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INTERIM UPDATE: The content in this Practice Bulletin has been updated as highlighted (or removed as necessary) to reflect a limited, focused change in the expanded definition of fetal growth restriction and delivery timing recommendations in the setting of fetal growth restriction.

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 weight within population-based norms is inconsistent. Communication between obstetric and newborn practitioners is facilitated by 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 or abdominal circumference 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 frequently used definition of fetal growth restriction is an estimated fetal

weight or abdominal circumference 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 (Box 1). Although the primary pathophysiologic mechanisms underlying these conditions are different, they often (but 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-mediated **thrombophilia**, 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).

Maternal Nutrition

Longitudinal studies of women who became pregnant 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 gestation pregnancies 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

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

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 restriction (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 (74–78). 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 (79). 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% (74, 80–82). If the ultrasonographically estimated fetal weight or the abdominal circumference 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 (5). Absent or reversed end-diastolic flow in the umbilical artery is associated with an increased risk of perinatal mortality (83–86). 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 (87, 88). 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 (89–92).

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 (93–101).

► ***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 (102).

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 (103). 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, 103, 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); and 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 a chromosomal abnormality, the risk 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 or in association with polyhydramnios is more commonly associated with chromosomal abnormalities (119), diagnosis of fetal growth restriction before 32 weeks or fetal growth restriction in combination with polyhydramnios or fetal malformation 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 (eg, nonstress tests or biophysical profiles) should not begin before a gestational age when delivery would be considered for perinatal benefit (30, 31, 120–123, 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. Once fetal growth restriction is diagnosed, serial umbilical artery assessment should be performed to assess for deterioration (5). Umbilical artery Doppler velocimetry used 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 (88). 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 (84–86, 127) and can affect decisions regarding timing of delivery in the context of fetal growth restriction (5). 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. In the 2-year follow-up of the Trial of Umbilical and Fetal Flow in Europe (TRUFFLE) study, investigators found that delivery based on late changes in the ductus venosus Doppler was associated with less neurodevelopmental deficiency at age 2 years compared with those delivered based on fetal heart rate tracing changes, though this strategy was associated with an increase in perinatal and infant mortality (128). Therefore, these flow measurements have not been shown to improve perinatal outcome, and the role of these measures in clinical practice remains uncertain (89, 90, 127, 129–131).

► ***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), the estimated gestational age, and other clinical findings such as antenatal fetal surveillance. 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 assessed 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 (132–134). 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, abdominal circumference less than the 10th percentile, or flattening of the growth curve as judged by the clinician) were randomized to undergo delivery or expectant management with delivery only if some other indication arose (135). 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 2011 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 weeks to 37 6/7 weeks of gestation in cases of fetal growth restriction with additional risk factors for adverse outcome (eg, oligohydramnios, abnormal Doppler studies, maternal risk factors, or comorbidities) (136). The 2020 Society for Maternal-Fetal Medicine (SMFM) Consult Series, Diagnosis and Management of Fetal Growth Restriction, further categorizes management of isolated fetal growth restriction based on the percentile of estimated fetal weight (5). For estimated fetal weight between the 3rd and 10th percentile and normal umbilical artery Doppler, delivery is suggested at 38 0/7 and 39 0/7 weeks of gestation. In cases of isolated fetal growth restriction with an estimated fetal weight less than the third percentile, delivery is recommended at 37 0/7 weeks of gestation or at diagnosis if diagnosed earlier (137). Earlier delivery is indicated in cases of absent or reverse umbilical artery flow (5, 137). See Committee Opinion 818, *Medically Indicated Late-Preterm and Early-Term Deliveries*, for detailed delivery timing guidance.

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 are recommended if delivery is anticipated before 33 6/7 weeks of gestation because they are associated with improved preterm neonatal outcomes. In addition, antenatal corticosteroids are recommended for women in whom delivery is anticipated between 34 0/7 weeks and 36 6/7 weeks of gestation, who are at risk of preterm delivery within 7 days, and who have not received a previous course of antenatal corticosteroids (138–142). 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 (143–146).

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, biophysical profiles, or both, is associated with improved outcomes in fetuses in which fetal growth restriction has been diagnosed.
- ▶ Antenatal corticosteroids are recommended if delivery is anticipated before 33 6/7 weeks of gestation

because they are associated with improved preterm neonatal outcomes. In addition, antenatal corticosteroids are recommended for women in whom delivery is anticipated between 34 0/7 and 36 6/7 weeks of gestation, who are at risk of preterm delivery within 7 days, and who have not received a previous course of antenatal corticosteroids.

