

## Fetal growth restriction: Evaluation and management

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**INTRODUCTION** — When ultrasound examination suggests fetal growth restriction (FGR), prenatal care involves confirming the suspected diagnosis, determining the cause and severity of FGR, counseling the parents, closely monitoring fetal growth and well-being, and determining the optimal time for and route of delivery. FGR resulting from intrinsic fetal factors such as aneuploidy, congenital malformations, or infection carries a guarded prognosis that often cannot be improved by any intervention. FGR related to uteroplacental insufficiency has a better prognosis, but the risk for adverse outcome remains increased.

This topic will discuss the evaluation and management of pregnancies complicated by FGR. The diagnosis of FGR and outcome of affected infants are reviewed separately. (See ["Fetal growth restriction: Diagnosis"](#) and ["Infants with fetal \(intrauterine\) growth restriction"](#).)

### INITIAL APPROACH

**Confirm the diagnosis** — The diagnosis of FGR is based on discrepancies between actual and expected sonographic biometric measurements for a given gestational age. Traditionally, it has been defined as <10<sup>th</sup> percentile weight for gestational age and this establishes the diagnosis as being small for gestational age (SGA). In our practice, when a fetus <10<sup>th</sup> percentile weight for gestational age is identified, we monitor fetal growth and fetal physiology over time. A normal growth trajectory, normal Doppler velocimetry of the umbilical artery, and normal amniotic fluid volume suggest a constitutionally small fetus or minimal fetal impact from uteroplacental insufficiency. (See ["Pregnancy management"](#) below.)

A weight <10<sup>th</sup> percentile definition is clinically practical, but it alone does not distinguish the constitutionally small fetus that achieves its normal growth potential and is not at increased risk of adverse outcome from the similarly small fetus whose growth potential is restricted and is at increased risk of perinatal morbidity and mortality. This definition also does not account for the fetus who is not small, but not achieving its growth potential because of intrinsic or environmental restrictions to normal growth. Distinguishing the constitutionally small fetus from the fetus with pathologic growth restriction can help the clinician avoid unnecessary interventions for pregnancies with a constitutionally small fetus and appropriately monitor and time delivery, which may be preterm, of the growth restricted fetus. However, this distinction is difficult to make prenatally. Characteristics that support a diagnosis of a constitutionally small fetus include modest smallness (ie, estimated weight between the 5<sup>th</sup> and 10<sup>th</sup> percentiles), normal growth velocity across gestation, normal physiology (ie, normal amniotic fluid volume and umbilical artery Doppler), abdominal circumference growth velocity above the lowest decile, and appropriate size in terms of maternal characteristics (height, weight, race/ethnicity). For example, when race/ethnicity was taken into account, the 5<sup>th</sup> percentiles for white, Hispanic, black, and Asian women were 2790, 2633, 2622, and 2621 grams, respectively, in a prospective study of 2334 healthy women with low-risk, singleton pregnancies from 12 medical centers in the United States. Using biometric standards derived solely from the group of white fetuses, as many as 15 percent of the non-white fetuses would have been classified as growth-restricted (<5<sup>th</sup> percentile) [1]. It is also important to distinguish normal from aberrant growth when considering dichorionic twin gestations. Growth is similar to that of singleton pregnancies until 32 weeks of gestation, at which point growth velocity patterns differ: abdominal circumference growth velocity in twins slows [2]. (See ["Twin pregnancy: Prenatal issues"](#), section on ["Evaluation of fetal growth and growth discordance"](#).)

Customized growth curves account for nonpathological maternal factors that affect birth weight. This allows interpretation of estimated fetal weight in the context of the individual fetus' growth potential, rather than against a population-based birthweight distribution. Estimated fetal weight is plotted on a customized growth curve that reflects the specific fetus' growth potential based on the mother's height, prepregnancy weight, parity, and ethnicity, all strong contributors to birth weight [3,4]. This approach may more reliably distinguish those fetuses who are truly growth restricted and at increased risk of morbidity and mortality from those who are small but normal [5]. However, routine clinical use of customized growth curves remains controversial as clear evidence of benefit has not been demonstrated and its use has implications on resource allocation. (See ["Fetal growth restriction: Diagnosis"](#), section on ["Customized growth curves"](#).)

Using a lower threshold to define FGR may also help distinguish the small fetus at increased risk of adverse outcome from the small fetus at low risk. As discussed above, FGR has been defined as <10<sup>th</sup> percentile weight for gestational age, even though most fetuses with weights between the 5<sup>th</sup> and 10<sup>th</sup> percentiles are constitutionally small and have normal neonatal outcomes. Use of a lower threshold for defining pathologic FGR is supported by findings of a large, prospective observational trial

(PORTO) that included over 1100 pregnancies with nonanomalous fetuses with estimated fetal weight <10<sup>th</sup> percentile on ultrasound examination [6]. Only 2 percent of fetuses at the 3<sup>rd</sup> to 10<sup>th</sup> percentile (5/254) experienced adverse perinatal outcome, while 6.2 percent of those <3<sup>rd</sup> percentile (51/826) had an adverse outcome and all eight mortalities were in this group. The combination of estimated fetal weight <3<sup>rd</sup> percentile and abnormal umbilical artery Doppler was a strong and consistent predictor of adverse outcome: 16.7 percent of these fetuses developed intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, or death. Abnormal Doppler in this study included both pulsatility index >95<sup>th</sup> centile and absent or reversed end-diastolic flow. An abnormal growth trajectory over time was another factor that predicted perinatal complications (eg, preterm birth, preeclampsia, neonatal morbidity) [7].

**Determine the cause** — The genetically predetermined growth potential of the fetus can be impaired as a result of maternal, placental, or fetal processes (table 1). To determine the cause of FGR, a complete history and physical examination is performed to assess for maternal disorders that have been associated with restricted fetal growth. In addition, obstetrical imaging and laboratory evaluations are performed to look for fetal and placental etiologies. However, the reason(s) for growth impairment cannot always be determined.

