

Doppler US in the Evaluation of Fetal Growth and Perinatal Health¹

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Abbreviations: ACOG = American Congress of Obstetricians and Gynecologists, CPR = cerebroplacental ratio, EDD = estimated due date, EDV = end-diastolic velocity, EFW = estimated fetal weight, LMP = last menstrual period, MCA = middle cerebral artery, MoM = multiple of the median, PI = pulsatility index, PORTO = Prospective Observational Trial to Optimize Pediatric Health, PSV = peak systolic velocity, SMFM = Society of Maternal-Fetal Medicine

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Diagnose fetal growth restriction and understand the limitations of this diagnosis.
- Discuss the current obstetric literature regarding the use of Doppler velocimetry surveillance in suspected fetal growth restriction.
- Describe the techniques used to acquire Doppler waveforms of the umbilical artery, MCA, and ductus venosus.

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Fetal growth restriction is commonly defined as an estimated fetal weight (EFW) that is below the 10th percentile for gestational age. It is associated with an increased risk of intrauterine demise, neonatal morbidity, and neonatal death; therefore, antenatal detection and surveillance with the optimization of delivery timing are necessary to improve pregnancy outcomes. If the estimated due date has been verified and the EFW is below the 10th percentile for gestational age, the underlying cause should be investigated, since the clinical management, outcome, and counseling options are largely dependent on the cause of the growth restriction. Serial ultrasonography (US) for the evaluation of fetal growth and umbilical artery Doppler velocimetry are used to guide pregnancy management decisions. This article describes the accurate US detection and surveillance of fetal growth restriction, discusses the current obstetric and radiology literature regarding the use of Doppler velocimetry in the setting of fetal growth restriction, and describes the techniques for performing umbilical artery Doppler velocimetry. Although various Doppler techniques have been described in the setting of fetal growth restriction, only umbilical artery Doppler assessment is recommended to identify fetuses most at risk for poor outcome and to guide the timing of delivery. The use of other Doppler waveforms in this setting remains investigational.

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Introduction

Fetal growth restriction, also known as intrauterine growth restriction, is a sonographic diagnosis most commonly used to describe a fetus with an estimated fetal weight (EFW) that is below the 10th percentile for gestational age. This definition is recommended by the American Congress of Obstetricians and Gynecologists (ACOG); however, various definitions exist globally and include EFW cutoff values below the fifth and third percentiles.

The use of a lower threshold for defining pathologic growth restriction is supported by the findings of the Prospective Observational Trial to Optimize Pediatric Health (PORTO), a trial that included 1116 pregnant women with nonanomalous fetuses with an EFW that was less than the 10th percentile. In this national prospective observational multicenter study, only 2% of fetuses in the third to 10th percentile experienced adverse perinatal outcomes. Of those in the third percentile, 6.2% had adverse outcomes, which included composite outcomes of intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and death.

TEACHING POINTS

- The definition recommended by the ACOG indicates that 10% of infants in any population will have a birth weight at or below the 10th percentile. This definition is problematic in that it includes normally grown fetuses at the lower end of the growth spectrum, as well as those with pathologic conditions in which the fetuses fail to achieve their inherent growth potential.
- Once an embryo is visible, the accuracy of gestational age estimation decreases with advancing gestational age; therefore, the EDD should be determined and documented as early as possible.
- Umbilical artery Doppler velocimetry has been extensively studied in the setting of fetal growth restriction and is a valuable tool for predicting perinatal outcomes.
- The SMFM recommends initiating an umbilical artery Doppler US assessment when growth restriction is suspected and the fetus is considered viable.
- The use of other Doppler waveforms (MCA, cerebroplacental ratio, and ductus venosus) in the setting of fetal growth restriction remains investigational.

There were four stillbirths and four neonatal deaths in this cohort. All eight perinatal deaths occurred in the group with an EFW below the third percentile (2). The Royal College of Obstetricians and Gynaecologists also considers that an abdominal circumference below the 10th percentile alone meets the criteria for growth restriction (3).

The definition recommended by the ACOG indicates that 10% of infants in any population will have a birth weight at or below the 10th percentile. This definition is problematic in that it includes normally grown fetuses at the lower end of the growth spectrum, as well as those with pathologic conditions in which the fetuses fail to achieve their inherent growth potential. This definition also fails to identify larger fetuses that have not achieved their growth potential. Whether this standard should be based on birth weights across gestation, on US EFWs across gestation, or on a customized standard remains controversial (4).