- ▶ 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), the estimated gestational age, and other clinical findings such as antenatal fetal surveillance.

References

1. Dunn PM. The search for perinatal definitions and standards. *Acta Paediatr Scand Suppl* 1985;319:7–16. (Level III)
2. World Health Organization. Report of a scientific group on health statistics methodology related to perinatal events. Document ICD/PE/74.4:1. Geneva: WHO; 1974. (Level III)
3. Hoffman HJ, Stark CR, Lundin FE Jr, Ashbrook JD. Analysis of birth weight, gestational age, and fetal viability, U. S. births, 1968. *Obstet Gynecol Surv* 1974;29:651–81. (Level II-3)
4. Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. *J Pediatr* 1967;71:159–63. (Level III)
5. Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: diagnosis and management of fetal growth restriction: (replaces clinical guideline number 3, April 2012). *Am J Obstet Gynecol* 2020;223:B2-17. (Level III)
6. Galan HL. Timing delivery of the growth-restricted fetus. *Semin Perinatol* 2011;35:262–9. (Level III)
7. Platz E, Newman R. Diagnosis of IUGR: traditional biometry. *Semin Perinatol* 2008;32:140–7. (Level III)
8. Xu H, Simonet F, Luo ZC. Optimal birth weight percentile cut-offs in defining small- or large-for-gestational-age. *Acta Paediatr* 2010;99:550–5. (Level II-3)