- **Fetal survey** – A detailed fetal anatomic survey should be performed in all cases since approximately 10 percent of FGR is accompanied by congenital anomalies [8] and 20 to 60 percent of malformed infants are small for gestational age [9]. Anomalies associated with FGR include omphalocele, diaphragmatic hernia, skeletal dysplasia, and some congenital heart defects.

A fetal echocardiogram is indicated if results of an expert (level II) ultrasound examination suggest any uncertainty that the heart is normal.

- **Fetal genetic studies** – A fetal karyotype/microarray is indicated in any of the following settings because of the increased risk of an abnormality:
  - Early (<24 weeks), severe (<5<sup>th</sup> percentile), symmetrical FGR
  - Major fetal structural abnormalities
  - Ultrasound markers associated with aneuploidy, such as increased nuchal fold and abnormal hand positioning

Ultrasound examination has high sensitivity for identifying trisomy 18, as high as 100 percent, when performed by an experienced ultrasonographer at 19 to 20 weeks of gestation in a fetus with multiple structural anomalies characteristic of the syndrome (see "[Sonographic findings associated with fetal aneuploidy](#)", section on '[Trisomy 18](#)'). If ultrasound examination strongly suggests trisomy 18 (positive predictive value depends on the number and types of ultrasound findings), the author uses a cell free DNA test to screen for trisomy 18. If cell free DNA testing is positive for trisomy 18 in this specific setting, the author does not perform amniocentesis to confirm the diagnosis. In a 2016 meta-analysis, the positive predictive value of cell free DNA for trisomy 18 in a general obstetric population and a high-risk population was 37 and 84 percent, respectively [10] and would be higher when associated with ultrasound findings characteristic of the syndrome. However, a karyotype should be obtained after delivery (or termination) to determine whether the trisomy was the result of a parental balanced translocation, as this will impact the recurrence risk in future pregnancies. If cell free DNA is negative for trisomy 18, the author performs genetic amniocentesis to perform a DNA microarray analysis on amniocytes; microarray has higher diagnostic yield than conventional karyotype [11]. The author uses the same approach if ultrasound examination is strongly suggestive of trisomy 13. (See "[Sonographic findings associated with fetal aneuploidy](#)", section on '[Trisomy 13](#)' and "[Use of chromosomal microarray in obstetrics](#)", section on '[Benefits](#)'.)

In most clinical settings, the combination of positive cell free DNA results and ultrasound findings do not provide sufficient diagnostic certainty to allow omission of fetal karyotype/microarray by genetic amniocentesis if pregnancy termination is planned because of suspected aneuploidy alone. In addition, a negative cell free DNA test does not exclude the possibility of a pathogenic chromosome abnormality not targeted by the test but associated with FGR.

After 24 weeks, we do not screen for fetal genetic abnormalities if anatomy is normal and FGR is asymmetric since the yield would be low, the etiology is most likely a maternal or placental disorder, and pregnancy termination is generally not an option.

Confined placental mosaicism is detected after delivery in approximately 10 percent of placentas associated with otherwise idiopathic FGR. We do not perform chorionic villus sampling in the second or third trimester to identify this abnormality antepartum because antenatal diagnosis would not change pregnancy management and the procedure is associated with a small risk of pregnancy complications. (See "[Chorionic villus sampling](#)", section on '[Confined placental mosaicism](#)'.)

- **Work-up for infection** – When infection is suspected clinically because of maternal history or physical examination or fetal ultrasound findings, maternal serum should be examined for seroconversion. Infections associated with FGR include cytomegalovirus, toxoplasmosis, rubella, and varicella. Amniotic fluid DNA testing can also be performed for specific infections, when indicated by the clinical setting. Sonographic markers for fetal infection are often nonspecific, but include

echogenicity and calcification of the brain and/or liver, and hydrops. (Refer to individual topic reviews on fetal infections during pregnancy).

Malaria in pregnancy can also cause FGR and is reviewed separately. (See "[Overview of malaria in pregnancy](#)".)

Assessment for congenital and acquired thrombophilic disorders is not recommended, as evidence for an association between the inherited thrombophilias and FGR is weak. (See "[Inherited thrombophilias in pregnancy](#)", section on 'Fetal growth restriction'.)

**PREGNANCY MANAGEMENT** — The following discussion applies to pregnancy management of FGR in structurally and chromosomally normal fetuses. Most of these cases are caused by uteroplacental insufficiency. Management of FGR associated with congenital or chromosomal anomalies depends on the specific abnormality, and is beyond the scope of this review.

The optimal approach to management of the pregnancy with suspected growth restriction related to uteroplacental insufficiency has not been established; there is very limited evidence from randomized trials [12]. Serial ultrasound evaluation of (1) fetal growth, (2) fetal behavior (biophysical profile [BPP]), and (3) impedance to blood flow in fetal arterial and venous vessels (Doppler velocimetry) represent the key elements of fetal assessment and guide pregnancy management decisions. The purpose is to identify those fetuses that are at highest risk of in utero demise and neonatal morbidity and thus may benefit from preterm delivery.

The temporal sequence of biophysical changes and Doppler changes in the peripheral and central circulatory systems of the growth restricted fetus are summarized below and in the figure ([figure 1](#)) [13-18]. Progression through the entire sequence does not always occur before delivery; Doppler abnormalities in some growth restricted fetuses progress slowly or not at all or along a different pathway [19]. The sequence is most likely to progress when FGR and Doppler abnormalities are identified in the second trimester and the Doppler indices worsen within the first two weeks of Doppler monitoring [20].