Fetal growth restriction is associated with increased risks of intrauterine demise, neonatal morbidity, and neonatal death, with the risks rising with the severity of the restriction (5). The perinatal mortality rates for fetuses and neonates weighing less than the 10th percentile but between 1500 and 2500 g were five to 30 times greater than those of newborns weighing between the 10th and 90th percentiles. For those weighing less than 1500 g, the rates were 70–100 times greater (6).

Additionally, epidemiologic studies have shown an association between fetal growth restriction and long-term health outcomes, including the development of cognitive delay in childhood (7) and of diseases in adulthood, such as obesity, type 2 diabetes mellitus, and coro-

nary heart disease, as well as an increased risk of stroke (8,9). Antenatal detection and surveillance with delivery timing optimization are necessary to improve pregnancy outcomes.

The purpose of this review is to describe how to diagnose fetal growth restriction, review the current obstetric and radiology literature regarding the use of Doppler velocimetry surveillance in suspected fetal growth restriction, and discuss the techniques used to acquire such images.

Determining Fetal Growth Restriction

Fetal weight is estimated by obtaining four standard US measurements: biparietal diameter, head circumference, abdominal circumference, and femur length (10). Contemporary US machines convert these four fetal biometric measurements to an EFW using published formulas and nomograms (11). The published formulas for calculating an EFW show a good correlation with actual birth weight; however, the variability of the estimate can be up to 20% (12).

One of the most commonly used models for calculating EFW was published by Hadlock et al (13). This model was developed using a relatively homogeneous study population of predominately middle-class white patients and may not represent normal growth patterns in different populations. The International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) is a multicenter multiethnic population-based project involving health institutions from eight geographically diverse countries (Brazil, China, India, Italy, Kenya, Oman, the United Kingdom, and the United States) to study fetal, newborn, and infant growth.

One component of this project was to use healthy cohorts with no risk factors for growth restriction to create prescriptive fetal-growth standards (14). These standards have been published and include five US measurements of fetal growth (head circumference, biparietal diameter, occipitofrontal diameter, abdominal circumference, and femur length), but they have yet to be adopted by major societies.

The accurate diagnosis of a growth-restricted fetus requires an accurately assigned estimated due date (EDD). The EDD is generally established at the first prenatal care visit. Traditionally, the first step in dating pregnancy is to determine the first day of the last menstrual period (LMP). Assuming a regular menstrual cycle of 28 days, with ovulation occurring on the 14th day, the EDD is 280 days after the first day of the LMP; however, this practice does not account for inaccurate patient recall of the LMP, irregularities in cycle length, early pregnancy bleeding, or variability in the timing of ovulation.