9. Ananth CV, Vintzileos AM. Distinguishing pathological from constitutional small for gestational age births in population-based studies. *Early Hum Dev* 2009;85:653–8. (Level II-3)
10. Bukowski R, Uchida T, Smith GC, Malone FD, Ball RH, Nyberg DA, et al. Individualized norms of optimal fetal growth: fetal growth potential. First and Second Trimester Evaluation of Risk (FASTER) Research Consortium. *Obstet Gynecol* 2008;111:1065–76. (Level II-2)
11. Gardosi J, Mul T, Mongelli M, Fagan D. Analysis of birthweight and gestational age in antepartum stillbirths. *Br J Obstet Gynaecol* 1998;105:524–30. (Level III)
12. Ounsted M, Moar VA, Scott A. Risk factors associated with small-for-dates and large-for-dates infants. *Br J Obstet Gynaecol* 1985;92:226–32. (Level II-3)
13. Cunningham FG, Cox SM, Harstad TW, Mason RA, Pritchard JA. Chronic renal disease and pregnancy outcome. *Am J Obstet Gynecol* 1990;163:453–9. (Level III)
14. Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Schouten HJ, Peeters LL. Maternal volume homeostasis in early pregnancy in relation to fetal growth restriction. *Obstet Gynecol* 1995;85:361–7. (Level III)
15. Antiphospholipid syndrome. Practice Bulletin No. 132. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2012;120:1514–21. (Level III)
16. Facco F, You W, Grobman W. Genetic thrombophilias and intrauterine growth restriction: a meta-analysis. *Obstet Gynecol* 2009;113:1206–16. (Level III)
17. Said JM, Higgins JR, Moses EK, Walker SP, Borg AJ, Monagle PT, et al. Inherited thrombophilia polymorphisms and pregnancy outcomes in nulliparous women. *Obstet Gynecol* 2010;115:5–13. (Level II-2)
18. Silver RM, Zhao Y, Spong CY, Sibai B, GJr Wendel, Wenstrom K, et al. Prothrombin gene G20210A mutation and obstetric complications. *Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units (NICHD MFMU) Network*. *Obstet Gynecol* 2010;115:14–20. (Level II-2)
19. Bada HS, Das A, Bauer CR, Shankaran S, Lester BM, Gard CC, et al. Low birth weight and preterm births: etiologic fraction attributable to prenatal drug exposure. *J Perinatol* 2005;25:631–7. (Level II-3)
20. Shu XO, Hatch MC, Mills J, Clemens J, Susser M. Maternal smoking, alcohol drinking, caffeine consumption, and fetal growth: results from a prospective study. *Epidemiology* 1995;6:115–20. (Level II-2)
21. Mills JL, Graubard BI, Harley EE, Rhoads GG, Berendes HW. Maternal alcohol consumption and birth weight. How much drinking during pregnancy is safe? *JAMA* 1984;252:1875–9. (Level II-2)
22. Virji SK. The relationship between alcohol consumption during pregnancy and infant birthweight. An epidemiologic study. *Acta Obstet Gynecol Scand* 1991;70:303–8. (Level II-3)
23. Naeye RL, Blanc W, Leblanc W, Khatamee MA. Fetal complications of maternal heroin addiction: abnormal growth, infections, and episodes of stress. *J Pediatr* 1973;83:1055–61. (Level III)
24. Fulroth R, Phillips B, Durand DJ. Perinatal outcome of infants exposed to cocaine and/or heroin in utero. *Am J Dis Child* 1989;143:905–10. (Level II-3)
25. Little BB, Snell LM, Klein VR, Gilstrap LCIII. Cocaine abuse during pregnancy: maternal and fetal implications. *Obstet Gynecol* 1989;73:157–60. (Level II-3)
26. Antonov AN. Children born during the siege of Leningrad in 1942. *J Pediatr* 1947;30:250–9. (Level III)
27. Smith CA. Effects of maternal under nutrition upon the newborn infant in Holland (1944–1945). *J Pediatr* 1947;30:229–43. (Level III)
28. Say L, Gulmezoglu AM, Hofmeyr GJ. Maternal nutrient supplementation for suspected impaired fetal growth. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD000148. DOI: 10.1002/14651858.CD000148. (Meta-analysis)
29. Guyer B, MacDorman MF, Martin JA, Peters KD, Strobino DM. Annual summary of vital statistics-1997. *Pediatrics* 1998;102:1333–49. (Level III)
30. Powers WF, Kiely JL. The risks confronting twins: a national perspective. *Am J Obstet Gynecol* 1994;170:456–61. (Level II-3)
31. Houlton MC, Marivate M, Philpott RH. The prediction of fetal growth retardation in twin pregnancy. *Br J Obstet Gynaecol* 1981;88:264–73. (Level II-3)
32. Mauldin JG, Newman RB. Neurologic morbidity associated with multiple gestation. *Female Patient* 1998;23(4):27–46. (Level III)
33. Denbow ML, Cox P, Taylor M, Hammal DM, Fisk NM. Placental angioarchitecture in monochorionic twin pregnancies: relationship to fetal growth, fetofetal transfusion syndrome, and pregnancy outcome. *Am J Obstet Gynecol* 2000;182:417–26. (Level III)
34. Maulik D. Fetal growth restriction: the etiology. *Clin Obstet Gynecol* 2006;49:228–35. (Level III)
35. Battino D, Granata T, Binelli S, Caccamo ML, Canevini MP, Canger R, et al. Intrauterine growth in the offspring of epileptic mothers. *Acta Neurol Scand* 1992;86:555–7. (Level III)
36. Mastroiacovo P, Bertollini R, Licata D. Fetal growth in the offspring of epileptic women: results of an Italian multicentric cohort study. *Acta Neurol Scand* 1988;78:110–4. (Level II-2)
37. Aviles A, Diaz-Maqueo JC, Talavera A, Guzman R, Garcia EL. Growth and development of children of mothers treated with chemotherapy during pregnancy: current status of 43 children. *Am J Hematol* 1991;36:243–8. (Level III)
38. Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980;68:122–40. (Level III)
39. Creasy RK, Resnik R, Iams JD, Lockwood CJ, Moore TR, editors. *Creasy and Resnik's maternal–fetal medicine: principles and practice*. 6th ed. Philadelphia (PA): Saunders Elsevier; 2009. (Level III)

