Assessing the 'at-risk' fetus: Doppler ultrasound

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Purpose of review

Doppler ultrasound has become an indispensable tool in evaluating pregnancies at risk for conditions such as preeclampsia, intrauterine growth restriction, fetal anemia, and umbilical cord abnormalities. Use of umbilical artery, middle cerebral artery, and uterine artery Doppler has been the mainstay of assessment.

Recent findings

Recent findings promote the use of ductus venosus Doppler to aid in timing delivery of severely growth-restricted fetuses. Whereas initially it appeared that abnormalities in ductus venosus waveform were the endpoint for pregnancies afflicted with intrauterine growth restriction, newer data suggest that these abnormalities may plateau prior to further fetal deterioration as witnessed by changes in the biophysical profile.

Summary

In this review, we will discuss current ultrasound Doppler literature and the recommendations of the experts. We observe that the best algorithm for incorporation of the ductus venosus into intrauterine growth restriction management is yet to be determined. This remains a subject of intense research aimed at optimizing pregnancy outcomes and will be important to follow to provide up-to-date care of our patients.

Keywords

Doppler, fetal anemia, intrauterine growth restriction, preeclampsia

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Introduction

Doppler ultrasound has emerged as one of the most objective methods to assess pregnancies at risk for or affected by preeclampsia, intrauterine growth restriction (IUGR), fetal anemia, and other adverse perinatal outcomes. Doppler ultrasound provides information on fetal and placental cardiovascular function on the basis of the vascular resistance of the vessel being assessed.

Doppler in assessing the 'at-risk' fetus was recognized almost two decades ago in a study published by Divon *et al.* [1]. In this study, IUGR fetuses with absent umbilical artery end-diastolic flow were followed daily with biophysical profile scoring and strict delivery criteria. The end result was no case of stillbirth or acidemia [1]. Doppler has subsequently become the mainstay of non-invasive assessment of the 'at-risk' fetus. The American College of Obstetrics and Gynecology (ACOG) advocates for the use of Doppler as an adjunct to standard antenatal testing to decrease mortality in cases of IUGR [2].

In this review, we will discuss the use of noncardiac Doppler ultrasound in pregnancies complicated by IUGR. We will outline the use of uterine artery Doppler in managing pregnancies with abnormal maternal serum analytes, maternal comorbidities such as connective tissue and hypertensive disease, and/or a history of preeclampsia. Additionally, the value of middle cerebral artery (MCA) Doppler in the surveillance of fetuses at risk for anemia will be reviewed.

Doppler indices

Indices considered when using ultrasound Doppler are the systolic/diastolic ratio (S/D ratio), the resistance index (which equals the systolic velocity–diastolic velocity/systolic velocity), and the pulsatility index (systolic velocity–diastolic velocity/mean velocity). These indices are reflective of vascular resistance and operate by detecting a change of sound frequency (and wavelength) due to motion of the sound source, the receiver, or a sound reflector [3•]. Whereas S/D ratios are more frequently used to assess arterial waveforms in the United States, some experts believe that the pulsatility index is a more reproducible index with the lowest margin of error [4••].

Intrauterine growth restriction

In cases of IUGR, redistribution of blood flow between the fetus and the placenta is diagnosed and followed using ultrasound Doppler. Primarily, an increase in vascular resistance of the placenta leads to abnormalities in the umbilical artery, and cerebral vasodilation leads to increased blood flow through the MCA [5••]. For the purposes of this review, we will take into consideration pathologically small fetuses and separate them from those fetuses which are constitutionally small and otherwise normal. Furthermore, we will concentrate on those fetuses that are growth restricted due to uteroplacental insufficiency. It is, nonetheless, important to bear in mind that IUGR may also be a finding in fetuses with aneuploidies or anomalies as well as those who are afflicted with in-utero infections.

Another important consideration in the evaluation of a fetus for IUGR is notation of the presence or absence of associated maternal disease. In IUGR fetuses with no other maternal pathology (i.e. preeclampsia), Doppler changes can be anticipated over a somewhat reliable time course in 50–70% of cases [6,7]. These changes are less consistent in patients with concomitant pathologies and thus the sequence of events for these IUGR fetuses is less predictable [8•].