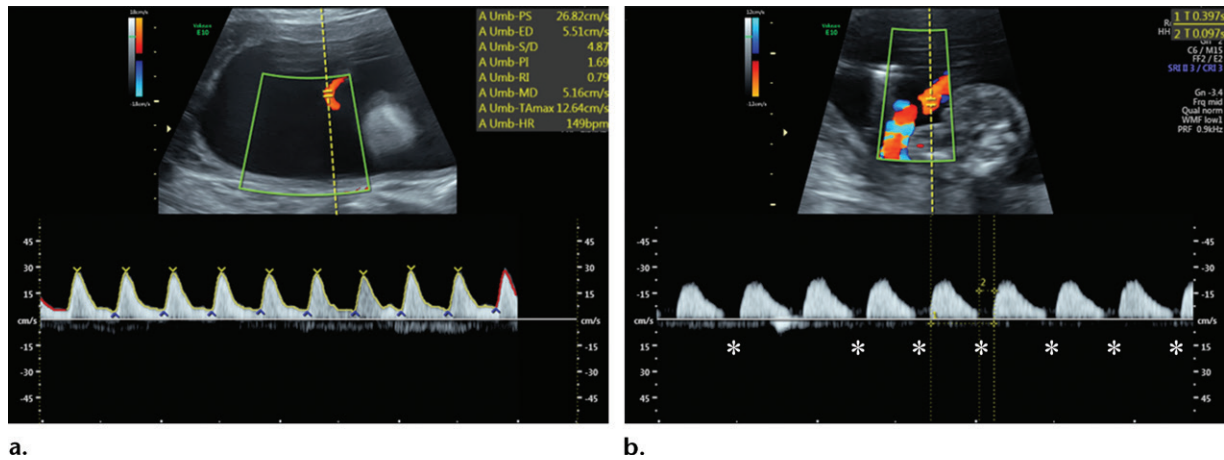


Figure 1. Duplex US images of the umbilical artery in a second-trimester fetus. **(a)** Color Doppler US image at the free loop of the umbilical cord shows a normal spectral waveform with continuous flow throughout the cardiac cycle. **(b)** Color Doppler US image just distal to the abdominal insertion of the umbilical cord shows an abnormal spectral waveform with absent end-diastolic flow (*).

For these patients, the ACOG recommends that US for gestational age assessment be performed at the first prenatal visit (12). For patients with uncertain or unreliable menstrual dating, first-trimester US is the most accurate method for determining EDD. Once an embryo is visible, the accuracy of gestational age estimation decreases with advancing gestational age; therefore, the EDD should be determined and documented as early as possible.

The measurement of the crown-rump length has an accuracy of ± 5 –7 days, up to and including 13 weeks 6 days gestation (15). A consensus opinion issued by the ACOG, American Institute of Ultrasound in Medicine, and Society for Maternal-Fetal Medicine (SMFM) recommends that if US dating before 9 weeks 0 days differs by more than 5 days from LMP dating, the EDD should be changed to correspond with the US dating (15).

The consensus opinion also recommends that if US dating between 9 weeks 0 days and 13 weeks 6 days differs by more than 7 days from LMP dating, the EDD should be changed to correspond with the US dating (15). If a patient presents for a first prenatal visit in the second or third trimester with uncertain or unreliable menstrual dating, EDD should be calculated using biometric parameters, including biparietal diameter, head circumference, abdominal circumference, and femur length.

If the US EFW is below the 10th percentile for gestational age, an accurate EDD should be verified. Once this has been verified, the underlying cause for the growth restriction should be determined, as the clinical management decisions, outcome, and counseling options are largely dependent on its cause.

The pathologic causes of fetal growth restriction can be categorized as maternal (eg, chronic

conditions associated with vascular disease), fetal (eg, chromosomal abnormalities), and placental (eg, abnormal placentation). Significant overlap of these entities exists, leading to a final common pathway of suboptimal uterine-placental perfusion and fetal nutrition. Careful review of the patient's history, physical examination, US, and fetal genetic or infectious laboratory testing in select cases can be diagnostic. A complete US evaluation should include the documentation of fetal movement and an assessment of amniotic fluid.

Oligohydramnios is a frequent finding in growth-restricted pregnancies caused by placental insufficiency and can be screened by measuring the amniotic fluid index or the maximum vertical pocket (16). Growth-restricted fetuses have a relatively high incidence of structural and genetic abnormalities; therefore, an anatomic survey is recommended if it has not been performed previously (17).

Review of Fetal Doppler Assessment

Once fetal growth restriction has been diagnosed, serial US for the evaluation of fetal growth and Doppler velocimetry are used to guide pregnancy management decisions, including the timing of delivery (17–19). Umbilical artery Doppler velocimetry has been extensively studied in the setting of fetal growth restriction and is a valuable tool for predicting perinatal outcomes (20). The temporal sequence of Doppler-measured flow abnormalities in the arterial and venous circulations of growth-restricted fetuses has been documented in the literature (21).

A fetus with severe growth restriction first demonstrates changes in the umbilical artery as decreased end-diastolic flow (Fig 1b) and then in the middle cerebral artery (MCA) as increased end-diastolic flow. This is followed by alterations

in the venous circulation, including the ductus venosus (decreased forward flow during atrial systole) and the umbilical vein (pulsatile flow). Doppler US of the ductus venosus and MCA provides information about the hemodynamic status of a growth-restricted fetus, but the clinical utility of the interrogation of these vessels has not yet been established (17).

