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Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction

(Replaces Clinical Guideline Number 3, April 2012)

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The American Institute of Ultrasound in Medicine (AIUM) supports this document review of the subject matter and believes it contributes to our understanding of the topic.

Fetal growth restriction can result from a variety of maternal, fetal, and placental conditions. It occurs in up to 10% of pregnancies and is a leading cause of infant morbidity and mortality. This complex obstetrical problem has disparate published diagnostic criteria, relatively low detection rates, and limited preventative and treatment options. The purpose of this Consult is to outline an evidence-based, standardized approach for the prenatal diagnosis and management of fetal growth restriction. The recommendations of the Society for Maternal-Fetal Medicine are as follows: (1) we recommend that fetal growth restriction be defined as an ultrasonographic estimated fetal weight or abdominal circumference below the 10th percentile for gestational age (GRADE 1B); (2) we recommend the use of population-based fetal growth references (such as Hadlock) in determining fetal weight percentiles (GRADE 1B); (3) we recommend against the use of low-molecular-weight heparin for the sole indication of prevention of recurrent fetal growth restriction (GRADE 1B); (4) we recommend against the use of sildenafil or activity restriction for in utero treatment of fetal growth restriction (GRADE 1B); (5) we recommend that a detailed obstetrical ultrasound examination (current procedural terminology code 76811) be performed with early-onset fetal growth restriction (<32 weeks of gestation) (GRADE 1B); (6) we recommend that women be offered fetal diagnostic testing, including chromosomal microarray analysis, when fetal growth restriction is detected and a fetal malformation, polyhydramnios, or both are also present regardless of gestational age (GRADE 1B); (7) we recommend that pregnant women be offered prenatal diagnostic testing with chromosomal microarray analysis when unexplained isolated fetal growth restriction is diagnosed at <32 weeks of gestation (GRADE 1C); (8) we recommend against screening for toxoplasmosis, rubella, or herpes in pregnancies with fetal growth restriction in the absence of other risk factors and recommend polymerase chain reaction for cytomegalovirus in women with unexplained fetal growth restriction who elect diagnostic testing with amniocentesis (GRADE 1C); (9) we recommend that once fetal growth restriction is diagnosed, serial umbilical artery Doppler assessment should be performed to assess for deterioration (GRADE 1C); (10) with decreased end-diastolic velocity (ie, flow ratios greater than the 95th percentile) or in pregnancies with severe fetal growth restriction (estimated fetal weight less than the third percentile), we suggest weekly umbilical artery Doppler evaluation (GRADE 2C); (11) we recommend Doppler assessment up to 2–3 times per week when umbilical artery absent end-diastolic velocity is detected (GRADE 1C); (12) in the setting of reversed end-diastolic velocity, we suggest hospitalization, administration of antenatal corticosteroids, heightened surveillance with cardiotocography at least 1–2 times per day, and consideration of delivery depending on the entire clinical picture and results of additional evaluation of fetal well-being (GRADE 2C); (13) we suggest that Doppler assessment of the ductus venosus, middle cerebral artery, or uterine artery not be used for routine clinical management of early- or late-onset fetal growth restriction (GRADE 2B); (14) we suggest weekly cardiotocography testing after viability for fetal growth restriction without absent/reversed end-diastolic velocity and that the frequency be increased when fetal growth restriction is complicated by absent/reversed end-diastolic velocity or other comorbidities or risk factors (GRADE 2C); (15) we recommend delivery at 37 weeks of gestation in pregnancies with fetal growth restriction and an umbilical artery Doppler waveform with decreased diastolic flow but without absent/reversed end-diastolic velocity or with severe fetal growth restriction with estimated fetal weight less than the third percentile (GRADE 1B); (16) we recommend delivery at 33–34 weeks of gestation for pregnancies with fetal growth restriction and absent end-diastolic velocity (GRADE 1B); (17) we recommend delivery at 30–32 weeks of gestation for pregnancies with fetal growth restriction and reversed end-diastolic velocity (GRADE 1B); (18) we suggest delivery at 38–39 weeks of gestation with fetal growth restriction when the estimated fetal weight is between the 3rd and 10th percentile and the umbilical artery Doppler is normal (GRADE 2C); (19) we suggest that for pregnancies with fetal growth restriction complicated by absent/reversed end-diastolic velocity, cesarean delivery should be considered based on the entire clinical scenario (GRADE 2C); (20) we recommend the use of antenatal corticosteroids if delivery is anticipated before 33 6/7 weeks of gestation or for pregnancies between 34 0/7 and 36 6/7 weeks of gestation in women without contraindications who are at risk of preterm delivery within 7 days and who have not received a prior course of antenatal corticosteroids (GRADE 1A); and (21) we recommend intrapartum magnesium sulfate for fetal and neonatal neuroprotection for women with pregnancies that are <32 weeks of gestation (GRADE 1A).

Key words: cardiotocography, Doppler, fetal growth restriction, fetal weight, umbilical artery

Introduction

Fetal growth restriction (FGR) can result from a variety of maternal, fetal, and placental conditions.[1] Although the primary underlying mechanisms for FGR are varied, they often share the same final common pathway of suboptimal fetal nutrition and uteroplacental perfusion.[1,2] Chromosomal disorders and congenital malformations are responsible for approximately 20% of FGR cases.[2,3] Suboptimal perfusion of the maternal placental circulation is the most common cause of FGR and accounts for 25–30% of all cases.[2,3]

FGR occurs in up to 10% of pregnancies and is a leading cause of infant morbidity and mortality.[1,4,5] In fetuses at all gestational ages with weights below the 10th percentile, the stillbirth rate is approximately 1.5%, which is twice the rate in fetuses with normal growth. With fetal weights below the fifth percentile, the stillbirth rate can be as high as 2.5%.[6,7] Furthermore, infants with birthweights below the 10th percentile are more likely to have severe acidosis at birth, low 5-minute Apgar scores, and neonatal intensive care unit admissions.[8] Prematurity further compounds the risk of adverse outcomes in FGR.[9] Studies report a 2- to 5-fold increased rate of perinatal death among preterm FGR fetuses compared with term FGR fetuses.[9] Perinatal outcomes are largely dependent on the severity of FGR, with the worst outcomes noted in fetuses with estimated fetal weights (EFWs) at less than the third percentile or in association with fetal Doppler abnormalities.[5,10]

In addition to its significant perinatal impact, FGR also has an impact on long-term health outcomes. It has been associated with metabolic programming that increases the risk of future development of metabolic syndrome and consequent cardiovascular and endocrine diseases.[11,12] It also can contribute to cardiac remodeling, leading to cardiovascular dysfunction that can persist into childhood and adolescence.[13,14] In addition, studies have shown an association between FGR and long-term neurologic impairment,[15–20] with rates of cognitive and learning disabilities as high as 20%–40% by school age.[21]

FGR remains a complex obstetrical problem with disparate published diagnostic criteria, relatively low detection rates, and limited preventative and treatment options.[22–25] Antenatal care of FGR is often complicated by the presence of maternal disease, such as hypertension, and optimal management involves balancing maternal, fetal, and neonatal risks. The purpose of this document is to outline an evidence-based, standardized approach for the prenatal diagnosis and management of FGR.