Umbilical artery

Umbilical artery Doppler has been used as one means to identify fetuses which are pathologically small. As with other arterial Dopplers, umbilical artery Doppler flow velocity waveform provides information on downstream peripheral vascular impedance, in this case of the placenta. Abnormalities in diastolic blood flow through the umbilical artery are often the first sign of IUGR after diagnosis of a fetus with an estimated weight (EFW) of less than 10% or an abdominal circumference less than 5% [5••]. Other manifestations which, when identified, aid in the diagnosis are listed below [9••].

(1) Biometric manifestations of fetal growth delay:
  (a) Sonographically EFW below the 10th percentile.
  (b) Abdominal circumference less than 5th percentile.
  (c) HC/AC ratio less than 10th percentile.
  (d) Individualized growth potential less than 10th percentile.
  (e) Abdominal circumference growth velocity less than 11 mm in 14 days.
(2) Vascular manifestations of placental dysfunction:
  (a) Increased uterine artery Doppler index and/or notching.
  (b) Increased umbilical artery Doppler index.
  (c) Decreased middle cerebral artery Doppler index.
  (d) Decreased cerebroplacental Doppler ratio.
  (e) Maximum amniotic fluid pocket less than 2 cm.
  (f) Amniotic fluid index less than 5 cm.

Signs of accelerating placental dysfunction, and thus worsening fetal status, are listed below [9••].

(1) Umbilical artery absent or reversed end-diastolic velocity.
(2) MCA Doppler evidence of brain sparing.
(3) Elevated venous Doppler indices.
(4) Reversal of ductus venosus atrial wave.
(5) Umbilical vein pulsations.
(6) Oligohydramnios.
(7) Abnormal biophysical profile score.
(8) Spontaneous late decelerations.

A decrease of the umbilical artery end-diastolic velocity (UAEDV) and increase in the resistance index or pulsatility index can be witnessed once 30% or more of the placental villous vasculature is abnormal [10]. Once damage to 60–70% of the villous tree is damaged, absent or reversed end-diastolic flow (A/REDF) occurs [11]. Unfortunately, fetal hypoxemia and acidemia may develop in up to 70% of fetuses before these late findings are noted [12]. This has led to investigations of the best strategy to guide management and intervention. Biophysical profile or modified biophysical profile remains integral to the assessment. The goal is to decipher the optimal time of delivery, especially in cases of severely premature infants, when each day *in utero* potentially affords a 2% increased chance of survival until 29 weeks gestation [13•].

Fetal cerebral circulation

The MCA is the intracranial vessel most commonly imaged due to its reproducibility and ease of identification. In the IUGR-afflicted fetus, an increase in diastolic blood velocity to the brain may be witnessed via the MCA Doppler. This is detected by a decrease in the S/D ratio or pulsatility index and is referred to as a 'brain-sparing effect.' Unlike cases of isoimmunization, when MCA peak systolic velocities (PSV) are increased in relation to decreased fetal hemoglobin and decreased blood viscosity, the IUGR fetus' hemoglobin is typically unaffected. The increase in MCA blood flow is thus thought to result from elevated fetal blood pressures which results in increased diastolic waveforms on Doppler, but this remains speculative [14•]. Additionally, hypoxemia and hypercapnia lead to brain auto-regulation, which preferentially shunts more oxygenated blood through the ductus venosus and into the head and upper extremities [15••]. Loss of the 'brain-sparing effect' was initially considered a finding sufficient to proceed with delivery. Newer parameters have been identified which correlate more closely with fetal hypoxia and acidosis sufficient to cause fetal death [16].