The general sequence of Doppler and biophysical changes in FGR is:

- A reduction in umbilical venous flow is the initial hemodynamic change. Venous flow is redistributed away from the fetal liver and towards the heart. Liver size decreases, causing a lag in fetal abdominal circumference, which is the first biometric sign of fetal growth restriction.
- Umbilical artery Doppler index increases (diminished end diastolic flow) due to increased resistance in the placental vasculature.
- Middle cerebral artery Doppler index decreases (increased end diastolic flow), resulting in preferential perfusion of the brain (brain-sparing effect).
- Increasing placental vascular resistance results in absent and then reversed end diastolic flow in the umbilical artery.
- Middle cerebral artery Doppler index normalizes or abnormally increases as diastolic flow falls due to loss of brain-sparing hemodynamic changes.
- As cardiac performance deteriorates due to chronic hypoxia and nutritional deprivation, absent or reversed end diastolic flow in the ductus venosus and pulsatile umbilical venous flow may develop. These can be preterminal events.

Near the end of this sequence, biophysical changes usually become apparent: The nonstress test becomes nonreactive, the BPP score falls, and late decelerations accompany contractions. However, the cardiovascular (Doppler) and behavioral (BPP) manifestations of fetal deterioration in FGR fetuses can occur largely independent of each other, resulting in discordant Doppler and BPP findings [21].

**Ambulatory monitoring** — Women with pregnancies complicated by FGR may maintain normal activities and are usually monitored as outpatients. There are no data on which to base indications for hospitalization. We and other experts [22] consider hospitalization for selected women who need daily or more frequent maternal or fetal assessment (eg, daily BPP score because of reversed diastolic flow). Hospitalization provides convenient access for daily fetal testing and allows prompt evaluation and intervention in the event of decreased fetal activity or other complications, but there is no evidence that hospitalization improves fetal growth or outcome [23]. Decisions about ambulatory versus in-hospital care should be made on a case-by-case basis.

**Fetal weight assessment** — Fetal weight estimates are calculated using various published equations and formulae. The computed weight is then plotted on a population-based or customized growth curve, which allows the clinician to determine when the estimated fetal weight (EFW) is below the 10<sup>th</sup> percentile ([table 2](#)) and to monitor growth velocity. Persistent growth deficiency in multiple examinations over many weeks strengthens the likelihood of FGR. Conversely, normal growth velocity in a small fetus suggests a constitutionally small but normal fetus.

Serial sonograms are obtained at two- to four-week intervals [24]; the longer end of this range is appropriate for the fetus with mild FGR (eg, EFW near the 10<sup>th</sup> percentile, normal amniotic fluid volume, normal Doppler findings), with a shorter interval for

the fetus with features of moderate or severe disease (eg, EFW  $\leq 5^{\text{th}}$  percentile, oligohydramnios, abnormal Doppler findings). (See "[Prenatal sonographic assessment of fetal weight](#)" and "[Fetal growth restriction: Diagnosis](#)", section on 'Customized growth curves'.)

**Nonstress test and biophysical profile** — Either the nonstress test with amniotic fluid volume determination or the BPP or a combination of both tests is reasonable for monitoring fetal well-being. The value of these tests is based primarily on two lines of evidence: (1) observational studies that reported lower rates of fetal death in pregnancies that underwent fetal testing than among historic controls with the same indication for testing but no fetal testing and (2) the same or lower rates of fetal death in tested pregnancies (primarily high risk) than in a contemporary untested general obstetrical population (primarily low risk). (See "[Nonstress test and contraction stress test](#)" and "[The fetal biophysical profile](#)".)

We prefer the BPP as it evaluates both acute and chronic fetal physiologic parameters, is relatively easy to perform, and fetal death within one week of a normal test score is rare [25]. If the nonstress test is used, amniotic fluid volume assessment should also be performed weekly. Chronic placental insufficiency results in both FGR and oligohydramnios and observational studies have reported that pregnancies complicated by FGR and oligohydramnios have a modestly increased risk of perinatal mortality [26,27]. Conversely, normal amniotic fluid volume is infrequently associated with either FGR or fetal demise, unless the cause is a congenital malformation or aneuploidy. (See "[Oligohydramnios](#)".)

Nonstress tests and BPPs are performed at least weekly. When FGR is associated with oligohydramnios, preeclampsia, decelerating fetal growth, severe growth restriction, increasing umbilical artery Doppler index, or other concerning findings, we increase testing to twice per week (eg, two BPPs, two nonstress tests, or one NST and one BPP). For fetuses with absent or reversed diastolic flow, testing is performed daily because these fetuses can deteriorate rapidly. (See "[Doppler ultrasound of the umbilical artery for fetal surveillance](#)".)

**Doppler velocimetry** — Doppler velocimetry of the umbilical artery is a good tool for fetal assessment in FGR when the etiology is placental dysfunction related to progressive obliteration of the villus vasculature. Placental vascular changes lead to fetal hemodynamic changes that can be evaluated by umbilical artery Doppler. Doppler of the ductus venosus and middle cerebral artery, as well as other fetal vessels, also provide information about fetal hemodynamic status, but the clinical utility of Doppler interrogation of vessels other than the umbilical artery has not been validated.

**Umbilical artery** — Doppler velocimetry of the umbilical artery is the primary surveillance tool for monitoring pregnancies in which FGR is suspected [28]. It has been well established by numerous randomized trials that monitoring umbilical artery Doppler can significantly reduce perinatal death, as well as unnecessary induction of labor in the preterm growth restricted fetus. A 2013 systematic review of 18 trials comparing the use of Doppler with no Doppler in high-risk pregnancies showed a 29 percent reduction in perinatal deaths (odds ratio [OR] 0.71, 95% CI 0.52-0.98; 1.2 versus 1.7 percent; number needed to treat 203), and significantly fewer labor inductions and cesarean deliveries [29].

