The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal-Fetal Medicine

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

NUMBER 134, MAY 2013

(Replaces Practice Bulletin Number 12, January 2000)

Fetal Growth Restriction

Fetal growth restriction, also known as intrauterine growth restriction, is a common complication of pregnancy that has been associated with a variety of adverse perinatal outcomes. There is a lack of consensus regarding terminology, etiology, and diagnostic criteria for fetal growth restriction, with uncertainty surrounding the optimal management and timing of delivery for the growth-restricted fetus. An additional challenge is the difficulty in differentiating between the fetus that is constitutionally small and fulfilling its growth potential and the small fetus that is not fulfilling its growth potential because of an underlying pathologic condition. The purpose of this document is to review the topic of fetal growth restriction with a focus on terminology, etiology, diagnostic and surveillance tools, and guidance for management and timing of delivery.

Background

Terminology

The terminology for classifying fetuses and newborns who have failed to achieve normal weight is inconsistent. Communication between obstetric and newborn practitioners is facilitated by the use of clearly defined terms that characterize fetal and newborn weight according to either the absolute weight or the weight percentile for a given gestational age (1–4). In this document, the term fetal growth restriction will be used to describe fetuses with an estimated fetal weight that is less than the 10th percentile for gestational age, whereas the term small for gestational age (SGA) will be used exclusively to describe newborns whose birth weight is less than the 10th percentile for gestational age.

Prevalence

The prevalence of fetal growth restriction depends on the definition used. As noted previously, the most widely used definition of fetal growth restriction in the United States is an estimated fetal weight that is less than the 10th percentile for gestational age (5). However, this definition does not take into account the individualized growth potential of each fetus, and its use may fail to identify larger fetuses that have not achieved their growth potential and may be at risk of adverse outcomes. Conversely, this definition will result in the misdiagnosis of fetal growth restriction for some constitutionally small fetuses (6–9). In an attempt to assess more accurately whether newborns and fetuses are of appropriate growth, investigators have devised formulas for individualized growth standards (10, 11). However, use of such formulas has not been shown to improve outcomes.

Etiology

The etiology of fetal growth restriction can be broadly categorized into maternal, fetal, and placental (see Box 1). Although the primary pathophysiologic mechanisms underlying these conditions are different, they often (but

Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics and the Society for Maternal-Fetal Medicine Publications Committee with the assistance of Henry Galan, MD, and William Grobman, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

not always) have the same final common pathway: suboptimal uterine–placental perfusion and fetal nutrition.

Maternal Disorders

Maternal medical conditions that may result in fetal growth restriction or SGA include any chronic disorder that is associated with vascular disease (12–14), such as pregnancy-related hypertensive diseases (12). Antiphospholipid syndrome, an acquired immune-meditated thrombophilic state, has been associated with fetal growth restriction (15). In contrast, hereditary thrombophilias, including the factor V Leiden mutation, the prothrombin mutation, or methylenetetrahydrofolate reductase gene mutations have not been found consistently to be associated with fetal growth restriction or SGA (16–18).

Substance Use and Abuse

Tobacco use during pregnancy, which is associated with a 3.5-fold increased risk of SGA, is a modifiable risk factor (12, 19). Other substances that have been associated with SGA include alcohol, cocaine, and narcotics (20–25). The risk of SGA associated with alcohol consumption is increased even with the intake of only one to two drinks daily (21).

Box 1. Etiology of Fetal Growth Restriction ⇦

- Maternal medical conditions
  - Pregestational diabetes mellitus
  - Renal insufficiency
  - Autoimmune disease (eg, systemic lupus erythematosus)
  - Cyanotic cardiac disease
  - Pregnancy-related hypertensive diseases of pregnancy (eg, chronic hypertension, gestational hypertension, or preeclampsia)
  - Antiphospholipid antibody syndrome
- Substance use and abuse (eg, tobacco, alcohol, cocaine, or narcotics)
- Multiple gestation
- Teratogen exposure (eg, cyclophosphamide, valproic acid, or antithrombotic drugs)
- Infectious diseases (eg, malaria, cytomegalovirus, rubella, toxoplasmosis, or syphilis)
- Genetic and structural disorders (eg, trisomy 13, trisomy 18, congenital heart disease, or gastroschisis)
- Placental disorders and umbilical cord abnormalities