40. Desai M, ter Kuile FO, Nosten F, McGready R, Asamo K, Brabin B, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis* 2007;7:93–104. (Level III)
41. Donner C, Liesnard C, Content J, Busine A, Aderca J, Rodesch F. Prenatal diagnosis of 52 pregnancies at risk for congenital cytomegalovirus infection. *Obstet Gynecol* 1993;82:481–6. (Level III)
42. Lambert JS, Watts DH, Mofenson L, Stiehm ER, Harris DR, Bethel J, et al. Risk factors for preterm birth, low birth weight, and intrauterine growth retardation in infants born to HIV-infected pregnant women receiving zidovudine. *Pediatric AIDS Clinical Trials Group 185 Team. AIDS* 2000;14:1389–99. (Level I)
43. Cailhol J, Jourdain G, Coeur SL, Traisathit P, Boonrod K, Prommas S, et al. Association of low CD4 cell count and intrauterine growth retardation in Thailand. *Perinatal HIV Prevention Trial Group. J Acquir Immune Defic Syndr* 2009;50:409–13. (Level I)
44. Iqbal SN, Kriebs J, Harman C, Alger L, Kopelman J, Turan O, et al. Predictors of fetal growth in maternal HIV disease. *Am J Perinatol* 2010;27:517–23. (Level II-3)
45. Eydoux P, Choiset A, Le Porrier N, Thepot F, Szpiro-Tapia S, Alliet J, et al. Chromosomal prenatal diagnosis: study of 936 cases of intrauterine abnormalities after ultrasound assessment. *Prenat Diagn* 1989;9:255–69. (Level III)
46. Wolstenholme J, Rooney DE, Davison EV. Confined placental mosaicism, IUGR, and adverse pregnancy outcome: a controlled retrospective U.K. collaborative survey. *Prenat Diagn* 1994;14:345–61. (Level II-2)
47. Wilkins-Haug L, Roberts DJ, Morton CC. Confined placental mosaicism and intrauterine growth retardation: a case-control analysis of placentas at delivery. *Am J Obstet Gynecol* 1995;172:44–50. (Level III)
48. Khoury MJ, Erickson JD, Cordero JF, McCarthy BJ. Congenital malformations and intrauterine growth retardation: a population study. *Pediatrics* 1988;82:83–90. (Level II-3)
49. Wallenstein MB, Harper LM, Odibo AO, Roehl KA, Longman RE, Macones GA, et al. Fetal congenital heart disease and intrauterine growth restriction: a retrospective cohort study. *J Matern Fetal Neonatal Med* 2012;25:662–5. (Level II-3)
50. Malik S, Cleves MA, Zhao W, Correa A, Hobbs CA. Association between congenital heart defects and small for gestational age. *National Birth Defects Prevention Study. Pediatrics* 2007;119:e976–82. (Level II-3)
51. Raynor BD, Richards D. Growth retardation in fetuses with gastroschisis. *J Ultrasound Med* 1997;16:13–6. (Level III)
52. Salafia CM, Minior VK, Pezzullo JC, Popek EJ, Rosenkrantz TS, Vintzileos AM. Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features. *Am J Obstet Gynecol* 1995;173:1049–57. (Level II-3)
53. Laurini R, Laurin J, Marsal K. Placental histology and fetal blood flow in intrauterine growth retardation. *Acta Obstet Gynecol Scand* 1994;73:529–34. (Level III)