Terminology and diagnostic criteria

FGR and small for gestational age (SGA) are terms sometimes used interchangeably in the literature and clinical practice. The term FGR has been used to describe a fetus with an EFW below the 10th percentile and SGA to describe a newborn whose birthweight is less than the 10th percentile for gestational age.[26] The use of the term intrauterine growth restriction (IUGR) should be abandoned in favor of FGR.

Fetuses with FGR are not always SGA at birth, and SGA neonates have often not been diagnosed as growth restricted on prenatal ultrasound.[27] Of fetuses diagnosed with FGR, approximately 18%–22% will be constitutionally small but healthy at birth with a normal outcome.[24] A significant challenge in the prenatal management of FGR is differentiating the constitutionally small fetus from one who is pathologically growth restricted and at risk for postnatal complications.

FGR is commonly defined as an ultrasonographic EFW below the 10th percentile for gestational age. A review of national guidelines for the diagnostic criteria for FGR from 6 countries (United States, United Kingdom, France, Ireland, Canada, and New Zealand) reveals a broad consensus on this definition of FGR.[24] However, there is significant variation in the diagnostic criteria used for FGR. Some diagnostic criteria are limited to fetal biometric measurements, whereas others incorporate abnormal Doppler findings.[28] Moreover, the biometric component of the FGR diagnostic criteria differs according to the choice of population vs customized reference growth standards, whether EFW is used alone or together with abdominal circumference (AC), and which cutoff is used to define abnormal growth.[24,29,30] For example, 3 of the 6 countries also include AC as a diagnostic criterion, with the United Kingdom and Canada using an AC cutoff of less than the 10th percentile and New Zealand using an AC cutoff of less than the 5th percentile.[24]

Evidence supports the use of AC as a diagnostic criterion for FGR. In a prospective study in 1000 low-risk pregnancies, an AC of less than the 10th percentile was found to have diagnostic accuracy similar to EFW less than the 10th percentile for the prediction of SGA.[31] In a meta-analysis published in 2017, an AC of less than the 10th percentile predicted SGA as well as ultrasonographic EFW less than the 10th percentile, with comparable sensitivity and specificity. Compared with other cutoffs, an AC of less than the fifth percentile has significantly lower sensitivity but higher specificity in predicting SGA.[32] Another systematic review and meta-analysis reported that AC and EFW performed similarly, and for a 10% fixed false-positive rate, AC had higher sensitivity.[33]

An alternative approach to the diagnosis of FGR includes the determination of fetal growth trajectory, generated from multiple ultrasound examinations, and the identification of the fetus that drops off its own growth trajectory. Theoretically, this approach takes into consideration the dynamic aspect of growth and the individualized growth potential of each fetus.[34] However, this approach requires multiple ultrasound examinations, and prospective studies fail to demonstrate the superiority of this approach in improving clinical outcomes.[35] **We recommend that FGR be defined as an**

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ultrasonographic EFW or AC below the 10th percentile for gestational age (GRADE 1B).

Ultrasonographic estimation of fetal weight

Accurate pregnancy dating is an important prerequisite for diagnosing FGR. Parameters for assigning gestational age by ultrasound have been recently updated.[36] Pregnancy dating is best established when first-trimester crown-rump length is used to either confirm menstrual dates or assign new dates.[36] Ultrasonographic fetal weight estimation is generated by the use of regression equations that combine biometric measurements of the fetal biparietal diameter, head circumference (HC), AC, and femur length; a multisociety task force has recently standardized criteria for these images obtained for fetal biometry.[37] The ultrasonographic EFW is then compared with a reference chart to generate a weight percentile.

The first ultrasonographic equation used to estimate fetal weight was published by Warsof et al in 1977, and since then, many others have been developed.[38] Considerable variation in accuracy was noted in a retrospective review of 26 formulas for ultrasonographic fetal weight estimation. For birthweights in the range of 1000−4500 g, formulas based on 3 or 4 fetal biometric indices were significantly more accurate in estimating fetal weights than formulas based on 1 or 2 indices.[39] In a review of the literature relating to methods and sources of inaccuracies in the estimation of fetal weight, the authors concluded that averaging of multiple measurements, improvements in image quality, uniform calibration of equipment, and regular audits may help to improve fetal weight estimation and reduce errors.[40]

Fetal growth nomograms generally represent either unadjusted population standards or customized standards that adjust for constitutional or physiological variations of fetal size based on sex and race.[35,41−44] The most widely used method for estimating fetal weight and calculating weight percentile in the United States is based on the Hadlock formula, which was generated from a study involving 392 pregnancies in predominantly white, middle-class women conducted at a single institution in Texas.[41] In some studies, the use of customized growth standards has been shown to improve the ability to distinguish growth-restricted fetuses from constitutionally small fetuses.[45−47]

Whether the use of customized growth standards translates to improved pregnancy outcomes was the subject of several recent studies: the INTERGROWTH-21st standard,[44] the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) standards,[48] and the World Health Organization (WHO) standard.[49,50] The INTERGROWTH-21st study included healthy pregnant women with no maternal or fetal risk factors from 8 countries and created a single universal standard for fetal growth without adjusting for ethnic variation.[44] The NICHD study, performed at 12 sites in the United States, developed racial/ethnic-specific standards of fetal growth.[48] Finally, the WHO study developed an overall growth standard based on data collected from 10 countries.[49,50]