Maternal Nutrition

Longitudinal studies of women who conceived and gave birth during famine periods have shown an association between SGA and maternal malnutrition (26, 27). In these studies, extremely poor protein intake before 26 weeks of gestation was associated with SGA, and severe caloric restriction (ie, intake of 600–900 kcal daily) was associated with modest reductions in birth weight. However, there is no high-quality evidence to suggest that additional nutrient intake in the absence of true maternal malnutrition increases fetal weight or improves the outcome in cases of suspected fetal growth restriction (28).

Multiple Gestation

Although twin pregnancies account for only 2–3% of live births in the United States, they account for 10–15% of adverse neonatal outcomes and are associated with an increased frequency of preterm births and SGA births (29–31). The risk of SGA in multiple gestations has been reported to be as high as 25% for twin pregnancies and 60% for triplet and quadruplet pregnancies (32). In addition, monochorionic twin pregnancies are at risk of SGA because of unequal placental sharing and twin–twin transfusion syndrome (33).

Teratogen Exposure

Exposure to certain maternal medications has been associated with fetal growth restriction. The effect of any particular medication is dependent on the inherent teratogenicity of the drug, the timing and duration of exposure, the dosage, and individual genetic predisposition for drug metabolism. Use of certain antineoplastic medications (eg, cyclophosphamide), antiepileptic drugs (eg, valproic acid), and antithrombotic drugs (eg, warfarin), has been associated with an increased risk of fetal growth restriction (34–38).

Infectious Diseases

It has been estimated that intrauterine infection may be the primary etiology underlying approximately 5–10% of cases of fetal growth restriction (39). Malaria accounts for most cases of infection-related fetal growth restriction worldwide (40). Other infections implicated as causes of fetal growth restriction include cytomegalovirus, rubella, toxoplasmosis, varicella, and syphilis (39, 41–44).

Genetic and Structural Disorders

Fetal growth restriction is associated with certain chromosomal abnormalities: at least 50% of fetuses with trisomy 13 or trisomy 18 have fetal growth restriction (45).

Confined placental mosaicism that is identified by chorionic villus sampling also has been associated with fetal growth restriction (46, 47).

Fetuses with many types of structural malformations (but without chromosomal or genetic abnormalities) also have an increased risk of fetal growth restriction (48). For example, fetuses and newborns with congenital heart disease are at an increased risk of fetal growth restriction and SGA, respectively, compared with fetuses and newborns without these malformations (49, 50). Gastroschisis is another malformation commonly associated with fetal growth restriction, which is present in up to 25% of cases of gastroschisis (51).

Placental Disorders and Umbilical Cord Abnormalities

Abnormal placentation that results in poor placental perfusion (ie, placental insufficiency) is the most common pathology associated with fetal growth restriction (52). An association between fetal growth restriction and certain placental disorders (eg, abruption, infarction, circumvallate shape, hemangioma, and chorioangioma) and umbilical cord abnormalities (eg, velamentous or marginal cord insertion) also has been suggested (34, 53–57). However, other placental disorders, such as placenta accreta and placenta previa, have not been associated consistently with fetal growth restriction (58).

Approximately 1% of all pregnancies are complicated by the presence of a single umbilical artery (59). Identification of a single umbilical artery, in the absence of additional anatomical or chromosomal abnormalities, has been associated with fetal growth restriction in some studies but not in others (60, 61).

Perinatal Morbidity and Mortality

Fetal growth restriction increases the risks of intrauterine demise, neonatal morbidity, and neonatal death (62). Furthermore, epidemiologic studies have revealed that growth-restricted fetuses are predisposed to the development of cognitive delay in childhood and diseases in adulthood (eg, obesity, type 2 diabetes mellitus, coronary artery disease, and stroke) (63, 64).