Normal diastolic flow is infrequently associated with significant perinatal morbidity or mortality and is strong evidence of fetal well-being, thus this finding provides support for delaying delivery when it is important to achieve further fetal maturity. In the Prospective Observational Trial to Optimize Pediatric Health (PORTO), growth restricted fetuses with normal umbilical artery Doppler had lower perinatal mortality than those with abnormal Doppler (2/698 [0.3 percent] versus 6/418 [1.4 percent]) and a lower rate of overall adverse outcome (9/698 [1.3 percent] versus 48/418 [11.5 percent]) [30]. Abnormal Doppler was defined as a pulsatility index  $>95^{\text{th}}$  centile or absent/reversed end-diastolic flow.

When 30 percent of the villous vasculature ceases to function, an increase in umbilical artery resistance leading to reduced end diastolic flow is consistently seen [31] and is a weak predictor of adverse outcome [32]. When 60 to 70 percent of the villous vasculature is obliterated, umbilical artery diastolic flow is absent or reversed and fetal prognosis is poor [31]. Reversed diastolic flow is associated with poorer neonatal outcomes than absent diastolic flow. As an example, a study that evaluated neonatal/perinatal mortality in 143 FGR pregnancies with either reversed or absent umbilical artery flow reported mortality was over fivefold higher with reversed flow [33]. (See "[Doppler ultrasound of the umbilical artery for fetal surveillance](#)".)

We perform weekly Doppler velocimetry of the umbilical artery upon diagnosis of FGR. If consecutive Doppler results are normal, we decrease the frequency of Doppler examination to two-week intervals. The two-week interval is reasonable for the fetus with estimated fetal weight  $\geq 5^{\text{th}}$  percentile, progressive growth, normal amniotic fluid volume, and no maternal risk factors for placental dysfunction. The Society for Maternal-Fetal Medicine suggests umbilical artery Doppler studies every one to two weeks initially, and if normal, the interval between examinations can be lengthened [28].

If umbilical artery diastolic flow is present but decreased (pulsatility index  $>95^{\text{th}}$  percentile), we perform weekly Doppler evaluation to look for progression to absent or reversed flow. Absent or reversed end diastolic flow in the umbilical artery can be a sign of impending fetal cardiovascular and metabolic deterioration. If either of these abnormal patterns is identified, delivery should be considered (see '[Our approach](#)' below). The decision to deliver in this setting is based on gestational age as long as daily nonstress or BPP testing is normal. The absence of abnormal flow patterns in the ductus venosus has been used to support the decision to extend such a pregnancy, and may enable the pregnancy to be prolonged for as long as two weeks; however, clinical use of this test is controversial [28].

An [online calculator](#) is available for determining gestational age-based reference ranges for umbilical artery pulsatility index >95<sup>th</sup> percentile.

**Ductus venosus** — Doppler interrogation of the ductus venosus provides information about the hemodynamic status of the fetus, but there is no convincing evidence that this information is useful for guiding clinical decisions about timing of delivery.

Flow in the venous circulation is forward and uniform in normal fetuses. Changes in the venous circulation in the growth restricted fetus, including absent or reversed flow in the ductus venosus (absent or reversed a wave) or pulsatile umbilical venous flow, are late findings, generally occurring about two weeks after changes are observed in the arterial circulation. With progressively increasing umbilical arterial resistance, fetal cardiac performance can become impaired and central venous pressure increases, resulting in reduced diastolic flow in the ductus venosus and other large veins. Vasodilatation of the ductus venosus further diverts nutrient and oxygen rich blood to the heart but enhances retrograde transmission of atrial pressure. The ductus venosus resistance index increases, ultimately with loss of the a wave. An absent or reversed ductus venosus a-wave indicates cardiovascular instability and can be a sign of impending acidemia and death [34,35]. Although overall sensitivity and specificity for fetal pH <7.20 are only 65 and 95 percent, respectively [34], the duration of the absent or reversed ductus venosus a-wave needs to be taken into account and appears to impact outcome independently of gestational age. Each day of this Doppler abnormality doubles the odds of stillbirth, and fetal survival for more than one week is unlikely [35].

Although the use of venous Doppler interrogation remains largely investigational [36,37], an increasing number of maternal-fetal medicine specialists are using this tool to avoid very preterm delivery in fetuses with absent or reversed end-diastolic arterial flow in the umbilical artery and reassuring antepartum fetal testing (nonstress test, BPP). In these pregnancies, the absence of abnormal flow patterns in the ductus venosus has been used to support the decision to extend the pregnancy to 32 to 34 weeks, if the nonstress test and BPP remain reassuring. As noted below (see '[Timing delivery](#)' below), the Trial of Umbilical and Fetal Flow in Europe (TRUFFLE) demonstrated no immediate neonatal benefit from delaying delivery until ductus venosus monitoring showed significant abnormalities (absent or reversed flow), and only a possible marginal benefit in neurodevelopment at two years of age [38].

**Middle cerebral artery** — Doppler interrogation of the middle cerebral artery (MCA) also provides information about the hemodynamic status of the fetus. The fetal brain in uncomplicated pregnancies has a high resistance circulation. With progressive hypoxia, blood flow increases to compensate for the decrease in available oxygen (brain-sparing effect). This results in a reduction in the Doppler parameters used to assess blood flow through the MCA: the peak systolic to end diastolic blood flow velocity ratio (S/D), resistance index, and pulsatility index [13-15,39-41]. Subsequent normalization of the indices may occur when the autoregulatory response becomes dysfunctional [42].

There is no convincing evidence that interrogation of the MCA Doppler alone is useful in guiding clinical decisions about timing of delivery, although MCA Doppler alterations may be useful as an adjunct to umbilical artery Doppler interrogation for assessing the severity of hypoxia and predicting neonatal outcome.