Although both the NICHD and WHO studies identified racial/ethnic differences in fetal growth, evidence to date indicates that the use of these new formulas in clinical practice does not improve the detection and outcome of FGR.[51−53] In a preterm population in France, the INTERGROWTH-21st formula was associated with a higher mean percentage error and a higher underestimation of birthweight at >28 weeks of gestation when compared with Hadlock. The Hadlock formula classified more infants within 10% of actual birthweight and was more accurate than the INTERGROWTH-21st in the overall estimation of weight for fetuses delivered between 22 and 34 weeks of gestation.[53] The diagnostic accuracy for estimating fetal weight and the prediction of neonatal morbidity was compared using the NICHD standard and Hadlock in 1514 pregnant women with different ethnicities. The Hadlock formula better predicted SGA and composite neonatal morbidity at birth and had a lower ultrasound-to-birthweight percentile discrepancy than the NICHD growth standard. Fetuses classified as growth restricted by Hadlock, but not by the NICHD growth standard, had significantly higher composite morbidity than fetuses of normal growth.[51] In view of these findings, **we recommend the use of population-based fetal growth references (such as Hadlock) in determining fetal weight percentiles (GRADE 1B).**

Classification of fetal growth restriction

Timing of diagnosis

FGR has been categorized as early or late onset based on gestational age at prenatal ultrasound diagnosis, with early-onset FGR diagnosed before 32 weeks of gestation and late-onset FGR diagnosed at or after 32 weeks of gestation. In a cohort of 656 pregnancies with FGR, a gestational age of 32 weeks at diagnosis was identified as the optimal cutoff to maximize the differences in associated comorbidities and pregnancy outcomes between early- and late-onset FGR.[54] The clinical spectrum of early- and late-onset FGR also differs; early-onset FGR is typically more severe, tends to follow an established Doppler pattern of fetal deterioration, is more commonly associated with maternal hypertensive disorders of pregnancy, and shows more significant placental dysfunction than late-onset FGR.[23,28,54−56] Fetuses with genetic abnormalities can also present with early-onset FGR, commonly in association with fetal and amniotic fluid abnormalities.[3] Late-onset FGR represents approximately 70%−80% of FGR cases and is typically milder in presentation.[55,56] Unlike early-onset FGR, late-onset FGR is less likely to be associated with maternal hypertensive disorders and typically has less extensive placental histopathologic findings of underperfusion.[57−59] In early-onset FGR, the pattern of Doppler deterioration progresses from abnormalities in the umbilical arteries and the ductus venosus to abnormal biophysical parameters.[55,56] In contrast, cardiovascular adaptation of late-onset FGR is

typically limited to the cerebral circulation and is commonly associated with normal Doppler of the umbilical arteries.[57,60,61]

Severity of fetal growth restriction

Studies have reviewed various ultrasonographic parameters to better identify growth-restricted fetuses at increased risk for perinatal morbidity and mortality.[28] The presence of abnormal umbilical artery Doppler indices has been found to predict adverse perinatal outcomes.[62] An EFW below the third percentile has also been associated with an increased risk of adverse perinatal outcome irrespective of umbilical and middle cerebral artery Doppler indices.[10] In a large retrospective cohort of more than 3 million singleton pregnancies, the risk of stillbirth at birthweights of less than the 3rd percentile was increased approximately 3-fold over the 3rd to 5th percentile group at nearly all gestational ages, and there was an increased risk of 4-fold to 7-fold over the 5th to 10th percentile group.[63] These results are consistent with neonatal data showing a significantly increased risk of morbidity and mortality in infants born at term with birthweights below the third percentile.[64] Therefore, an EFW below the third percentile has been found to represent a more severe form of FGR.

Symmetric and asymmetric fetal growth restriction

FGR has been classified as symmetric or asymmetric based on the ratio between the head circumference and the abdominal circumference (HC/AC). In the past, such classification was thought to provide valuable information about the timing of pregnancy insult and the etiology and prognosis of FGR.[65] More recently, growth and developmental delay have been evaluated from birth to the age of 4 years and shown to be similar in symmetric and asymmetric growth-restricted preterm newborns.[66] Furthermore, HC/AC was not found to be an independent predictor of adverse pregnancy outcomes.[67]

Management of fetal growth restriction

General considerations

There are currently no preventative strategies or treatments for FGR that have been proven to be effective. There is no consistent evidence that nutritional and dietary supplements or bed rest prevents FGR or reduces the incidence of SGA births.[68–71] The use of prophylactic low-dose aspirin was shown to provide a modest risk reduction in FGR and SGA in 2 meta-analyses.[72,73] However, this finding was not confirmed in the Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial, which was primarily designed for preterm preeclampsia prevention.[74,75] Due to the conflicting evidence on the role of low-dose aspirin in the prevention of recurrent FGR in otherwise low-risk women, the American College of Obstetricians and Gynecologists recommends against the use of low-dose aspirin for the sole indication of FGR prevention.[76] Furthermore, the use of low-molecular-weight heparin has not been shown to reduce the risk of recurrent placenta-mediated pregnancy complications in at-risk women.[75,77,78] At present, there is no evidence that therapeutic interventions, including sildenafil to augment uteroplacental perfusion through vasodilation, improve placental perfusion and outcome in pregnancies with FGR.[75,79] **We recommend against the use of low-molecular-weight heparin for the sole indication of prevention of recurrent FGR (GRADE 1B). We also recommend against sildenafil or activity restriction for in utero treatment of FGR (GRADE 1B).**

Management of FGR is based on early diagnosis, optimal fetal surveillance, and timely delivery that reduces perinatal mortality and minimizes short- and long-term morbidity. In pregnancies with FGR, delivery decisions require balancing the risk of prematurity against that of stillbirth. The decision to deliver is typically guided by maternal factors, such as the presence of maternal hypertension, and by fetal comorbidities, such as the degree of growth restriction and the severity of abnormal fetal surveillance results. There is currently no consensus on the best approach to the management of FGR, despite a large body of literature on the subject. This lack of agreement is primarily due to the paucity of randomized trials and the heterogeneity of study populations.

