gestational ages and to exhibit unusual placental pathologies, in comparison with the typical UPVI found in the majority of early-onset IUGR pregnancies with bilateral abnormal UtAD waveforms.[12] Among the placental diagnoses after delivery, chronic intervillositis[27] was significantly associated with normal UtAD waveforms. This is an important diagnosis to establish by placental pathology, since it has a high recurrence risk and no effective interventions to prevent disease recurrence.[27] A second rare histopathologic diagnosis, also unrelated to uteroplacental perfusion, namely massive perivillous fibrin deposition,[30] was close to significance and also carries a high recurrence risk.[32] Identification of this diagnosis may alter future management plans, including the potential for novel drugs, such as pravastatin.[33] Both conditions may coexist in severe cases of IUGR.[34] Interpregnancy discussion of the management implications of these diagnoses is, therefore, important and illustrates the potential value of disease-specific counseling in placenta-related disorders.

The initial sonographic evaluation of suspected early-onset IUGR needs to be comprehensive,

given the range of underlying causes.[1] [8] The examination, therefore, includes the need for careful assessment for underlying fetal abnormalities associated with IUGR, including features of specific aneuploidies, since early-onset IUGR with normal UtAD is associated with an increased risk of fetal aneuploidy.[35] In the absence of fetal markers of aneuploidy in the setting of normal UtAD, the evaluation of placental size and shape may reveal abnormalities that alert the clinician to an underlying diagnosis of placental dysfunction.[9] [36] We, therefore, suggest that UtAD should be incorporated into the initial sonographic evaluation of early-onset IUGR with abnormal UAD waveforms, at least in tertiary care settings following in utero transfer for further management.

The strengths of our study include the single-center sample size, given that early severe IUGR is a rare diagnosis in unselected pregnancies, and our institutional interests in placental pathology. Nevertheless, the study design is retrospective, subject to inherent selection bias in a referral setting, and is underpowered given the underlying diversity of placental pathology in the context of managing early-onset IUGR pregnancies. Due to the nature of a regional referral practice in fetal medicine, the distribution of gestational age at initial assessments was understandably broad, though the median gestational age (24 weeks) was similar across all three subgroups. Furthermore, we were able to interpret UtAD Doppler mean PI results using a recently published high-quality reference range.[13]

The classic pathology associated with early-onset “placental IUGR” is the combination of gross and histopathologic findings that indicate UPVI[12] [14] [37] [38] [39] together with features of CRS.[22] [40] Though UPVI pathology dominates in preterm IUGR, there is a considerable degree of heterogeneity, with infiltration of the placenta by the maternal immune system in 20 to 30% of cases.[5] [41] The extent to which the presence or absence of such additional lesions is relevant to subsequent infant neurodevelopment, or to prognosis in future pregnancies, is presently unknown. In one small study, only 2 of 19 women with early-onset IUGR pregnancies and abnormal UAD waveforms demonstrated a similar recurrence in a subsequent pregnancy, although no placental pathology information was reported.[42] Recent research data suggest that the recurrence risk[43] and type of pathology[5] may be influenced by fetal sex, which may be a potential confounding factor in this context.

Since most placental pathologies are considered progressive, they will ultimately damage greater amounts of previously functional placental villi to further impair umbilical blood flow. It is, therefore, interesting to speculate why around 10% of pregnancies exhibited improved EDF. One potential explanation is the temporary observation of reappearing, or increased EDF, in response to administration of maternal corticosteroids to promote lung maturation, a variable response seen in most IUGR fetuses, lasting up to 7 days.[44] Since steroids may have been given by the referring physician, and the fetal responses are variable, we are unable to assess the contribution of steroids to this phenomenon. An alternative explanation may be differing sites of umbilical cord Doppler sampling between examinations, since EDF increases toward the placental cord root.[45] This phenomenon was, however, not associated with chorangiosis (adaptive angiogenesis) previously noted in severe IUGR pregnancies with persistent EDF in the umbilical arteries.[46] The umbilical cord itself may contribute to UAD, with anecdotal well-documented examples of cord obstruction, typically with a long, hypercoiled cord.[47] Our observation of a significantly increased rate of hypercoiling in the normal UtAD group provides yet another example of how abnormal UAD may occur, when UtAD is normal.

Unanswered questions arising from our study include the potential utility of combining a placental sonographic assessment with UtAD in the context of early-onset IUGR, in an attempt to predict the underling placental pathology and identify cases that are most likely to benefit from the expense of placental pathology. In research settings, it will be important to include placental pathology as a key outcome. Tracking subsequent pregnancies by placental diagnosis, for example, within larger multicenter consortiums dedicated to research in early-onset IUGR, such as Truffle consortium in Europe[48] or the Sildenafil Therapy In Dismal 387 prognosis Early-onset intrauterine growth Restriction (STRIDER) Study Group in the Netherlands,[49] provide clinicians with more robust evidence to justify placental pathology-based counseling and management in future pregnancies.