**Cerebroplacental ratio** — The cerebroplacental Doppler ratio (CPR) is the MCA pulsatility index (or resistance index) divided by the umbilical artery pulsatility index (or resistance index). A low CPR indicates fetal blood flow redistribution (brain sparing) and is predictive of adverse neonatal outcome [43]. In the PORTO trial [30], the rate of serious adverse neonatal outcome with low CPR (<1) was 18 percent (27/146) versus 2 percent (14/735) when CPR was higher [44]. Adverse outcome was a composite of intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and death.

CPR was most useful for predicting adverse neonatal outcome when the umbilical artery Doppler pulsatility index was >95<sup>th</sup> centile. The additional finding of an abnormal CPR in these cases improved the prediction of an adverse neonatal outcome to a level similar to that found with absent or reversed umbilical artery end diastolic flow.

In other studies, an abnormal CPR has been associated with abnormal fetal growth velocity [45], an increased risk for neonatal intensive care unit admission, and urgent cesarean delivery for fetal distress after 37 weeks, independent of fetal weight [46,47].

CPR may be of value for more accurately predicting risk of adverse outcome in FGR when used as an adjunct to the umbilical artery Doppler. However, the most appropriate threshold CPR value for predicting adverse outcome, the significance of normalization of previously abnormal CPR, and the potential role of CPR in management of pregnancies complicated by FGR in late pregnancy require additional study before this ratio can be recommended for routine clinical use in FGR pregnancies.

**Antenatal steroids** — Ideally, one course of antenatal corticosteroids is given between 24 and 34 weeks of gestation in the week before delivery is expected. Timing is estimated based on multiple factors, including the severity of FGR, Doppler findings, comorbid conditions, and rate of deterioration in fetal status. (See "[Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery](#)".)

The efficacy of antenatal steroids for reducing neonatal morbidity and mortality in the preterm growth restricted neonate remains controversial, with two large studies showing conflicting results [48,49]. Until definitive information is available, a



course of antenatal steroids should be administered as multiple series have found that both spontaneous and indicated preterm deliveries are more common in growth-restricted fetuses [50-52].

Three studies observed that growth restricted fetuses with absent end diastolic flow often show transient improvement in blood flow after glucocorticoid administration [53-55]. Fetuses that did not show increased end diastolic flow appeared to have poorer neonatal outcomes. The reason sicker fetuses are unable to mount a vascular response to glucocorticoid administration is unclear. One action of glucocorticoids is to enhance the tropic effect of catecholamines on heart muscle. It is hypothesized that inotropy does not improve in sicker fetuses because they have impaired cardiac wall compliance.

**Maternal interventions** — There is no convincing evidence that any intervention in healthy women improves the growth of growth restricted fetuses. Numerous approaches have been tried in small randomized trials, including maternal nutritional supplementation, oxygen therapy, and interventions to improve blood flow to the placenta, such as plasma volume expansion, low-dose [aspirin](#), bed rest, and [sildenafil](#) [23,56-60].

Antihypertensive therapy of hypertensive gravidas does not improve fetal growth [61].

In smokers, an intensive smoking cessation program may be of value and has other pregnancy and health benefits [62,63]. (See "[Cigarette smoking: Impact on pregnancy and the neonate](#)".)

**Timing delivery** — There is little consensus about the optimum time to deliver the growth restricted fetus [64]. The following key trials attempted to answer the question of when to intervene in these pregnancies, without a clear conclusion:

- The **Growth Restriction Intervention Trial** randomly assigned pregnant women between 24 and 36 weeks with FGR to immediate (n = 296) or delayed (n = 291) delivery if their obstetrician was uncertain about when to intervene [64]. Forty percent of these pregnancies had absent or reversed end diastolic umbilical artery flow. In the delayed delivery group, delivery occurred when the obstetrician was no longer uncertain about intervening, which took a median 4.9 days.

The immediate delivery group had fewer stillbirths (2 versus 9 with delayed delivery) but more neonatal and infant deaths (27 versus 18), especially when randomization occurred before 31 weeks. Follow-up data up to age 13 years showed no differences between groups in cognition, language, motor, or parent-assessed behavior scores on standardized tests; follow-up was achieved in approximately 70 percent of survivors [65,66]. Cognition scores were close to the standardized normal range.

These data suggest that delaying delivery of the very preterm growth restricted fetus in the setting of uncertainty results in some stillbirths, but immediate delivery produces an almost equal number of neonatal deaths, and neither approach results in better long-term neurodevelopmental outcome. Although widely cited, these studies are difficult to evaluate due to the lack of standard criteria for intervention.

- The **Disproportionate Intrauterine Growth Intervention Trial At Term** trial (DIGITAT) randomly assigned 650 pregnant women over 36.0 weeks of gestation with suspected FGR to induction of labor or expectant monitoring [67-69]. The primary outcome was a composite measure of adverse neonatal outcome (death before hospital discharge, five-minute Apgar score <7, umbilical artery pH <7.05, or admission to the intensive care unit) [67]. Neonatal morbidity was analyzed separately using Morbidity Assessment Index for Newborns (MAIN) score [68].

The induction group delivered 10 days earlier and weighed 130 g less (mean difference -130 g, 95% CI -188 g to -71 g) than the expectantly managed group, but had statistically similar composite adverse outcome (6.1 versus 5.3 percent with expectant management) and cesarean delivery rates (about 14 percent) [67]. MAIN scores were also similar for both groups; the only significant difference was a higher proportion of hyperbilirubinemia in the induction group (10.4 versus 5.7 percent) [68]. In addition, developmental and behavioral outcomes at two years of age were similar for both groups [69]. The authors concluded that both approaches were reasonable, and the choice should depend on patient preference.