Umbilical Artery Doppler US

Umbilical artery Doppler velocimetry assesses the resistance of blood perfusion in the fetoplacental unit and is the primary surveillance tool for fetuses with growth restriction. Maternal or placental conditions that obliterate small muscular arteries in the placental villi (eg, hypertension, diabetes, thrombophilia, and confined placental mosaicism) result in a progressive decrease in end-diastolic flow in the umbilical artery waveform until it is absent and then reversed (Fig 1) (19).

PORTO showed that the strongest and most substantial association with adverse perinatal outcomes in growth-restricted fetuses was found when an abnormal umbilical artery Doppler velocimetry was present, defined as a pulsatility index (PI) greater than the 95th percentile or as absent or reversed end-diastolic flow (2). Conversely, adverse perinatal outcomes are uncommon in growth-restricted fetuses with normal results at umbilical artery Doppler velocimetry.

A secondary analysis of the PORTO study showed that growth-restricted fetuses with normal umbilical artery Doppler US images had lower perinatal mortality than those with abnormal Doppler US images (0.3% vs 1.4%; $P = .01$) and a lower rate of overall adverse outcomes, defined as a composite of intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, or death (1.3% vs 11.5%; $P < .0001$) (22).

Multiple randomized trials have shown that the surveillance of growth-restricted fetuses with umbilical artery Doppler US can reduce perinatal death and avoid obstetric interventions. A Cochrane Database analysis reviewed 18 randomized trials comparing outcomes in high-risk pregnancies with or without the use of Doppler US. When Doppler US was used, there was an observed reduction in perinatal mortality of 29% (relative risk [RR] = 0.71; 95% confidence interval [CI] = 0.52–0.98; 1.2% vs 1.7%; number needed to treat = 203), as well as a reduction in labor inductions (RR = 0.89, 95% CI = 0.80–0.99) and cesarean deliveries (RR = 0.90, 95% CI = 0.84–0.97) (23).

The SMFM recommends initiating an umbilical artery Doppler US assessment when

growth restriction is suspected and the fetus is considered viable (19). Doppler waveforms of the umbilical artery can be obtained from any segment along the umbilical cord. However, it is important to consider that waveforms obtained near the placental end reflect downstream resistance with higher end-diastolic velocity (EDV) than waveforms obtained near the abdominal cord insertion. The higher EDV near the placental end results in a lower systolic-to-diastolic ratio, defined as peak systolic velocity (PSV)/EDV, and a lower resistive index value, defined as $PSV - EDV/PSV$.

Although it is not a universally accepted standard, the SMFM recommends interrogating the umbilical artery at the abdominal cord insertion to optimize reproducibility, presumably across examiners and/or over serial examinations of the same patient. Alternatively, the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommends taking Doppler US measurements at the free loop of the umbilical cord for simplicity and consistency (24). An exception to this would be in a case of multiple pregnancies, for which the ISUOG recommends Doppler interrogation at the abdominal cord insertion, given the potential difficulty in assigning a cord loop to a specific fetus.

Regardless of the location chosen, consistency in the interrogation site when obtaining serial US umbilical artery measurements is key to assessing changes in the status of a specific fetus. The ISUOG also highlights the importance of using appropriate reference ranges according to the site of interrogation (24). The systolic-to-diastolic ratio and PI should be obtained in the absence of fetal breathing (19), which is generally visualized as episodic and irregular between episodes of apnea. If abnormal waveforms are obtained with the patient in the supine position, they can be repeated with the patient in the lateral position to ensure that maternal positioning is not responsible for the abnormality.

MCA Doppler US

The fetal brain in normal pregnancies has high-resistance circulation with continuous forward flow that is present throughout the cardiac cycle. When fetal hypoxemia is present in growth restriction, a phenomenon of blood flow redistribution occurs, known as the *brain-sparing reflex*, to compensate for the decrease in available oxygen. Blood is preferentially redistributed to the brain, heart, and adrenal glands at the expense of the peripheral circulation. The MCA represents a major branch of the circle of Willis and is easily accessible for Doppler US interrogation. MCA waveforms can be obtained to measure the PSV,