54. Shanklin DR. The influence of placental lesions on the newborn infant. *Pediatr Clin North Am* 1970;17:25–42. (Level II-3)
55. Ananth CV, Demissie K, Smulian JC, Vintzileos AM. Relationship among placenta previa, fetal growth restriction, and preterm delivery: a population-based study. *Obstet Gynecol* 2001;98:299–306. (Level II-3)
56. Ananth CV, Wilcox AJ. Placental abruption and perinatal mortality in the United States. *Am J Epidemiol* 2001;153:332–7. (Level II-3)
57. Chapman MG, Furness ET, Jones WR, Sheat JH. Significance of the ultrasound location of placental site in early pregnancy. *Br J Obstet Gynaecol* 1979;86:846–8. (Level III)
58. Harper LM, Odibo AO, Macones GA, Crane JP, Cahill AG. Effect of placenta previa on fetal growth. *Am J Obstet Gynecol* 2010;203:330.e1–e5. (Level II-2)
59. Pollack RN, Divon MY. Intrauterine growth retardation: definition, classification, and etiology. *Clin Obstet Gynecol* 1992;35:99–107. (Level III)
60. Thummala MR, Raju TN, Langenberg P. Isolated single umbilical artery anomaly and the risk for congenital malformations: a meta-analysis. *J Pediatr Surg* 1998;33:580–5. (Meta-Analysis)
61. Heifetz SA. Single umbilical artery. A statistical analysis of 237 autopsy cases and review of the literature. *Perspect Pediatr Pathol* 1984;8:345–78. (Level III)
62. Resnik R. Intrauterine growth restriction. *Obstet Gynecol* 2002;99:490–6. (Level III)
63. Pallotto EK, Kilbride HW. Perinatal outcome and later implications of intrauterine growth restriction. *Clin Obstet Gynecol* 2006;49:257–69. (Level III)
64. Barker DJ. Adult consequences of fetal growth restriction. *Clin Obstet Gynecol* 2006;49:270–83. (Level III)
65. Clausson B, Cnattingius S, Axelsson O. Outcomes of post-term births: the role of fetal growth restriction and malformations. *Obstet Gynecol* 1999;94:758–62. (Level II-3)
66. Getahun D, Ananth CV, Kinzler WL. Risk factors for antepartum and intrapartum stillbirth: a population-based study. *Am J Obstet Gynecol* 2007;196:499–507. (Level II-3)
67. Ego A, Subtil D, Grange G, Thiebaugeorges O, Senat MV, Vayssiere C, et al. Customized versus population-based birth weight standards for identifying growth restricted infants: a French multicenter study. *Am J Obstet Gynecol* 2006;194:1042–9. (Level II-3)
68. Vergani P, Roncaglia N, Locatelli A, Andreotti C, Crippa I, Pezzullo JC, et al. Antenatal predictors of neonatal outcome in fetal growth restriction with absent end-diastolic flow in the umbilical artery. *Am J Obstet Gynecol* 2005;193:1213–8. (Level II-3)
69. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. *N Engl J Med* 1999;340:1234–8. (Level II-2)
70. Hartung J, Kalache KD, Heyna C, Heling KS, Kuhlig M, Wauer R, et al. Outcome of 60 neonates who had ARED