- The **TRUFFLE** randomized trial assessed whether changes in the fetal ductus venosus Doppler waveform could be used to guide timing of delivery of growth restricted fetuses with a high umbilical artery Doppler pulsatility index (>95<sup>th</sup> percentile) instead of the conventional approach using cardiotocography short-term variation (STV) [38]. The primary outcome measure was survival without neurodevelopmental impairment at two years of age. Pregnancies were randomly assigned to one of three monitoring approaches: cardiotocography with delivery for reduced STV, ductus venosus monitoring with delivery for early ductus venosus changes (pulsatility index >95<sup>th</sup> percentile), or ductus venosus monitoring with delivery for late ductus venosus changes (a wave indicating absent or reversed flow). The proportion of infants surviving without neurodevelopmental impairment was 77 to 85 percent, with no significant differences among the three groups. Among survivors, delaying delivery until the development of late ductus venosus changes resulted in an improvement in survival without neurodevelopmental impairment (95 percent versus 91 percent for the early ductus venosus changes group and 85 percent in the reduced STV group); however, this came at the cost of a small increase in unexpected fetal demise (0/166 in the STV group versus 3/167 in the early ductal changes group versus 4/170 in the late ductal changes group). There were no differences in immediate neonatal composite morbidity or mortality.

These findings do not support a change in clinical practice, given that the improvement in neurodevelopment was offset, in part, by an increase in fetal demise. Moreover, the number of neurodevelopmentally impaired children in each group was small (7 in the late ductal changes group, 12 in the early changes group, and 20 in the STV group); thus a larger trial may have resulted in a different outcome. Lastly, it is not clear that the investigators adjusted neurodevelopmental outcome scores for the mother's educational level.

**Our approach** — We time the delivery of the growth restricted fetus based on a combination of factors, including: gestational age, Doppler ultrasound of the umbilical artery, BPP score (or nonstress test), and the presence or absence of risk factors for, or signs of, uteroplacental insufficiency. The goal is to maximize fetal maturity and growth while minimizing the risks of fetal or neonatal mortality and short-term and long-term morbidity.

Reversed diastolic flow in the umbilical artery is a strong precursor of fetal demise (see '[Umbilical artery](#)' above). We deliver fetuses  $\geq 32$  weeks of gestation with reversed diastolic flow. Morbidity and mortality related to preterm delivery is relatively high before 32 weeks of gestation [[70,71](#)], between 26 and 29 weeks of gestation, each day in utero has been estimated to improve survival by 1 to 2 percent [[72](#)]. Therefore, before 32 weeks, we perform daily fetal monitoring using a BPP score in an attempt to delay delivery until 32 weeks or until the BPP score becomes abnormal. (See '[Nonstress test and biophysical profile](#)' above.)

Absent diastolic flow in the umbilical artery is also predictive of fetal death, but the risk is less imminent than with reversed diastolic flow. We deliver fetuses  $\geq 34$  weeks of gestation with absent diastolic flow. Before 34 weeks, we perform daily fetal monitoring using a BPP score in an attempt to delay delivery until 34 weeks or until the BPP score becomes abnormal.

Decreased diastolic flow (pulsatility index  $>95^{\text{th}}$  percentile) in the umbilical artery is a weak predictor of fetal death. We perform a BPP twice per week and deliver these fetuses at term or when the BPP score becomes abnormal. Delivery at 37 to 38 weeks is reasonable if umbilical artery flow is decreased and risk factors for, or signs of, uteroplacental insufficiency are present, such as oligohydramnios, preeclampsia or hypertension, renal insufficiency, fetal growth arrest, estimated weight  $<5^{\text{th}}$  percentile, or prior birth of a small for gestational age infant.

Normal umbilical artery Doppler provides strong evidence of fetal well-being, especially in the absence of risk factors for, or signs of, uteroplacental insufficiency. We deliver these fetuses at 39 to 40 weeks of gestation.

Delivery should not be delayed beyond 40 weeks of gestation. The risk of intrauterine fetal demise significantly increases at term, particularly as the severity of FGR increases. As an example, in a retrospective cohort study, the risk of intrauterine fetal death at 39 weeks was estimated as 32 per 10,000 ongoing pregnancies for fetal weight  $<3^{\text{rd}}$  percentile, 23 per 10,000 ongoing pregnancies for fetal weight  $<5^{\text{th}}$  percentile, 13 per 10,000 ongoing pregnancies for fetal weight  $<10^{\text{th}}$  percentile, and 2 per 10,000 ongoing pregnancies for fetal weight  $\geq 10^{\text{th}}$  percentile [[73](#)].

An unfavorable cervix is not a reason to avoid induction. In a secondary analysis of data from the DIGITAT and HYPITAT trials (pregnancies complicated by FGR and hypertension), induction of labor at term in women with median Bishop scores of 3 (range 1 to 6) was not associated with a higher rate of cesarean delivery than expectant management and approximately 85 percent of women in both groups achieved a vaginal delivery [[74](#)]. Prostaglandins or a balloon catheter was used for cervical ripening.

**INTRAPARTUM MANAGEMENT** — Growth restricted fetuses may exist in a state of mild-to-moderate chronic oxygen and substrate deprivation. Potential consequences include antepartum or intrapartum fetal heart rate abnormalities, passage of meconium with risk of aspiration, and neonatal polycythemia, impaired thermoregulation, hypoglycemia, and other metabolic abnormalities (see '[Infants with fetal \(intrauterine\) growth restriction](#)', section on '[Outcomes](#)'). Consequently, it is important to optimize the timing of delivery (see '[Our approach](#)' above), perform continuous intrapartum fetal monitoring to detect nonreassuring fetal heart rate patterns suggestive of progressive hypoxia during labor, and provide skilled neonatal care in the delivery room [[75](#)]. Umbilical cord blood analysis should be considered as a component of establishing baseline neonatal status. (See '[Umbilical cord blood acid-base analysis at delivery](#)', section on '[Indications for fetal acid-base analysis](#)'.)