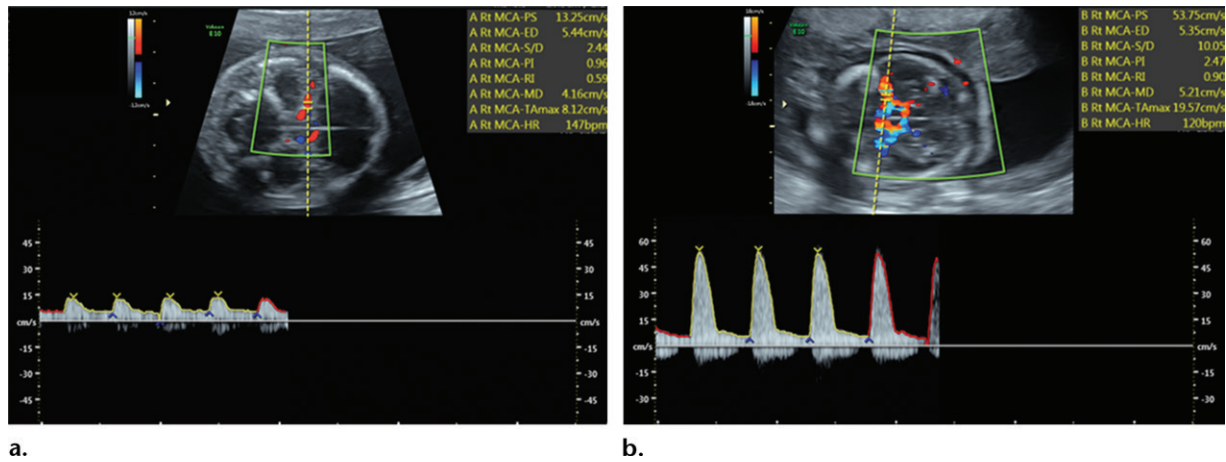


Figure 2. Pulsed duplex US images of the MCA at an axial section of the fetal brain performed for the evaluation of fetal anemia. **(a)** Pulsed color Doppler US image of a fetus at 20 weeks 2 days gestation shows a normal spectral waveform. The multiple of the median (MoM) was 0.51. **(b)** Pulsed color Doppler US image of a fetus at 21 weeks 6 days gestation shows an abnormal spectral waveform with an elevated PSV. The MoM was 1.93.

Expected MCA PSV as a Function of Gestational Age				
Gestational Age (wk)	MoM (cm/sec)			
	1.00 (median)	1.29	1.50	1.55
18	23.2	29.9	34.8	36.0
20	25.5	32.8	38.2	39.5
22	27.9	36.0	41.9	43.3
24	30.7	39.5	46.0	47.5
26	33.6	43.3	50.4	52.1
28	36.9	47.6	55.4	57.2
30	40.5	52.2	60.7	62.8
32	44.4	57.3	66.6	68.9
34	48.7	62.9	73.1	75.6
36	53.5	69.0	80.2	82.9
38	58.7	75.7	88.0	91.0
40	64.4	83.0	96.6	99.8

Note.—Reprinted, with permission, from reference 26.

EDV, and PI. The brain-sparing reflex is characterized by increased EDV in the MCA, which is reflected as a low PI.

The MCA can be identified at color or power Doppler US. An axial image of the fetal head is obtained at the level of the sphenoid bone, and the transducer is angled until the circle of Willis is visualized. A 2-mm pulsed wave Doppler gate is placed at the proximal third of the MCA, while the angle of insonation is kept between the ultrasound beam and the vessel, as close to 0° as possible (25,26).

Pulsed Doppler US parameters are generated from three or more consecutive waveforms. The highest point of the waveform is considered the PSV in centimeters per second (Fig 2). In clinical practice, the MCA PSV is commonly used as a noninvasive method for detecting fetal anemia.

The MCA PSV is converted to a multiple of the median (MoM) by the previously described equation (26). An elevated MCA PSV greater than 1.5 MoM is used to time intrauterine transfusion in pregnancies at risk for fetal anemia. The expected MCA PSV as a function of gestational age and the associated MoM (Table) is commonly calculated using online resources, such as those available at the website <http://www.perinatology.com> (25,27).