Mari and colleagues have reported on use of the MCA-PSV in IUGR fetuses. In their report, MCA-PSV more accurately predicted perinatal mortality than use of the MCA pulsatility index. MCA-PSV was found to increase progressively with advancing gestational age in all fetuses with a tendency to decrease slightly just prior to fetal biophysical deterioration or fetal demise. Yet despite this slight decrease, the MCA-PSV constantly remained above the upper limit of normal until hours before delivery. Therefore, the authors believe that this parameter more closely parallels the immediate condition of the fetus [3•,17•].

Ductus venosus

As part of ascertainment of a temporal sequence of events preceding fetal hypoxia, acidemia, or death in the IUGR fetus, many investigators have turned to the ductus venosus. The ductus venosus carries the most rapidly moving blood in the venous system, and thus is easily identifiable by the aliasing seen on Doppler ultrasound. Abnormal ductus venosus flow is currently thought to herald the last stage of fetal deterioration and an absent or reversed atrial waveform is always concerning. Several authors have reported that reversal of atrial systole in the ductus venosus is an indication for delivery, especially after 32 weeks' gestation or administration of antenatal corticosteroids.

Reversed flow in the ductus venosus results from a decline and subsequent reversal in forward blood flow velocity during atrial systole. The abnormality in forward cardiac function may be related to worsening placental disease, impaired cardiac function due to metabolic compromise, redistribution of hepatoportal blood flow through the liver, or a combination of these. Reversal of the ductus venosus has previously been reported as one of the most severe and ominous venous Doppler abnormalities [18•,19••].

Eager to learn from mistakes made in the past with other obstetric interventions, however, Mari and colleagues have proposed that ductus venosus-reversed flow (DVRF) should not be an indication for delivery in the early third trimester for all cases of IUGR [18•]. The authors feel that further information should be obtained regarding ductus venosus and other Doppler deterioration before implementing a practice for all IUGR fetuses. They have also reported that IUGR fetuses progress less predictably if accompanied by maternal comorbidities (i.e. preeclampsia, diabetes) [20••]. The basis for the recommendation to continue fetal surveillance and delay delivery is also based on the finding that the majority of fetuses with DVRF were not found to be acidemic. This is, however, in contrast to studies by Hecher *et al.* [21] and Rizzo *et al.* [22] that found a strong association between acidemia and reversal of 'a' wave velocities in the ductus venosus and inferior vena cava [21,22].

In cases in which delayed delivery after DVRF is attempted, umbilical vein waveform should be monitored for the development of pulsations. The mitral and tricuspid valves should be monitored for regurgitation. Additionally, fetal biophysical profile and nonstress tests (NSTs) should guide the provider to optimize delivery outcome [19••].

Umbilical vein

Venous Dopplers, including the umbilical vein, provide information about forward cardiac function in the fetus. Normally after 15 weeks' gestation the umbilical vein has continuous forward blood flow. Umbilical vein pulsations may be witnessed in two scenarios: during fetal breathing and in the presence of fetal cardiac failure in cases of fetal hydrops or severe IUGR [18•]. When found in the latter scenario, it is often accompanied by reversal of the umbilical artery end-diastolic flow and reversal of the atrial 'kick' on ductus venosus waveform. This is an ominous finding [23].

Intrauterine growth restriction staging

Numerous authors have proposed staging schemes for the assessment and management of IUGR. Pardi *et al.* [24] initially NSTs and umbilical artery assessments to stage the severity of IUGR. In this staging system, the rate of hypoxia/acidemia jumped from 5% in group II to 60% in group III with little ability to provide information on the fetuses which were somewhere in between these two risk groups. Later, the incorporation of additional fetal vessels into the assessment enabled closer surveillance of the progression of IUGR.

Mari and colleagues have developed a staging system for IUGR based on fetal biometry, Doppler changes in four previously discussed fetal vessels and one cardiac valve, amniotic fluid, and clinical parameters. Stage I IUGR fetuses are considered to be mildly growth restricted and are managed as outpatients. Stage II patients are admitted for close, frequent observation. Stage III patients are those at high risk for fetal demise. This staging system is applicable across gestational ages [20••].