Fetal growth restriction is associated with a significantly increased risk of stillbirth, with the most severely affected fetuses being at greatest risk (65). At fetal weights less than the 10th percentile for gestational age, the risk of fetal death is approximately 1.5%, which is twice the background rate of fetuses of normal growth. Comparatively, the risk of fetal death increases to 2.5% at fetal weights less than the 5th percentile for gestational age (66, 67). Growth-restricted fetuses with absent or reversed end-diastolic flow of the umbilical artery are at particular increased risk of adverse outcomes and have an increased frequency of neonatal mortality and morbidity (68).

Small-for-gestational-age newborns are predisposed to complications, including hypoglycemia, hyperbilirubinemia, hypothermia, intraventricular hemorrhage, necrotizing enterocolitis, seizures, sepsis, respiratory distress syndrome, and neonatal death (69–73).

Screening for Fetal Growth Restriction

Physical Examination or History

Fundal height measured in centimeters (between 24–38 weeks of gestation) approximates the gestational age and is used to screen for fetal growth less than or greater than the 10th percentile (74). A single fundal height measurement at 32–34 weeks of gestation has been reported to be approximately 65–85% sensitive and 96% specific for detecting the growth-restricted fetus (75–79). Maternal obesity and uterine leiomyomas are factors that may limit the accuracy of fundal height measurement as a screening tool. If the accuracy of fundal height is compromised because of such factors, ultrasonography may be a better screening modality.

Ultrasonographic Diagnosis and Evaluation

To assess for fetal growth restriction, four biometric measures are commonly used: 1) biparietal diameter, 2) head circumference, 3) abdominal circumference, and 4) femur length. The biometric measurements can be combined to generate an estimated fetal weight (80). The estimate may deviate from the birth weight by up to 20% in 95% of cases, and for the remaining 5% of cases, the deviation is even greater than 20% (78, 81–83). If the ultrasonographically estimated fetal weight is below the 10th percentile for gestational age, further evaluation should be considered, such as amniotic fluid assessment and Doppler blood flow studies of the umbilical artery. Because growth-restricted fetuses have a high incidence of structural and genetic abnormalities, an ultrasonographic examination of fetal anatomy also is recommended if not performed already.

The utility of Doppler velocimetry evaluation, especially of the umbilical artery, has been studied and reviewed extensively in cases of fetal growth restriction (84). Absent or reversed end-diastolic flow in the umbilical artery is associated with an increased risk of perinatal mortality (85–88). The rate of perinatal death is reduced by as much as 29% when umbilical artery Doppler velocimetry is added to standard antepartum testing in the setting of fetal growth restriction (89, 90). Flow in the ductus venosus also has been measured in

an attempt to assess fetal status, but its use has not been shown to improve outcomes (91–94).

Clinical Considerations and Recommendations

▶ *How should pregnancies be screened for fetal growth restriction, and how is screening accomplished?*

All pregnant patients should be screened for risk factors for fetal growth restriction through a review of medical and obstetric history. Fundal height measurements should be performed at each prenatal care visit after 24 weeks of gestation. A discrepancy between weeks of gestational age and fundal height measurement of greater than 3 has been proposed for identifying a fetus that may be growth restricted (74). The practitioner should keep in mind the potential limitation of assessing fundal height in the presence of maternal obesity, multiple pregnancy, or a history of leiomyomas; in multiple gestations or in cases where the fundus cannot be palpated, an ultrasound examination is preferred as a screening tool. Ultrasonographic screening also may be used in the presence of maternal factors that increase the risk of fetal growth restriction.

Although other approaches to fetal growth restriction screening have been studied (including universal third-trimester ultrasonography, uterine artery Doppler velocimetry, and measurement of analytes, such as pregnancy-associated plasma protein A) there is no evidence that these fetal growth restriction screening methods improve outcomes (95–102).

▶ *How should women with a prior birth of a small for gestational age newborn be evaluated?*

The risk of recurrence of an SGA birth is approximately 20% (9). Any patient with a prior birth of an SGA newborn should have her medical and obstetric histories reviewed to help identify any additional risk factors, particularly modifiable risk factors. In these women, it may be reasonable to perform serial ultrasonography for growth assessment, although the optimal surveillance regimen has not been determined. Maternal history of a prior SGA newborn with normal fetal growth in the current pregnancy is not an indication for antenatal fetal heart rate testing, biophysical profile testing, or umbilical artery Doppler velocimetry (103).