The MCA PSV has also been studied in the setting of fetal growth restriction. Limited studies have shown that the PSV is a better predictor of perinatal mortality in fetal growth restriction than the PI (28), but more studies are needed to confirm this finding. Other studies have tried to determine the value of MCA Doppler US in predicting the risk of cesarean delivery for

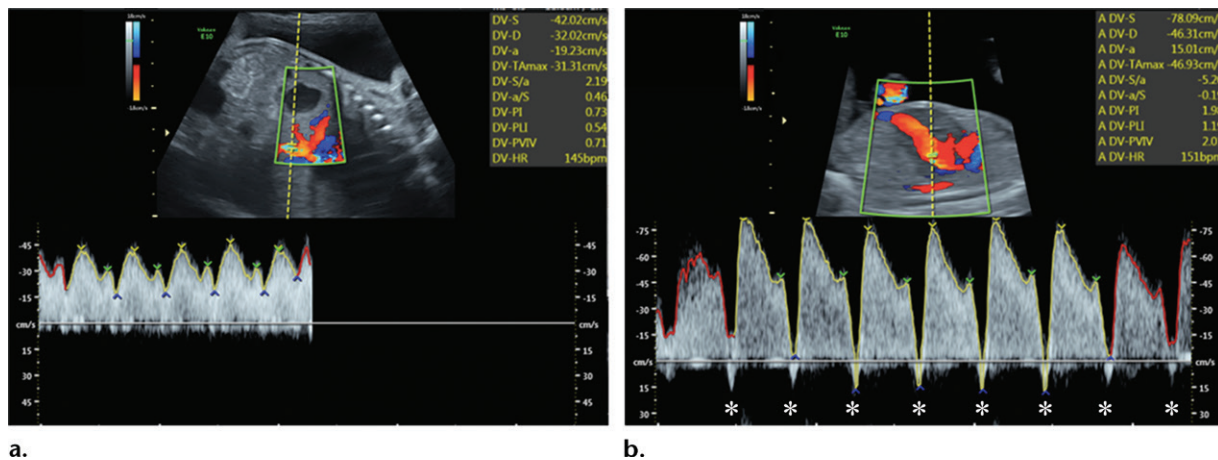


Figure 3. Duplex US images of the ductus venosus. (a) Oblique transverse color Doppler US image through the upper abdomen of a fetus at 30 weeks 2 days gestation shows a normal spectral waveform at the ductus venosus. Forward flow is seen throughout the cardiac cycle. (b) Midsagittal longitudinal Doppler US image of the trunk of a fetus at 21 weeks 4 days gestation shows an abnormal spectral waveform with a reversed A wave (*).

nonreassuring fetal status and the risk of neonatal acidosis in growth-restricted fetuses with normal umbilical artery Doppler US.

In this subset of fetuses, MCA vasodilatation was associated with the highest risk of cesarean delivery (67.7% vs 32.4%; $P < .001$) and cesarean delivery for nonreassuring fetal status (58.1% vs 24%; $P < .001$). MCA vasodilatation was associated with an increased risk of neonatal acidosis (odds ratio = 9.0) (29).

Despite these associations, MCA Doppler US interrogation of growth-restricted fetuses has not been evaluated in randomized trials, and no specific interventions are known to improve outcomes based on abnormal findings. At this time, there is not enough evidence that MCA Doppler US alone is useful for informing decisions about the timing of delivery in fetal growth restriction (19).

Cerebroplacental Ratio

The cerebroplacental ratio (CPR) has been proposed as a predictor of adverse pregnancy outcomes and has been studied in the setting of fetal growth restriction (30). It is calculated by dividing the MCA PI by the umbilical artery PI, and it is used as an assessment of fetal brain sparing. The CPR represents the interaction of alterations in blood flow to the brain caused by increased diastolic flow due to hypoxia-induced cerebrovascular dilatation and increased placental resistance, resulting in decreased diastolic flow of the umbilical artery. A fetus is considered to have fetal brain sparing when this ratio is less than the fifth percentile for gestational age (31).

Fetuses with growth restriction and an abnormal CPR, born at term, have been shown to be at higher risk for deficits in cognitive functioning and academic achievement at 6–8 years of age

than those with a normal CPR (32). A recent systematic review of 21 studies found that regardless of birth weight, an abnormal CPR detected at term is associated with cesarean delivery for intrapartum fetal compromise, meconium-stained amniotic fluid, low Apgar scores (<7 at 1 and 5 minutes), neonatal acidosis, and neonatal intensive care unit admission (33).

Another study of the CPR at term showed that an abnormal CPR was a marker of impaired fetal growth velocity and the need for operative delivery for fetal compromise (34). Although not a universally adopted method, some have argued that CPR be used in fetuses undergoing third-trimester US or antepartum testing. More studies are needed to confirm its use in these settings.