As part of the initial assessment they recommend that, in the presence of a fetus with an estimated weight below the 10th percentile, the amniotic fluid be assessed and the stage be determined. Stage I fetuses have an abnormal umbilical artery pulsatility index but no absence or reversal of end-diastolic flow. Additionally, stage I fetuses may have an abnormal MCA pulsatility index, but the MCA-PSV is normal [20••].

In stage II the fetus has absent or reversed umbilical artery end-diastolic flow, elevated MCA-PSV, abnormal ductus venosus pulsatility index (including absent atrial waveform), and pulsation of the umbilical vein. Stage III, which carries a 50–85% fetal mortality rate, includes ductus venosus reversed flow, umbilical vein reversed flow, tricuspid valve E/A ratio of at least 1, or tricuspid valve regurgitation.

The authors further subdivide the stages into categories 'a' and 'b' depending on whether the IUGR is 'idiopathic' (category a) or there is additional maternal or fetal pathology (category b). All of these factors, in addition to the consideration of gestation age, must be considered when weighing the risks of prematurity versus the risks of in-utero fetal deterioration [20••].

Turan *et al.* [4••] frame IUGR subtypes depending on the gestational age at initial diagnosis and speed of Doppler deterioration. Cases of IUGR diagnosed less than 32 weeks are typically more severe with a rapid progression over 2–3 weeks. In these cases, Doppler deterioration to A/REDV of the umbilical arteries, brain sparing on MCA, and abnormal ductus venosus and umbilical vein pulsations preceded delivery. The goal in severe IUGR is to administer steroids and surveillance fetuses intensively with Doppler and biophysical profile for signs of acidemia. Most of these fetuses are delivered around 30 weeks' gestation with an average latency of 27 days [4••].

In the progressive or intermediate subtype the average latency is 38 days, and delivery usually is not necessary until 34 weeks. Unlike severe forms, the intermediate IUGR fetuses more commonly deteriorate over 3–4 weeks. In these cases, A/REDV of umbilical arteries and brain sparing may occur, but ductus venosus and UV abnormalities are less common.

The late and milder cases of IUGR demonstrate minimal Doppler changes. These fetuses usually do not exhibit any signs of compromise until more than 34 weeks and have a 46-day latency. Ductus venosus waveforms are rarely abnormal, and brain sparing may be the only change to herald delivery as low biophysical scores are atypical [4••].

An integrated approach seems most appropriate when using any Doppler algorithm in management. This includes an assessment of amniotic fluid, NST, or biophysical profile [25]. Using this approach, Cosmi and colleagues [25] compared two groups of IUGR fetuses. The first group was followed until they exhibited complete deterioration of all Doppler parameters. The second group was followed until an abnormal BPP or cardiotocography was noted, no deterioration in Doppler. There were no differences in perinatal outcome. Even in cases of A/REDV of the ductus venosus, the BPP remained normal for up to 8 days. In cases of extreme prematurity, 8 days is highly beneficial [25]. The best management scheme for IUGR remains to be determined, but it is likely that, for optimal management, the IUGR fetus should be categorized as not all IUGR fetuses are alike.

Doppler applications beyond intrauterine growth restriction

Doppler ultrasound has been used in scenarios other than IUGR to monitor fetuses at risk for anemia secondary to red cell alloimmunization or parvovirus infection. Uterine artery Doppler and umbilical artery studies provide a tool to predict adverse perinatal outcomes in women with pregnancies at risk.

Middle cerebral artery Doppler in fetal anemia

MCA Doppler assessment is now the mainstay of surveillance in anemic fetuses. A PSV above 1.50 MoM in fetuses at risk for anemia has been reported to have a sensitivity of 100% [confidence interval (CI) 86–100%] in cases of red cell alloimmunization and other cases of fetal anemia [26,27]. MCA-PSV has been confirmed to be more reliable than an amniocentesis with measurement of delta OD 450 in several studies [28–30]. Adoption of MCA-PSV Doppler to assess fetuses at risk for anemia is one of the most marked shifts to noninvasive testing in obstetrics over the past decade. What remains unclear is the exact utilization and value of MCA-PSV assessment for subsequent transfusions in the anemic fetus.