The risk of fetal heart rate abnormalities related to hypoxia is highest among fetuses with abnormal Doppler velocimetry. In one large series, no fetus with normal Doppler velocimetry was delivered with metabolic acidemia associated with chronic hypoxemia [[76](#)]. Compared with growth restricted fetuses with normal umbilical artery Doppler ratios, growth restricted fetuses with a systolic/diastolic ratio  $>90^{\text{th}}$  percentile for gestational age had significantly lower umbilical artery and vein pH values at birth (artery 7.23  $\pm$  0.08 versus 7.25  $\pm$  0.1; vein, 7.31  $\pm$  0.01 versus 7.34  $\pm$  0.09), an increased likelihood of nonreassuring fetal heart rate patterns (26 versus 9 percent), more admissions to the neonatal intensive care unit (41 versus 31 percent), and a higher incidence of respiratory distress (66 versus 27 percent).

If antenatal testing (nonstress test or biophysical profile) is normal, a trial of labor with continuous intrapartum monitoring is reasonable [[77,78](#)]. However, the frequency of cesarean delivery for nonreassuring fetal heart rate tracing is increased, given the increased prevalence of chronic hypoxia and oligohydramnios among these fetuses.

For fetuses less than 32 weeks of gestation, [magnesium sulfate](#) is given before delivery for neuroprotection. (See '[Neuroprotective effects of in utero exposure to magnesium sulfate](#)'.)

## PROGNOSIS

**Perinatal** — Stillbirth, neonatal death, neonatal morbidity, and abnormal neurodevelopmental outcome are more common in growth restricted fetuses than in those with normal growth ([figure 2](#)). (See "[Infants with fetal \(intrauterine\) growth restriction](#)".)

An association has been observed between poor fetal growth, early accelerated postnatal growth, and later development of obesity, metabolic dysfunction, insulin sensitivity, type 2 diabetes, and cardiovascular and renal disorders. This association has been attributed to partial resetting of fetal metabolic homeostasis and endocrine systems in response to in utero nutritional deprivation. (See "[Infants with fetal \(intrauterine\) growth restriction](#)", [section on 'Adult chronic disorders'](#).)

**Maternal** — The birth of a newborn with idiopathic growth restriction may be predictive of an increased long-term maternal risk of ischemic heart disease. A population-based study that linked discharge data from singleton first births in Scotland between 1981 and 1985 to the mothers' hospital admissions and deaths over the next 15 to 19 years observed the maternal risk of ischemic heart disease admission or death was associated with delivering a newborn in the lowest birthweight quintile for gestational age (adjusted hazard ratio 1.9, 95% CI 1.5-2.4) [[79](#)]. The combination of growth restriction, preterm birth, and preeclampsia increased the risk of ischemic heart disease admission or death sevenfold.

**RECURRENCE RISK** — There is a tendency to repeat small for gestational age (SGA) deliveries in successive pregnancies [[80-83](#)]. As an example, a prospective national cohort study from the Netherlands reported that the risk of a non-anomalous SGA birth (<5<sup>th</sup> percentile) in the second pregnancy of women whose first delivery was "SGA" versus "not SGA" was 23 and 3 percent, respectively [[81](#)].

Furthermore, uteroplacental insufficiency may manifest in different ways in different pregnancies. Growth restriction, preterm delivery, preeclampsia, abruption, and stillbirth can all be sequelae of impaired placental function. The association between the birth of a SGA infant in a first pregnancy and stillbirth in a subsequent pregnancy was illustrated by analysis of data from the Swedish Birth Register ([table 3](#)) [[84](#)]; subsequent studies from the United States and Australia reported similar findings [[85,86](#)]. The highest risk of stillbirth was in women who delivered a preterm SGA infant. Another series suggested a sibling delivered after the birth of a SGA infant (even if mildly SGA) was at increased risk of sudden infant death syndrome [[87](#)].

**Prevention in subsequent pregnancies** — In subsequent pregnancies, we address any potentially treatable causes of FGR (eg, cessation of smoking and alcohol intake, chemoprophylaxis and mosquito avoidance in areas where malaria is prevalent, balanced energy/protein supplementation in women with significant nutritional deficiencies) (see individual topic reviews). Avoiding a short or long interpregnancy interval may also be beneficial. (See "[Interpregnancy interval and obstetrical complications](#)".)

Although some randomized trials reported that low-dose [aspirin](#) prophylaxis during pregnancy reduced the risk of recurrent FGR in women at high risk (eg, FGR in a previous pregnancy) [[88,89](#)], larger randomized trials did not confirm significant risk reduction [[90](#)]. However, aspirin may be effective when FGR is secondary to preeclampsia since aspirin appears to reduce the risk of developing preeclampsia in women at moderate to high risk of developing the disorder. These data are reviewed separately. (See "[Preeclampsia: Prevention](#)", [section on 'Antiplatelet agents'](#).)

Whether anticoagulation with [unfractionated heparin](#) or low-molecular weight heparin reduces the risk of recurrent placenta-mediated late pregnancy complications, such as growth restriction, is unclear. In a 2016 meta-analysis using individual patient data from eight randomized trials of low-molecular-weight heparin (LMWH) therapy versus no LMWH for women with any prior placenta-mediated pregnancy complications, the intervention did not significantly reduce the incidence of the primary composite outcome (early-onset or severe preeclampsia, small for gestation age infant [SGA] <5<sup>th</sup> percentile, abruption, pregnancy loss  $\geq 20$  weeks of gestation): 62/444 (14 percent) versus 95/443 (22 percent), relative risk 0.64, 95% CI 0.36-1.11 [[91](#)]. These data support avoidance of anticoagulation in women with previous placenta-mediated disease, given the lack of clear benefit and potential risks of anticoagulation, cost, and inconvenience. However, additional study is warranted to specifically address risk of SGA recurrence in women with previous SGA treated with/without LMWH, as well as deficiencies in existing data, such as differences in LMWH treatment protocols (dose, initiation/duration of treatment, concurrent use of [aspirin](#)).