Despite these limitations, accumulating evidence suggests a benefit to the use of umbilical artery Doppler in the surveillance of FGR. Furthermore, the presence of a standardized protocol for diagnosis and management appears to be associated with more favorable outcomes, as evidenced in the better-than-expected perinatal morbidity and mortality in the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE).[80] Results of this trial, which standardized the approach to care and criteria for delivery, are in contrast to those of the Growth Restriction Intervention Trial (GRIT),[81,82] which left management to the discretion of the managing providers. The single most important prognostic factor in preterm fetuses with growth restriction is the gestational age at delivery.[80,83] A large longitudinal cohort study on FGR showed an increase of 1%–2% in intact survival for every additional day spent in utero up until 32 weeks of gestation.[83] An algorithm for the diagnosis and management of FGR is provided in Figure 1.

Maternal hypertensive disease is common in early-onset FGR and plays an important role in pregnancy outcomes. In TRUFFLE, maternal hypertension was present in 50% of pregnancies during the study and 70% of pregnancies at the time of delivery. The presence of maternal hypertension was one of the most important independent determinants of poor outcomes.[16,80] Pregnant women with hypertension had a significantly shorter median interval from study enrollment to delivery, and newborns of mothers with hypertension were delivered at an earlier gestational age and had lower birthweights.[80] Women with early-onset FGR should be closely monitored for the development of hypertensive disorders of pregnancy.

Summary of recommendations

Number	Recommendations	Grade
1	We recommend that FGR be defined as an ultrasonographic EFW or AC below the 10th percentile for gestational age.	1B Strong recommendation, moderate-quality evidence
2	We recommend the use of population-based fetal growth references (such as Hadlock) in determining fetal weight percentiles.	1B Strong recommendation, moderate-quality evidence
3	We recommend against the use of low-molecular-weight heparin for the sole indication of prevention of recurrent FGR.	1B Strong recommendation, moderate-quality evidence
4	We recommend against the use of sildenafil or activity restriction for in utero treatment of FGR.	1B Strong recommendation, moderate-quality evidence
5	We recommend that a detailed obstetrical ultrasound examination (CPT code 76811) be performed with early-onset FGR (<32 weeks of gestation) because up to 20% of cases are associated with fetal or chromosomal abnormalities.	1B Strong recommendation, moderate-quality evidence
6	We recommend that women be offered fetal diagnostic testing, including CMA, when FGR is detected and a fetal malformation, polyhydramnios, or both are also present regardless of gestational age.	1B Strong recommendation, moderate-quality evidence
7	We recommend that pregnant women be offered prenatal diagnostic testing with CMA when unexplained isolated FGR is diagnosed at <32 weeks of gestation.	1C Strong recommendation, low-quality evidence
8	We recommend against screening for toxoplasmosis, rubella, or herpes in pregnancies with FGR in the absence of other risk factors and recommend PCR for CMV in women with unexplained FGR who elect diagnostic testing with amniocentesis.	1C Strong recommendation, low-quality evidence
9	We recommend that once FGR is diagnosed, serial umbilical artery Doppler assessment should be performed to assess for deterioration.	1C Strong recommendation, low-quality evidence
10	With decreased end-diastolic velocity (ie, flow ratios greater than the 95th percentile) or in pregnancies with severe FGR (EFW less than the 3rd percentile), we suggest weekly umbilical artery Doppler evaluation.	2C Weak recommendation, low-quality evidence
11	We recommend Doppler assessment up to 2–3 times per week when umbilical AEDV is detected because of the potential for deterioration and development of REDV.	1C Strong recommendation, low-quality evidence
12	In the setting of REDV, we suggest hospitalization, administration of antenatal corticosteroids, heightened surveillance with CTG at least 1–2 times per day, and consideration of delivery depending on the entire clinical picture and results of additional evaluation of fetal well-being.	2C Weak recommendation, low-quality evidence
13	We suggest that Doppler assessment of the ductus venosus, middle cerebral artery, or uterine artery not be used for routine clinical management of early- or late-onset FGR.	2B Weak recommendation, moderate-quality evidence
14	We suggest weekly CTG testing after viability for FGR without AEDV/REDV and that the frequency be increased when FGR is complicated by AEDV/REDV or other comorbidities or risk factors.	2C Weak recommendation, low-quality evidence
15	We recommend delivery at 37 weeks of gestation in pregnancies with FGR and an umbilical artery Doppler waveform with decreased diastolic flow but without AEDV/REDV or with severe FGR with EFW less than the third percentile.	1B Strong recommendation, moderate-quality evidence
16	We recommend delivery at 33–34 weeks of gestation for pregnancies with FGR and AEDV.	1B Strong recommendation, moderate-quality evidence
17	We recommend delivery at 30–32 weeks of gestation for pregnancies with FGR and REDV.	1B Strong recommendation, moderate-quality evidence
18	We suggest delivery at 38–39 weeks of gestation with FGR when the EFW is between the 3rd and 10th percentile and the umbilical artery Doppler is normal.	2C Weak recommendation, low-quality evidence

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Summary of recommendations *(continued)*

Number	Recommendations	Grade
19	We suggest that for pregnancies with FGR complicated by AEDV/REDV, cesarean delivery should be considered based on the entire clinical scenario.	2C Weak recommendation, low-quality evidence
20	We recommend the use of antenatal corticosteroids if delivery is anticipated before 33 6/7 weeks of gestation or for pregnancies between 34 0/7 and 36 6/7 weeks of gestation in women without contraindications who are at risk of preterm delivery within 7 days and who have not received a previous course of antenatal corticosteroids.	1A Strong recommendation, high-quality evidence
21	We recommend intrapartum magnesium sulfate for fetal and neonatal neuroprotection for women with pregnancies that are <32 weeks of gestation.	1A Strong recommendation, high-quality evidence

AC, abdominal circumference; *AEDV*, artery absent end-diastolic velocity; *CMA*, chromosomal microarray analysis; *CMV*, cytomegalovirus; *CPT*, current procedural terminology; *CTG*, cardiotocography; *EFW*, estimated fetal weight; *FGR*, fetal growth restriction; *PCR*, polymerase chain reaction; *REDV*, reversed end-diastolic velocity.