Uterine artery Doppler

The uterine artery is the most commonly assessed vessel as it is used to predict adverse pregnancy outcomes in women at risk. In normal pregnancies, a significant decrease in the S/D ratio or resistance index values is expected with advancing gestation until 24–26 weeks. Twenty-two to 24 weeks appears to be the gestational age at which the sensitivity of identifying patients with preeclampsia or IUGR is highest. The negative predictive value is also high at this gestational age. A decrease in resistance over time represents appropriate invasion of the trophoblast leading to spiral artery remodeling and a low resistance system in which to exchange maternal and fetal oxygen, nutrients, metabolites, and wastes. Absence of this transition from high to low impedance is associated with a higher incidence of hypertensive disease, abruption, intrauterine fetal demise (IUFD), preterm birth, and IUGR [31••,32••].

Abnormal uterine artery Doppler has been associated with prematurity, IUGR, preeclampsia, nonreassuring fetal heart tracing, and cesarean delivery. Murakoshi *et al.* [33] proposed a scoring system to predict the chance of adverse outcomes using uterine artery Dopplers. This score awarded 1 point for a notch and 1 point for a low end-diastolic flow in each waveform, bilaterally. In example, a score of 4 would indicate bilaterally high S/D ratios with bilateral notches. Those with a score of 4 had an 83% rate of adverse perinatal outcomes, 48% with a score of 3, 31% for a score of 2, and little increased risk for a score of less than 2 [33].

Women with abnormal serum analyte screening results such as elevated alpha feto protein (AFP), inhibin or human chorionic gonadotrophin (hCG), or decreased free estriol are candidates for uterine artery Doppler assessment. Dugoff *et al.* [34,35] assessed the adverse perinatal outcomes of preeclampsia, severe preeclampsia, IUGR, abruption, preterm premature rupture of membranes (PPROM), and fetal demise in the presence of abnormal hCG, AFP alone, and when paired with uterine artery Doppler. The combination of abnormal analyte in the presence of abnormal Doppler was associated with a markedly increased risk of preeclampsia, IUGR, placental abruption, and fetal demise [34,35].

Umbilical cord compression

Whereas umbilical cord abnormalities such as true-knot, cord stricture, velamentous cord insertion, or marginal cord insertion are commonly noted postpartum, there is limited literature regarding the associated ultrasonographic and Doppler findings *in utero*. Notching of the umbilical artery Doppler waveform is a reported finding in monoamniotic twin surveillance as well as in cases of umbilical artery compression due to structure or cord narrowing [36–38].

Abuhamad and co-authors investigated the prevalence and significance of umbilical artery waveform notching in a prospective study. Twenty-nine cases of umbilical artery waveform notching were identified during the study period. The authors found no difference in gestational age at delivery, birthweight, or artery pH between cases and controls. There was a trend toward an increased risk of meconium and cesarean delivery. Additionally, there was a significant finding of an increased risk of cesarean delivery for nonreassuring fetal heart rate tracings in the study group.

Seventy-two percent of cases versus 14% of controls had associated umbilical cord abnormalities on postpartum examination. This led the investigators to surmise that the presence of an umbilical artery Doppler waveform notch should prompt targeted ultrasound to look for cord or placental abnormalities. However, at this point, umbilical artery Doppler is not part of routine obstetric ultrasound and further investigation is needed before this should become standard of care [39].

Conclusion

Sequential studies of IUGR Doppler waveforms from different vascular areas can be used to assess the overall wellbeing of the fetus at risk for acidosis, death, or cardiac failure. Nonetheless, uncertainties concerning the relationship between Doppler changes and their metabolic equivalent remain with the exception being the triumph of MCA-PSV in cases of fetal anemia. Gestational age, Doppler waveforms, antenatal testing, and maternal status should all be taken into consideration to guide optimal timing of delivery to minimize extreme prematurity but also to prevent intrauterine injury, in the case of the IUGR fetus. Studies are ongoing to determine the optimal timing of the severely growth restricted fetus remote from term.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 197–198).

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