Other maternal risk factors for SGA have been evaluated. One criterion for the diagnosis of antiphospholipid syndrome includes a prior pregnancy affected by a morphologically normal growth-restricted fetus that required delivery before 34 weeks of gestation. However, there is insufficient evidence that screening and treatment in a subsequent pregnancy improves outcome (104). Heterozygosity for the inherited thrombophilias (eg, factor V Leiden mutation and prothrombin mutation) has not consistently been associated with fetal growth restriction, and maternal testing for these thrombophilias is not indicated (17, 104).

▶ *Can fetal growth restriction be prevented?*

A variety of approaches have been undertaken to prevent fetal growth restriction. Many nutritional and dietary supplemental strategies to prevent fetal growth restriction have been studied, although none has been effective. These include individualized nutritional counseling (105); increased consumption of fish, low-fat meats, grains, fruits, and vegetables (106); consumption of a low-salt diet (107); supplementation with iron (108), zinc (109), calcium (110), protein (111), magnesium (112), and vitamin D (113). Therefore, nutritional and dietary supplemental strategies for the prevention of fetal growth restriction are not effective and are not recommended.

Similarly, there is no consistent evidence that either inpatient or outpatient bed rest prevents fetal growth restriction or reduces the incidence of SGA births (114). In women with a history of an SGA birth, some experts have advocated for the use of aspirin to prevent placental insufficiency; however, there is insufficient evidence for such therapy to be routinely indicated for fetal growth restriction prevention (115–118).

▶ *When should genetic counseling and prenatal diagnostic testing be offered in the case of fetal growth restriction?*

Although fetal growth restriction alone may be associated with an aneuploid fetus, the risk of aneuploidy is increased if fetal structural abnormalities also are present. Thus, the combination of fetal growth restriction and a structural defect should prompt patient counseling about the type of anomaly and consideration of prenatal diagnostic testing. Also, because fetal growth restriction detected earlier in gestation is more commonly associated with aneuploidy (119), midtrimester onset of fetal growth restriction is an indication to offer genetic counseling and prenatal diagnostic testing.

▶ *How should a pregnancy complicated by fetal growth restriction be evaluated and managed?*

Ultrasonography remains the best method for evaluating the growth-restricted fetus. Monitoring the

growth-restricted fetus includes serial ultrasonographic measurements of fetal biometry and amniotic fluid volume. Antenatal surveillance with umbilical artery Doppler velocimetry and antepartum testing (eg, nonstress tests or biophysical profiles) should not begin before a gestational age when delivery would be considered for perinatal benefit (30, 31, 120–124). The optimal interval for fetal growth assessment and the optimal surveillance regimen have not been established. Most growth-restricted fetuses can be adequately evaluated with serial ultrasonography every 3–4 weeks; ultrasound assessment of growth should not be performed more frequently than every 2 weeks because the inherent error associated with ultrasonographic measurements can preclude an accurate assessment of interval growth (125, 126).

▶ *What is the role of Doppler velocimetry in evaluating a pregnancy complicated by fetal growth restriction?*

Umbilical artery Doppler velocimetry plays an important role in the management of a pregnancy complicated by a diagnosis of fetal growth restriction. Its use, in conjunction with standard fetal surveillance, such as nonstress tests, biophysical profiles, or both, is associated with improved outcomes in fetuses in which fetal growth restriction has been diagnosed (90). Doppler assessment may provide insight into the etiology of fetal growth restriction because increased impedance in the umbilical artery suggests that the pregnancy is complicated by underlying placental insufficiency. Also, absent or reversed end-diastolic flow in the umbilical artery is associated with an increased frequency of perinatal mortality (86–88, 127) and can affect decisions regarding timing of delivery in the context of fetal growth restriction (84). Investigation of other fetal blood vessels with Doppler velocimetry, including assessments of the middle cerebral artery and the precordial venous system, has been explored in the setting of fetal growth restriction. However, these flow measurements have not been shown to improve perinatal outcome, and the role of these measures in clinical practice remains uncertain (91, 92, 127, 128–130).