Ductus Venosus Doppler US

Doppler waveforms of the ductus venosus represent the physiologic status of the right ventricle. Abnormalities in the fetal venous circulation reflect central cardiac failure. The normal Doppler waveform is characteristically biphasic. The first peak is the highest and corresponds to ventricular systole (S wave). The second peak is the second highest and corresponds to early ventricular diastole (D wave), which is followed by a nadir in late diastole that corresponds to the atrial contraction (A wave) (Fig 3a).

In normal fetuses, flow in the venous circulation is forward and uniform (toward the fetal heart) throughout the cardiac cycle (Fig 3a). Decreased, absent, or reversed flow in the A wave may represent increased end-diastolic pressure from increased right ventricular afterload (Fig 3b). An absent or reversed ductus venosus A wave is a late finding and a sign of impending acidemia or death, usually within 7 days (35).

Doppler US has been used by some perinatologists to avoid preterm deliveries in fetuses with early-onset growth restriction and absent or reversed end-diastolic arterial flow in the umbilical artery with normal antepartum fetal testing. The Trial of Umbilical and Fetal Flow in Europe (TRUFFLE) assessed whether changes in the fetal ductus venosus Doppler waveform in growth-restricted fetuses with a high umbilical artery Doppler PI (>95th percentile) could be used to guide timing of delivery. They compared this to the conventional approach using fetal cardiocography (electronic fetal heart tracings).

No immediate neonatal benefit was found from delaying delivery until the ductus venosus monitoring showed substantial abnormalities (absent or reversed flow), and there was only a possible marginal benefit in neurodevelopment at 2 years of age (survival without neurodevelopmental impairment, 95% vs 85%; $P = .005$) (36). However, this came at the cost of a small, nonsignificant increase in unexpected fetal demise and infant mortality.

A post hoc sensitivity analysis was performed on the TRUFFLE data to further explore this apparent nonsignificant increase in perinatal death (37). This secondary analysis focused on women who delivered before 32 completed weeks (317 of the original 503 patients), after which the study protocol was no longer followed. This post hoc analysis found no difference in the proportion of infants surviving without neuroimpairment (83% vs 77%, $P = .21$) when comparing the timing of delivery based on an abnormal ductus venosus Doppler US or abnormal cardiocography. However, when analyzing only the surviving infants, the prevalence of neurologic impairment in the group being monitored with ductus venosus Doppler US and cardiocography was half that of the group being monitored with cardiocography alone (7% vs 15%; RR = 0.50 [0.25–1.00]; $P = .049$).

It further found that perinatal mortality (neonatal and fetal death) was similar in the group being monitored with ductus venosus Doppler US and cardiocography and the group being monitored with standard cardiocography alone (10% vs 7%). However, all seven fetal deaths occurred in the group being monitored with ductus venosus Doppler US and cardiocography.

After an in-depth review of the demographics, inclusion criteria, obstetric characteristics, and most recent monitoring parameter, the authors concluded that the uneven distribution of fetal deaths in the group being monitored with ductus venosus Doppler US and cardiocography was likely due to chance. If these seven pregnancies had been allocated to the group being monitored with cardiocography alone, six of the seven

would similarly not have been delivered, as their last cardiocography results were above the cardiocography group cutoff to trigger delivery.

The authors' final conclusions were that, before 32 weeks, delaying delivery until abnormalities are seen at ductus venosus Doppler US or cardiocography is "probably safe and possibly benefits long-term outcome" in survivors (37).

There are no randomized trials involving the use of ductus venosus Doppler US in the management of fetal growth restriction. Further research on the use of ductus venosus Doppler waveforms in this setting is needed.

Conclusion

Although an EFW below the 10th percentile for gestational age is the most commonly used definition of fetal growth restriction, it is not without controversy. This definition includes normally grown fetuses at the lower end of the growth spectrum, as well as those with pathologic conditions in which the fetus fails to achieve its inherent growth potential. US surveillance with umbilical artery Doppler US is recommended, when the fetus is considered viable, to identify fetuses most at risk for poor outcome and to guide timing of delivery. The use of other Doppler waveforms (MCA, CPR, and ductus venosus) in the setting of fetal growth restriction remains investigational.

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