- flow prenatally compared with a matched control group of appropriate-for-gestational age preterm neonates. *Ultrasound Obstet Gynecol* 2005;25:566–72. (Level II-2)
71. Shand AW, Hornbuckle J, Nathan E, Dickinson JE, French NP. Small for gestational age preterm infants and relationship of abnormal umbilical artery Doppler blood flow to perinatal mortality and neurodevelopmental outcomes. *Aust N Z J Obstet Gynaecol* 2009;49:52–8. (Level II-2)
 72. Jones RA, Robertson NR. Problems of the small-for-dates baby. *Clin Obstet Gynaecol* 1984;11:499–524. (Level III)
 73. Alkalay AL, Graham JMJr, Pomerance JJ. Evaluation of neonates born with intrauterine growth retardation: review and practice guidelines. *J Perinatol* 1998;18:142–51. (Level III)
 74. Sparks TN, Cheng YW, McLaughlin B, Esakoff TF, Caughey AB. Fundal height: a useful screening tool for fetal growth? *J Matern Fetal Neonatal Med* 2011;24:708–12. (Level II-2)
 75. Leeson S, Aziz N. Customised fetal growth assessment. *Br J Obstet Gynaecol* 1997;104:648–51. (Level III)
 76. Jahn A, Razum O, Berle P. Routine screening for intrauterine growth retardation in Germany: low sensitivity and questionable benefit for diagnosed cases. *Acta Obstet Gynecol Scand* 1998;77:643–8. (Level II-3)
 77. Kean LH, Liu DT. Antenatal care as a screening tool for the detection of small for gestational age babies in the low risk population. *J Obstet Gynaecol* 1996;16:77–82. (Level II-3)
 78. Goetzinger KR, Tuuli MG, Odibo AO, Roehl KA, Macones GA, Cahill AG. Screening for fetal growth disorders by clinical exam in the era of obesity. *J Perinatol* 2012. DOI: 10.1038/jp.2012.130. (Level II-2)
 79. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study. *Am J Obstet Gynecol* 1985;151:333–7. (Level III)
 80. Hadlock FP, Harrist RB, Carpenter RJ, Deter RL, Park SK. Sonographic estimation of fetal weight. The value of femur length in addition to head and abdomen measurements. *Radiology* 1984;150:535–40. (Level III)
 81. Chien PF, Owen P, Khan KS. Validity of ultrasound estimation of fetal weight. *Obstet Gynecol* 2000;95:856–60. (Level II-2)
 82. Dudley NJ. A systematic review of the ultrasound estimation of fetal weight. *Ultrasound Obstet Gynecol* 2005;25:80–9. (Level III)
 83. Kingdom JC, Burrell SJ, Kaufmann P. Pathology and clinical implications of abnormal umbilical artery Doppler waveforms. *Ultrasound Obstet Gynecol* 1997;9:271–86. (Level III)
 84. Pardi G, Cetin I, Marconi AM, Lanfranchi A, Bozzetti P, Ferrazzi E, et al. Diagnostic value of blood sampling in fetuses with growth retardation. *N Engl J Med* 1993;328:692–6. (Level III)
 85. Nicolaides KH, Bilardo CM, Soothill PW, Campbell S. Absence of end diastolic frequencies in umbilical artery: a sign of fetal hypoxia and acidosis. *BMJ* 1988;297:1026–7. (Level III)
 86. Bilardo CM, Nicolaides KH, Campbell S. Doppler measurements of fetal and uteroplacental circulations: relationship with umbilical venous blood gases measured at cordocentesis. *Am J Obstet Gynecol* 1990;162:115–20. (Level III)
 87. Giles W, Bisits A. Clinical use of Doppler ultrasound in pregnancy: information from six randomised trials. *Fetal Diagn Ther* 1993;8:247–55. (Level III)
 88. Casanova R, Chuang A, Goepfert AR, Hueppchen NA, Weiss PM, Beckmann CR, et al. Beckmann and Ling's obstetrics and gynecology. 8th ed. Philadelphia (PA): Wolters Kluwer; 2019. (Level III)
 89. Rizzo G, Capponi A, Arduini D, Romanini C. The value of fetal arterial, cardiac and venous flows in predicting pH and blood gases measured in umbilical blood at cordocentesis in growth retarded fetuses. *Br J Obstet Gynaecol* 1995;102:963–9. (Level III)
 90. Hecher K, Snijders R, Campbell S, Nicolaides K. Fetal venous, intracardiac, and arterial blood flow measurements in intrauterine growth retardation: relationship with fetal blood gases. *Am J Obstet Gynecol* 1995;173:10–5. (Level III)
 91. Baschat AA. Doppler application in the delivery timing of the preterm growth-restricted fetus: another step in the right direction. *Ultrasound Obstet Gynecol* 2004;23:111–8. (Level III)
 92. Ghidini A. Doppler of the ductus venosus in severe preterm fetal growth restriction: a test in search of a purpose? *Obstet Gynecol* 2007;109:250–2. (Level III)
 93. Irwin JC, Suen LF, Martina NA, Mark SP, Giudice LC. Role of the IGF system in trophoblast invasion and preeclampsia. *Hum Reprod* 1999;14(suppl 2):90–6. (Level III)
 94. Spencer K, Cowans NJ, Avgidou K, Molina F, Nicolaides KH. First-trimester biochemical markers of aneuploidy and the prediction of small-for-gestational age fetuses. *Ultrasound Obstet Gynecol* 2008;31:15–9. (Level II-3)
 95. Krantz D, Goetzl L, Simpson JL, Thom E, Zachary J, Hallahan TW, et al. Association of extreme first-trimester free human chorionic gonadotropin-beta, pregnancy-associated plasma protein A, and nuchal translucency with intrauterine growth restriction and other adverse pregnancy outcomes. First Trimester Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening (BUN) Study Group. *Am J Obstet Gynecol* 2004;191:1452–8. (Level II-2)
 96. Goetzl L, Krantz D, Simpson JL, Silver RK, Zachary JM, Pergament E, et al. Pregnancy-associated plasma protein A, free beta-hCG, nuchal translucency, and risk of pregnancy loss. *Obstet Gynecol* 2004;104:30–6. (Level II-2)
 97. Dugoff L. First- and second-trimester maternal serum markers for aneuploidy and adverse obstetric outcomes. Society for Maternal-Fetal Medicine. *Obstet Gynecol* 2010;115:1052–61. (Level II-2)
 98. Zhong Y, Tuuli M, Odibo AO. First-trimester assessment of placenta function and the prediction of preeclampsia