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Initial diagnosis

With the initial diagnosis of FGR and if not previously performed, **we recommend that a detailed obstetrical ultrasound examination (current procedural terminology code 76811) be performed with early-onset FGR because up to 20% of cases are associated with fetal or chromosomal abnormalities[2,3,84,85] (GRADE 1B).** The combination of FGR with a fetal malformation or polyhydramnios should prompt genetic counseling and consideration of prenatal diagnostic testing.[86] **We recommend that women be offered fetal diagnostic testing, including chromosomal microarray analysis (CMA), when FGR is detected and a fetal malformation, polyhydramnios, or both are also present regardless of gestational age (GRADE 1B).**

Although chromosome abnormalities are more frequent in pregnancies with structural anomalies and FGR, in a systematic review that included fetuses with no structural malformations, the mean rate of chromosomal abnormalities was 6.4%. Only a fraction of the studies included women in the third trimester with apparently isolated FGR, but no karyotype abnormalities were identified in those women. Due to substantial heterogeneity of the selected studies in the systemic review, meta-analytic methods, such as calculating the effect estimates, could not be applied.[87] More recent studies have evaluated the role of CMA in fetuses with early-onset growth restriction and no structural malformations; such studies have identified a 4%–10% incremental yield of CMA over karyotype.[88–90] **We recommend that pregnant women be offered prenatal diagnostic testing with CMA when unexplained isolated FGR is diagnosed at <32 weeks of gestation (GRADE 1C).**

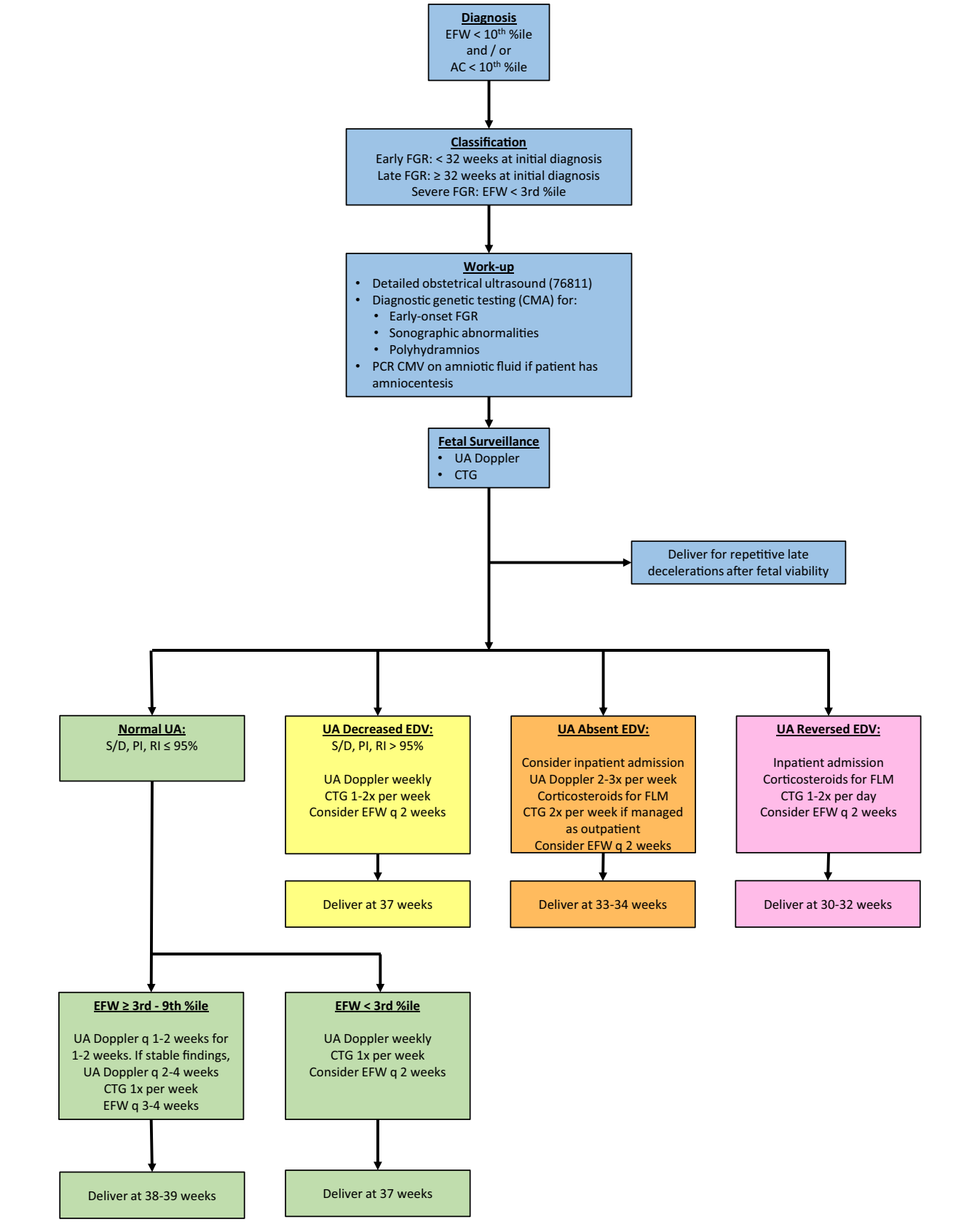
The association of maternal infections with FGR was recently evaluated in a study that included 319 pregnancies. No cases of maternal or congenital infection with toxoplasma, rubella, or herpes were found, whereas 6 (1.8%) fetuses were diagnosed as having congenital cytomegalovirus (CMV). Two (0.6%) of the fetuses with congenital CMV had no ultrasonographic findings other than FGR.[91] In another prospective cohort study of 48 pregnancies with FGR, 1 newborn (2.1%) was diagnosed with congenital CMV.[92] **We recommend against screening for toxoplasmosis, rubella, or herpes in pregnancies with FGR in the absence of other risk factors and recommend polymerase chain reaction (PCR) for CMV in women with unexplained FGR who elect diagnostic testing with amniocentesis (GRADE 1C).** However, given the low incidence of CMV in cases of FGR, the lack of effective antenatal interventions, and the limited utility of serologic testing for CMV in the third trimester, routine infectious serologies may not be warranted in the absence of risk factors or ultrasonographic markers of fetal infection.[91–94] PCR is the preferred testing approach for CMV and should be performed in women with unexplained FGR who undergo diagnostic testing with amniocentesis.

Umbilical artery Doppler

Umbilical artery Doppler assesses the impedance to blood flow along the fetal component of the placental unit. As early as 14 weeks of gestation, low impedance of the fetal placental circulation permits continuous forward flow in the umbilical artery throughout the cardiac cycle.[95] Doppler waveforms of the umbilical artery can be obtained from any segment along the umbilical cord. Waveforms obtained near the placental end of the cord reflect downstream impedance and show higher end-diastolic blood flow velocity than waveforms obtained near the fetal cord insertion.[95] In general, this variation in umbilical artery Doppler end-diastolic flow along the umbilical cord is minimal and not significant enough to affect clinical decision-making.