▶ *When should a growth-restricted fetus be delivered?*

The optimal timing of delivery of the growth-restricted fetus depends on the underlying etiology of the growth restriction (if known) as well as the estimated gestational age. For example, altering the timing of delivery for fetuses with aneuploidy or congenital infection may not improve the outcome. Furthermore, in some cases patients may elect nonintervention. For example, some women may choose to forgo delivery of a severely growth-restricted fetus at 25 weeks of gestation even if there is an increased risk of fetal death. Management may be enhanced by an individualized and multidisciplinary approach. When intervention for perinatal benefit is the preferred option, antenatal fetal surveillance may help guide the timing of delivery. Fetal growth restriction alone is not an indication for cesarean delivery and the route of delivery should be based on other clinical circumstances.

The Growth Restriction Intervention Trial is currently the only published randomized trial to assess the timing of delivery of the early preterm (less than 34 weeks of gestation) growth-restricted fetus. In this trial, women with growth-restricted fetuses whose obstetricians were uncertain whether delivery would be beneficial, were randomized to either the early delivery group (delivery within 48 hours) or to the expectant management group (with antepartum surveillance until it was felt that delivery should not be delayed any longer). The rates of betamethasone administration were the same in both groups. Perinatal survival was similar, and at the 6–12-year follow-up there were no differences in cognitive, language, behavior, or motor abilities of the children born to women in the early-delivery group versus those in the expectant management group (131–133). In the Disproportionate Intrauterine Growth Intervention Trial at Term, women with singleton gestations at or beyond 36 weeks with suspected fetal growth restriction (defined as an estimated fetal weight less than the 10th percentile) were randomized to undergo delivery or expectant management with delivery only if some other indication arose (134). There were no differences in composite neonatal outcome between these two groups, although the study cohort was not large enough to determine whether individual outcomes, such as perinatal death, were affected by the different management approaches.

No adequately powered randomized trials have been performed to determine the optimal time for delivery of the growth-restricted fetus between 34 weeks and 36 weeks of gestation. Based on existing data regarding timing of delivery as well as expert consensus, a joint conference of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the Society for Maternal-Fetal Medicine, and the American College of Obstetricians and Gynecologists suggested the following two timing strategies when fetal growth restriction has been diagnosed: 1) delivery at 38 0/7–39 6/7 weeks of gestation in cases of isolated fetal growth restriction and 2) delivery at 34 0/7–37 6/7 weeks of gestation in cases of fetal growth restriction with additional risk factors for adverse

outcome (eg, oligohydramnios, abnormal umbilical artery Doppler velocimetry results, maternal risk factors, or co-morbidities) (135).

When delivery for fetal growth restriction is anticipated before 34 weeks of gestation, the delivery should be planned at a center with a neonatal intensive care unit and, ideally, after consultation with a maternal–fetal specialist. Antenatal corticosteroids should be administered before delivery because they are associated with improved preterm neonatal outcomes (136–138). For cases in which delivery occurs before 32 weeks of gestation, magnesium sulfate should be considered for fetal and neonatal neuroprotection in accordance with one of the accepted published protocols (139–142).

Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- Umbilical artery Doppler velocimetry used in conjunction with standard fetal surveillance, such as nonstress tests, or biophysical profiles, or both, is associated with improved outcomes in fetuses in which fetal growth restriction has been diagnosed.
- When delivery for fetal growth restriction is anticipated before 34 weeks of gestation, antenatal corticosteroids should be administered before delivery because they are associated with improved preterm neonatal outcomes.
- For cases in which delivery occurs before 32 weeks of gestation, magnesium sulfate should be considered for fetal and neonatal neuroprotection.
- Nutritional and dietary supplemental strategies for the prevention of fetal growth restriction are not effective and are not recommended.

The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):

- Fetal growth restriction alone is not an indication for cesarean delivery.
- The optimal timing of delivery of the growth-restricted fetus depends on the underlying etiology of the growth restriction (if known) as well as the estimated gestational age.

Proposed Performance Measure

Percentage of pregnant women with suspected fetal growth restriction in whom a plan for assessment and surveillance of fetal growth and well-being is initiated, if delivery is not pursued at the time of diagnosis

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1990–January 2013. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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Fetal growth restriction. Practice Bulletin No. 134. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;121:1122–33.