- and intrauterine growth restriction. *Prenat Diagn* 2010;30:293–308. (Level III)
99. Poon LC, Stratieva V, Piras S, Piri S, Nicolaides KH. Hypertensive disorders in pregnancy: combined screening by uterine artery Doppler, blood pressure and serum PAPP-A at 11–13 weeks. *Prenat Diagn* 2010;30:216–23. (Level II-2)
 100. Goetzinger KR, Singla A, Gerkowicz S, Dicke JM, Gray DL, Odibo AO. Predicting the risk of pre-eclampsia between 11 and 13 weeks' gestation by combining maternal characteristics and serum analytes, PAPP-A and free beta-hCG. *Prenat Diagn* 2010;30:1138–42. (Level II-3)
 101. Alfiveric Z, Stampalija T, Medley N. Fetal and umbilical Doppler ultrasound in normal pregnancy. *Cochrane Database of Systematic Reviews* 2015, Issue 4. Art. No.: CD001450. DOI: 10.1002/14651858.CD001450.pub4. (Systematic Review and Meta-Analysis)
 102. Morris RK, Malin G, Robson SC, Kleijnen J, Zamora J, Khan KS. Fetal umbilical artery Doppler to predict compromise of fetal/neonatal wellbeing in a high-risk population: systematic review and bivariate meta-analysis. *Ultrasound Obstet Gynecol* 2011;37:135–42. (Meta-analysis)
 103. Silver RM, Varner MW, Reddy U, Goldenberg R, Pinar H, Conway D, et al. Work-up of stillbirth: a review of the evidence. *Am J Obstet Gynecol* 2007;196:433–44. (Level III)
 104. Inherited thrombophilias in pregnancy. *ACOG Practice Bulletin No. 197*. American College of Obstetricians and Gynecologists [published erratum appears in *Obstet Gynecol* 2018;132:1069]. *Obstet Gynecol* 2018;132:e18–34. (Level III)
 105. Kafatos AG, Vlachonikolis IG, Codrington CA. Nutrition during pregnancy: the effects of an educational intervention program in Greece. *Am J Clin Nutr* 1989;50:970–9. (Level II-1)
 106. Khoury J, Henriksen T, Christophersen B, Tonstad S. Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial. *Am J Obstet Gynecol* 2005;193:1292–301. (Level I)
 107. Steegers EA, Van Lakwijk HP, Jongsma HW, Fast JH, De Boo T, Eskes TK, et al. (Patho)physiological implications of chronic dietary sodium restriction during pregnancy; a longitudinal prospective randomized study. *Br J Obstet Gynaecol* 1991;98:980–7. (Level I)
 108. Pena-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Daily oral iron supplementation during pregnancy. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD004736. DOI: 10.1002/14651858.CD004736.pub4. (Level III)
 109. Mori R, Ota E, Middleton P, Tobe-Gai R, Mahomed K, Bhutta ZA. Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database of Systematic Reviews* 2012, Issue 7. Art. No.: CD000230. DOI: 10.1002/14651858.CD000230.pub4. (Meta-analysis)
 110. Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database of Systematic Reviews* 2010, Issue 8. Art. No.: CD001059. DOI: 10.1002/14651858.CD001059.pub3. (Meta-analysis)
 111. Ota E, Tobe-Gai R, Mori R, Farrar D. Antenatal dietary advice and supplementation to increase energy and protein intake. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD000032. DOI: 10.1002/14651858.CD000032.pub2. (Meta-analysis)
 112. Makrides M, Crowther CA. Magnesium supplementation in pregnancy. *Cochrane Database of Systematic Reviews* 2001, Issue 4. Art. No.: CD000937. DOI: 10.1002/14651858.CD000937. (Meta-analysis)
 113. De-Regil LM, Palacios C, Ansary A, Kulier R, Pena-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No.: CD008873. DOI: 10.1002/14651858.CD008873.pub2. (Meta-analysis)
 114. Say L, Gulmezoglu AM, Hofmeyr GJ. Bed rest in hospital for suspected impaired fetal growth. *Cochrane Database of Systematic Reviews* 1996, Issue 1. Art. No.: CD000034. DOI: 10.1002/14651858.CD000034. (Meta-analysis)
 115. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010;116:402–14. (Meta-analysis)
 116. Peleg D, Kennedy CM, Hunter SK. Intrauterine growth restriction: identification and management. *Am Fam Physician* 1998;58:453–60, 466–7. (Level III)
 117. Gulmezolu M, de Onis M, Villar J. Effectiveness of interventions to prevent or treat impaired fetal growth. *Obstet Gynecol Surv* 1997;52:139–49. (Level III)
 118. Leitch H, Egarter C, Husslein P, Kaider A, Schemper M. A meta-analysis of low dose aspirin for the prevention of intrauterine growth retardation. *Br J Obstet Gynaecol* 1997;104:450–9. (Meta-analysis)
 119. Bahado-Singh RO, Lynch L, Deren O, Morroti R, Copel JA, Mahoney MJ, et al. First-trimester growth restriction and fetal aneuploidy: the effect of type of aneuploidy and gestational age. *Am J Obstet Gynecol* 1997;176:976–80. (Level II-3)
 120. Sassoon DA, Castro LC, Davis JL, Hobel CJ. Perinatal outcome in triplet versus twin gestations. *Obstet Gynecol* 1990;75:817–20. (Level II-2)
 121. Alexandr JM, Hammond KR, Steinkampf MP. Multifetal reduction of high-order multiple pregnancy: comparison of obstetrical outcome with nonreduced twin gestations. *Fertil Steril* 1995;64:1201–3. (Level III)
 122. Silver R, Helfand BT, Russell TL, Ragin A, Sholl JS, MacGregor SN. Multifetal reduction increases the risk of preterm delivery and fetal growth restriction in twins: a case-control study. *Fertil Steril* 1997;67:30–3. (Level II-2)
 123. Multifetal gestations: twin, triplet, and higher-order multifetal pregnancies. *ACOG Practice Bulletin No. 169*. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2016;128:e131–46. (Level III)