The pulsatility index (PI), resistance index (RI), or systolic-to-diastolic (S/D) ratio can be used for quantification of the Doppler waveform in the umbilical artery, although recent studies have generally used either the PI or RI.[5,16,28,30,80,83] An abnormal umbilical artery Doppler is defined as a PI, RI, or S/D ratio greater than the 95th percentile for gestational age or an absent or reversed end-diastolic velocity (AEDV or

FIGURE 1
Algorithm for the diagnosis and management of fetal growth restriction



REDV). The progression from an abnormal umbilical artery Doppler with a decreased diastolic flow to AEDV/REDV can take several days to weeks, especially in the absence of maternal disease. In a large study on FGR, the mean time-to-delivery interval for umbilical artery PI greater than the 95th percentile, AEDV, and REDV was 26, 13, and 4 days, respectively.[62]

An abnormal umbilical artery Doppler waveform reflects the presence of placental insufficiency and can help differentiate the growth-restricted fetus from the constitutionally small fetus. Incorporation of umbilical artery Doppler evaluation in the management of high-risk pregnancies has been shown to significantly reduce the risk of perinatal death, induction of labor, and cesarean delivery. As such, it is an essential component of fetal surveillance in FGR.[96,97] In contrast, a systematic review of 5 trials found no evidence of maternal or neonatal benefit from the routine use of umbilical artery Doppler in low-risk pregnancies.[98]

AEDV/REDV in the umbilical artery reflects the presence of significant placental deterioration and is associated with high perinatal mortality. The finding of AEDV/REDV of the umbilical artery can be intermittent; this likely represents the continuum of Doppler deterioration that occurs before the absent or reversed flow becomes persistent.[99] A meta-analysis of 31 studies on the risk of fetal death in FGR before 34 weeks of gestation reported odds ratios for fetal death of 3.59 (95% confidence interval [CI], 2.3–5.6) and 7.27 (95% CI, 4.6–11.4) for AEDV and REDV, respectively. Pooled data from this meta-analysis also revealed a risk of stillbirth of 6.8% for AEDV and 19% for REDV in the umbilical artery or ductus venosus.[100] These risks of stillbirth are higher than the risk of infant mortality or severe morbidity at 33–34 weeks for AEDV and at 30–32 weeks for REDV as reported in TRUFFLE.[80]

Evidence suggests that umbilical artery Doppler does not reliably predict adverse pregnancy outcome in late-onset FGR.[101] This result is probably related to the lower frequency of placental pathologic findings in late-onset FGR when compared with early-onset FGR.[102–104] Experimental modeling suggests that a threshold of placental vascular obliteration is required before umbilical artery Doppler abnormalities are seen; therefore, the presence of a normal umbilical artery Doppler in late-onset FGR does not rule out placental disease.[105,106]

There are currently no randomized trials with adequate sample size to inform recommendations regarding the optimal frequency of umbilical artery Doppler for FGR surveillance.[107] Protocols vary from weekly umbilical artery Doppler to a 2- to 4-week interval.[24,108] A prospective observational study of the progression of Doppler abnormalities in FGR suggests that rapid progression, if it is going to occur, is typically noted within the first 2 weeks after diagnosis.[24,108] **We recommend that once FGR is diagnosed, serial umbilical artery Doppler assessment should be performed to assess for deterioration (GRADE 1C).** This assessment should initially occur every 1-2 weeks. If the umbilical artery Doppler remains normal after this initial assessment, a less frequent interval of umbilical artery Doppler testing (eg, every 2–4 weeks) may be considered.[108]

With decreased end-diastolic velocity (ie, flow ratios greater than the 95th percentile) or in pregnancies with severe FGR (EFW less than the 3rd percentile), we suggest weekly umbilical artery Doppler evaluation[24,95] (GRADE 2C). We recommend Doppler assessment up to 2–3 times per week when umbilical artery AEDV is detected due to the potential for deterioration and development of REDV (GRADE 1C). In the setting of REDV, we suggest hospitalization, administration of antenatal corticosteroids, heightened surveillance with cardiotocography (CTG) at least 1–2 times per day, and consideration of delivery depending on the entire clinical picture and results of additional evaluation of fetal well-being (GRADE 2C). Hospital admission should be considered if fetal surveillance of more often than 3 times per week is deemed necessary. Once FGR is diagnosed, assessment of fetal growth and weight should be performed at least every 3–4 weeks; consideration can be given for a 2-week interval in cases of severe FGR or with abnormal umbilical artery Doppler.[109]

Ductus venosus Doppler

Longitudinal studies have shown that Doppler abnormalities of the ductus venosus in FGR reflect an advanced stage of fetal compromise, associated with increased perinatal morbidity and mortality.[2,23,55,110–117] A meta-analysis of FGR at <34 weeks of gestation reported odds ratios for stillbirth of 11.16 (95% CI, 6.31–19.73) for absent or reversed A-wave of the ductus venosus and a frequency of stillbirth of 20%; the risk of stillbirth with a reversed A-wave was 46%.[100] In FGR, Doppler abnormalities of the ductus venosus primarily reflect increased central venous pressure, resulting from increased right ventricular end-diastolic pressure and decreased cardiac muscle compliance.[110,118] Reversed A-wave of the ductus venosus in FGR signifies more significant fetal cardiac compromise.[119] Doppler abnormalities of the ductus venosus in the setting of a normal umbilical artery Doppler indicate an alternative pathophysiological etiology, possibly related to the presence of fetal cardiac, vascular, or genetic abnormalities, and thus are most often not reflective of significant placental disease.

TRUFFLE compared ductus venosus Doppler and computer-generated short-term fetal heart rate variability (cSTV)

AC, abdominal circumference; *CMA*, chromosomal microarray analysis; *CMV*, cytomegalovirus; *CTG*, cardiotocography; *EDV*, end-diastolic velocity; *EFW*, estimated fetal weight; *FGR*, fetal growth restriction; *FLM*, fetal lung maturity; *PCR*, polymerase chain reaction; *PI*, pulsatility index; *RI*, resistance index; *S/D*, systolic-to-diastolic ratio; *UA*, umbilical artery.

in the monitoring and timing of delivery in early-onset FGR. After correction for prematurity, survival without neurologic impairment was found to be significantly higher in the group delivered according to late ductus venosus changes (95%) compared with cSTV (85%).[16] However, caution is urged when extrapolating the findings of TRUFFLE to practice in the United States. TRUFFLE compared cSTV with ductus venosus Doppler, and results cannot be generalized to the visual interpretation of CTG. Furthermore, absent or reversed A-wave of the ductus venosus represents an advanced stage of fetal compromise and is uncommon. Even in pregnancies with AEDV/REDV of the umbilical artery, late Doppler abnormalities of the ductus venosus are noted in only about 41% of fetuses.[117] After 32 weeks of gestation, abnormal CTG findings will almost invariably precede Doppler abnormalities of the ductus venosus.[111] In TRUFFLE, delivery decisions guided by ductus venosus Doppler findings only accounted for about 11% of pregnancies allocated to the late ductus venosus findings group because most delivered due to other fetal or maternal indications.[115,120,121] Prospective research is needed to further elucidate the role of ductus venosus Doppler in pregnancies with early-onset FGR before its use in routine surveillance of pregnancies with FGR can be recommended.

Middle cerebral artery Doppler

The middle cerebral artery is the largest vessel of the fetal cerebral circulation and carries about 80% of cerebral blood flow.[122] Fetal hypoxemia associated with growth restriction results in cerebral vasodilation, an early adaptive mechanism termed the brain-sparing effect. Measurement of flow through the middle cerebral artery using Doppler can identify cerebral vasodilation, which can be quantified using PI or the cerebroplacental ratio (CPR). CPR is calculated by dividing the middle cerebral artery PI by the umbilical artery PI.[123–126] The role of middle cerebral artery Doppler in the management of early-onset FGR has been evaluated in several studies.[127–129] In a meta-analysis of 35 studies, abnormal middle cerebral artery Doppler had a low likelihood ratio (LR) for prediction of perinatal mortality (LR 1.36 [1.10–1.67]) and adverse perinatal outcome (LR 2.77 [1.93–3.96]).[130] Similarly, in a secondary analysis of data from TRUFFLE, middle cerebral artery Doppler did not add useful information beyond umbilical artery and ductus venosus Doppler assessments for optimizing the timing of delivery.[131]

Studies have found that 15%–20% of late-onset growth-restricted fetuses with normal umbilical blood flow have middle cerebral artery Doppler findings of cerebral vasodilation, and CPR has also been studied for its utility in predicting adverse outcomes and guiding the timing of delivery in late-onset cases.[101,115,132–137] The Prospective Observational Trial to Optimize Pediatric Health in IUGR (PORTO) study evaluated the optimal management of fetuses with FGR at 24 0/7 to 36 6/7 weeks of gestation, including multivessel Doppler measurement and CPR. Data from this study showed that CPR evaluation had a sensitivity of 66% and specificity of 85% for the prediction of adverse outcomes.[138] However, a large systematic review and meta-analysis on the prognostic accuracy of CPR and middle cerebral artery Doppler for adverse perinatal outcomes in FGR revealed few high-quality studies and reported large variations in sensitivity and specificity.[139] The available evidence does not indicate improved accuracy of CPR over umbilical artery Doppler, and clinical trials are needed to evaluate the effectiveness of CPR in guiding clinical management, especially in late-onset FGR, before its use in routine surveillance of pregnancies with FGR can be recommended.[139]

Uterine artery Doppler

Uterine artery Doppler assesses the maternal component of placental blood flow and is a marker of remodeling of the spiral arteries by trophoblastic cellular invasion. In normal pregnancies, spiral artery remodeling results in a low-impedance circulation, which is reflected in the uterine arteries by the presence of high velocity and continuous forward flow in diastole.[140] This pregnancy adaptation optimizes the intervillous placental blood flow and delivery of oxygen and nutrients to the fetus. Severe early-onset FGR is characterized by failure of trophoblastic invasion of the myometrial spiral arteries, resulting in reduced uteroplacental perfusion.[140]

Abnormal uterine artery Doppler, defined as a PI greater than the 95th percentile for gestational age or the presence of a diastolic notch, has been associated with adverse pregnancy outcomes, including preeclampsia, FGR, and perinatal mortality.[137,141–147] However, uterine artery Doppler has limited diagnostic accuracy and clinical utility in predicting FGR, SGA birth, and perinatal mortality.[148,149] Although FGR detection rates >90% have been reported in first- and second-trimester prediction models that combine maternal factors, biochemical markers, and uterine artery Doppler, lack of external validation or demonstration of improved pregnancy outcomes limits their clinical applicability.[145,150,151] Based on the available evidence, uterine artery Doppler does not add clinically valuable information for diagnosis or management.

We suggest that Doppler assessment of the ductus venosus, middle cerebral artery, or uterine artery not be used for routine clinical management of early- or late-onset FGR (GRADE 2B).

Cardiotocography

CTG is currently accepted as the primary method for fetal surveillance in high-risk pregnancies in the United States. Despite the absence of large prospective studies on the role of CTG in the management of FGR, a normal CTG in pregnancies with FGR is more likely to be associated with a normal perinatal outcome, and the presence of spontaneous repetitive late decelerations is accepted as an indication for delivery in viable pregnancies with FGR, irrespective of Doppler findings.[121] Although there is limited

evidence to support the frequency of CTG in pregnancies with FGR, it is reasonable to initiate testing at diagnosis after viability, or at a gestational age at which an abnormal finding would trigger intervention.[24] **We suggest weekly CTG testing after viability for FGR without AEDV/REDV and that the frequency be increased when FGR is complicated by AEDV/REDV or other comorbidities or risk factors (GRADE 2C).**

Biophysical profile

Observational studies have indicated that an abnormal biophysical profile (BPP) is a late manifestation of placental disease that appears to become abnormal 48–72 hours after ductus venosus Doppler abnormalities in 90% of cases.[152] More recent studies have questioned the value of BPP in fetal surveillance of high-risk pregnancies, including early-onset severe FGR, because of a high prevalence of false-positive and false-negative results. A Cochrane review concluded that available evidence from randomized controlled trials does not support the use of BPP as a test of fetal well-being in high-risk pregnancies.[153,154] Although fetal deterioration has been reported to be independently reflected by Doppler and BPP testing, further studies are required to prove the usefulness of BPP or of combining these testing modalities.[155]