124. Machin A. Velamentous cord insertion in monochorionic twin gestation. An added risk factor. *J Reprod Med* 1997; 42:785–9. (Level III)
125. Divon MY, Chamberlain PF, Sipos L, Manning FA, Platt LD. Identification of the small for gestational age fetus with the use of gestational age-independent indices of fetal growth. *Am J Obstet Gynecol* 1986;155:1197–201. (Level II-3)
126. Mongelli M, Ek S, Tambyrajia R. Screening for fetal growth restriction: a mathematical model of the effect of time interval and ultrasound error. *Obstet Gynecol* 1998; 92:908–12. (Level II-3)
127. Arabin B, Bergmann PL, Saling E. Simultaneous assessment of blood flow velocity waveforms in uteroplacental vessels, the umbilical artery, the fetal aorta and the fetal common carotid artery. *Fetal Ther* 1987;2:17–26. (Level III)
128. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, et al. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. TRUFFLE study group [published erratum appears in *Lancet* 2015;385:2152]. *Lancet* 2015;385:2162–72. (Level I)
129. Veille JC, Kanaan C. Duplex Doppler ultrasonographic evaluation of the fetal renal artery in normal and abnormal fetuses. *Am J Obstet Gynecol* 1989;161:1502–7. (Level III)
130. Gramellini D, Folli MC, Raboni S, Vadora E, Meriardi A. Cerebral-umbilical Doppler ratio as a predictor of adverse perinatal outcome. *Obstet Gynecol* 1992;79:416–20. (Level III)
131. Bahado-Singh RO, Kovanci E, Jeffres A, Oz U, Deren O, Copel J, et al. The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. *Am J Obstet Gynecol* 1999;180:750–6. (Level II-3)
132. A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. GRIT Study Group. *BJOG* 2003;110:27–32. (Level I)
133. Thornton JG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. GRIT study group. *Lancet* 2004;364:513–20. (Level I)
134. Walker DM, Marlow N, Upstone L, Gross H, Hornbuckle J, Vail A, et al. The Growth Restriction Intervention Trial: long-term outcomes in a randomized trial of timing of delivery in fetal growth restriction. *Am J Obstet Gynecol* 2011;204:34.e1–e9. (Level I)
135. Boers KE, Vijgen SM, Bijlenga D, van der Post JA, Bekedam DJ, Kwee A, et al. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). DIGITAT Study Group. *BMJ* 2010;341:c7087. (Level I)
136. Spong CY, Mercer BM, D’Alton M, Kilpatrick S, Blackwell S, Saade G. Timing of indicated late-preterm and early-term birth. *Obstet Gynecol* 2011;118:323–33. (Level III)
137. Medically indicated late-preterm and early-term deliveries. ACOG Committee Opinion No. 818. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2021;137:e29–33. (Level III)
138. Antenatal corticosteroids revisited: repeat courses. NIH Consensus Statement 2000;17:1–18. (Level III)
139. Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD004454. DOI: 10.1002/14651858.CD004454.pub2. (Meta-analysis)
140. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Statement 1994;12:1–24. (Level III)
141. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, et al. Antenatal betamethasone for women at risk for late preterm delivery. NICHD Maternal-Fetal Medicine Units Network. *N Engl J Med* 2016;374:1311–20. (Level I)
142. Antenatal corticosteroid therapy for fetal maturation. Committee Opinion No. 713. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2017;130:e102–9. (Level III)
143. Crowther CA, Verkuyl DA, Neilson JP, Bannerman C, Ashurst HM. The effects of hospitalization for rest on fetal growth, neonatal morbidity and length of gestation in twin pregnancy. *Br J Obstet Gynaecol* 1990;97:872–7. (Level I)
144. Marret S, Marpeau L, Zupan-Simunek V, Eurin D, Leveque C, Hellot MF, et al. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial*. PREMAG Trial Group. *BJOG* 2007;114:310–8. (Level I)
145. Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. Eunice Kennedy Shriver NICHD Maternal–Fetal Medicine Units Network. *N Engl J Med* 2008;359:895–905. (Level I)
146. Magnesium sulfate before anticipated preterm birth for neuroprotection. Committee Opinion No. 455. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2010;115:669–71. (Level III)

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 1985 and March 2018. 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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