Amniotic fluid volume

Oligohydramnios is defined as a single deepest vertical pocket of amniotic fluid of less than 2 cm. The PORTO study, which included more than 1100 pregnancies with FGR, noted that amniotic fluid volume abnormalities did not independently increase the risk for adverse outcomes in FGR.[30] There is currently a paucity of data on the role of amniotic fluid volume measurement in FGR management and delivery.[30] However, current guidelines on medically indicated late-preterm and early-term deliveries suggest delivery at 34 0/7 to 37 6/7 weeks of gestation for FGR associated with oligohydramnios.[156]

Neonatal outcomes and delivery timing

The decision for delivery in FGR is driven by fetal and maternal factors. Fetal factors include EFW, gestational age, and findings on fetal surveillance. Maternal factors include the presence of comorbidities, such as hypertension. In the periviable period, the decision for delivery may be challenging because the rates of perinatal death, neurodevelopmental impairment, and other adverse outcomes are high in this gestational age window.[157–159]

Survival of very preterm neonates gradually decreases with decreasing weight percentiles.[160–163] Neonatal mortality in SGA infants born between 24 and 29 weeks of gestation is increased 2-fold to 4-fold when compared with appropriately grown neonates.[4,164–166] In a large European study, birthweights between the 10th and 25th percentiles were associated with a 2-fold increase in mortality when compared with the 50th to 75th percentile weight group.[167] In early-onset FGR associated with abnormal Doppler studies, neonatal survival increased from 13% at 24 weeks to 43% at 25 weeks and 58%-76% at 26 weeks of gestation. Intact survival was 0% at 24 weeks, 13% at 25 weeks, and 6%–31% at 26 weeks of gestation.[159] Given the high rate of adverse outcomes, thresholds of 26 weeks of gestation, 500 g, or both have been suggested for the delivery of pregnancies with severe early-onset FGR.[55,80,83,159] With recent advances in neonatal care and survival of fetuses at the limits of viability, the decision for delivery before 26 weeks of gestation or at 500 g should include coordination of care between maternal-fetal medicine and neonatology services, along with comprehensive patient counseling on neonatal morbidity and mortality and shared decision-making regarding pregnancy management.

The evidence supporting the timing of delivery in pregnancies with FGR and abnormal umbilical artery Doppler but without AEDV/REDV is limited.[168] In a retrospective cohort study of pregnancies with FGR, no difference in composite neonatal outcome was seen between delivery at 39 weeks of gestation in fetuses with normal umbilical artery Doppler and delivery at 37 weeks of gestation in fetuses with elevated umbilical artery S/D ratio.[168] A large US cohort study reported that delivery at 37 weeks of gestation results in a decrease in the stillbirth rate in the presence of risk factors, such as FGR.[169] **We recommend delivery at 37 weeks of gestation in pregnancies with FGR and an umbilical artery Doppler waveform with decreased diastolic flow (S/D, RI, or PI greater than the 95th percentile) but without AEDV/REDV or with severe FGR with EFW less than the 3rd percentile (GRADE 1B).**

As discussed previously, neonatal morbidity and mortality rates associated with AEDV are higher than rates of complications of prematurity at 33–34 weeks of gestation.[100] **Therefore, we recommend delivery at 33–34 weeks of gestation for pregnancies with FGR and AEDV (GRADE 1B).** In the presence of REDV, neonatal morbidity and mortality rates are higher than complications of prematurity at 30–32 weeks of gestation.[100] **Therefore, we recommend delivery at 30–32 weeks of gestation for pregnancies with FGR and REDV (GRADE 1B). We suggest delivery at 38–39 weeks of gestation with FGR when the EFW is between the 3rd and 10th percentile and the umbilical artery Doppler is normal (GRADE 2C).**

There are limited data to inform recommendations regarding the mode of delivery in pregnancies complicated by FGR. Growth-restricted fetuses, particularly those with AEDV/REDV, are at an increased risk for decelerations in labor, emergency cesarean delivery, and metabolic acidemia at delivery.[170,171] Older studies reported rates of intrapartum fetal heart rate decelerations requiring cesarean delivery in 75%–95% of pregnancies with FGR and AEDV/REDV.[172,173] National guidelines from 4 countries recommend cesarean delivery when FGR is complicated by AEDV/REDV of the umbilical artery.[24] In recent studies that reported outcomes of pregnancies complicated by FGR with AEDV/REDV, the mode of delivery was primarily by cesarean, thus rendering it impossible to determine the likelihood of adverse outcomes associated with

The Society for Maternal-Fetal Medicine grading system: grading of recommendations assessment, development, and evaluation[176]

Grade of recommendation	Clarity of risk and benefit	Quality of supporting evidence	Implications
1A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens or vice versa.	Consistent evidence from well-performed, randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Strong recommendation that can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation that applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1C. Strong recommendation, low-quality evidence	Benefits seem to outweigh risks and burdens or vice versa.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Strong recommendation that applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.
2A. Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens.	Consistent evidence from well-performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Weak recommendation; best action may differ depending on circumstances or patients or societal values.
2B. Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an effect on confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances.
2C. Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation; other alternatives may be equally reasonable.
Best practice	Recommendation in which either (1) there is an enormous amount of indirect evidence that clearly justifies strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize) or (2) recommendation to the contrary would be unethical.	—	—

Adapted from Guyatt et al.[177]

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spontaneous or induced vaginal delivery.[86] Given these data and outcomes, **we suggest that for pregnancies with FGR complicated by AEDV/REDV, cesarean delivery should be considered based on the entire clinical scenario (GRADE 2C).**

In accordance with other guidelines,[174] **we recommend the use of antenatal corticosteroids if delivery is anticipated before 33 6/7 weeks of gestation or for pregnancies between 34 0/7 and 36 6/7 weeks of gestation in women without contraindications who**

are at risk of preterm delivery within 7 days and who have not received a previous course of antenatal corticosteroids[175] (GRADE 1A). We also recommend intrapartum magnesium sulfate for fetal and neonatal neuroprotection for women with pregnancies that are less than 32 weeks of gestation (GRADE 1A).

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