Dietary changes and supplements, antihypertensive therapy of hypertensive women, beta-mimetics, and bedrest do not prevent FGR [[23,61,92,93](#)].

**Management of subsequent pregnancies** — Accurate dating by early ultrasonography is important to establish gestational age and intermittent ultrasound examinations are used to monitor fetal growth. Otherwise, prenatal management is routine. If fetal growth is normal, FGR in a previous pregnancy is not an indication for antepartum fetal surveillance with nonstress tests, biophysical profiles, or umbilical artery Doppler velocimetry [[94](#)].

## SELECTED GUIDELINES

- [American College of Obstetricians and Gynecologists](#) (members only)
- [Royal College of Obstetricians and Gynaecologists](#)
- [American College of Radiology](#)
- French College of Gynaecologists and Obstetricians [[95](#)]



**SUMMARY AND RECOMMENDATIONS** — Evaluation and management of suspected fetal growth restriction (FGR) involves accurate determination of gestational age, confirming the diagnosis, determining the reason the fetus is small, distinguishing between the constitutionally small and the growth restricted fetus, monitoring the fetal growth trajectory, managing maternal comorbidities, and serial assessment of fetal well-being, with preterm delivery, when indicated.

### Initial approach

- An estimated fetal weight <10<sup>th</sup> percentile signifies a small for gestational age fetus. It is then the clinician's task to distinguish between the constitutionally small fetus that achieves its normal growth potential and is not at increased risk of adverse outcome from the similarly small fetus whose growth potential is restricted and is at increased risk of perinatal morbidity and mortality (ie, FGR). (See ['Confirm the diagnosis'](#) above.)
- We perform a detailed fetal anatomic survey in all cases of fetal growth restriction since major congenital anomalies are frequently associated with failure to maintain normal fetal growth. (See ['Determine the cause'](#) above.)
- Evaluation of the fetal karyotype/microarray is indicated if FGR is associated with structural anomalies, ultrasound markers of aneuploidy, or early severe FGR (<5<sup>th</sup> percentile before 24 weeks of gestation). (See ['Determine the cause'](#) above.)
- Maternal serum is examined for seroconversion if FGR is associated with maternal history or fetal ultrasound findings suggestive of infection, most commonly cytomegalovirus or toxoplasmosis. (See ['Determine the cause'](#) above.)

### Antepartum management

- Serial ultrasound evaluation of (1) fetal growth, (2) fetal behavior (biophysical profile or nonstress test), and (3) impedance to blood flow in fetal vessels (Doppler velocimetry) represent the key elements of fetal assessment and guide pregnancy management decisions. The purpose is to identify those fetuses that are at highest risk of in utero demise and neonatal morbidity and thus may benefit from preterm delivery. The frequency is based upon the severity of findings and whether the examinations are being done to monitor fetal well-being (one to seven times per week) or fetal growth (every two to four weeks). (See ['Fetal weight assessment'](#) above and ['Nonstress test and biophysical profile'](#) above and ['Umbilical artery'](#) above.)
- We recommend Doppler velocimetry of the umbilical artery for monitoring pregnancies with suspected growth restriction ([Grade 1A](#)). Delivery prompted by abnormal Doppler ultrasonography reduces the frequency of perinatal death. Normal Doppler findings are reassuring and thus potentially allow prolongation of pregnancy and reduction in the number of unnecessary preterm deliveries. Doppler assessment of the venous circulation may provide additional information for decision making in the very preterm fetus, but remains investigational. (See ['Doppler velocimetry'](#) above.)
- We recommend one course of antenatal corticosteroids between 24 and 34 weeks of gestation in the week before delivery is expected ([Grade 1A](#)). Earlier administration is indicated if delivery and aggressive neonatal intervention are planned (see ["Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery"](#)). Timing is estimated based on multiple factors, including the severity of FGR, Doppler findings, comorbid conditions, and rate of deterioration in fetal status. (See ['Antenatal steroids'](#) above.)

### Delivery

- We time the delivery of the growth restricted fetus based on a combination of factors, including: gestational age, Doppler ultrasound of the umbilical artery, biophysical profile score (or nonstress test), and the presence or absence of risk factors for, or signs of, uteroplacental insufficiency. The goal is to maximize fetal maturity and growth while minimizing the risks of fetal or neonatal mortality and short-term and long-term morbidity. For pregnancies with FGR and normal biophysical profile scores or nonstress tests (see ['Our approach'](#) above):
  - We deliver fetuses with reversed diastolic flow at ≥32 weeks of gestation.
  - We deliver fetuses with absent diastolic flow at ≥34 weeks of gestation.
  - We deliver fetuses with decreased diastolic flow (pulsatility index >95<sup>th</sup> percentile) at term. Early term delivery (37 to 38 weeks) is reasonable if risk factors for, or signs of, uteroplacental insufficiency are present, such as oligohydramnios, preeclampsia or hypertension, renal insufficiency, fetal growth arrest, estimated weight <5<sup>th</sup> percentile, or prior birth of a small for gestational age infant.
  - We deliver fetuses with normal umbilical artery Doppler at 39 to 40 weeks of gestation.

### Recurrence

- There is a tendency to repeat small for gestational age or low birth weight deliveries in successive pregnancies. Growth restriction, preterm delivery, preeclampsia, abruption, and stillbirth can all be sequelae of impaired placental function that may manifest in different ways in different pregnancies. (See ['Recurrence risk'](#) above.)

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## GRAPHICS

### Causes of and risk factors for fetal growth restriction

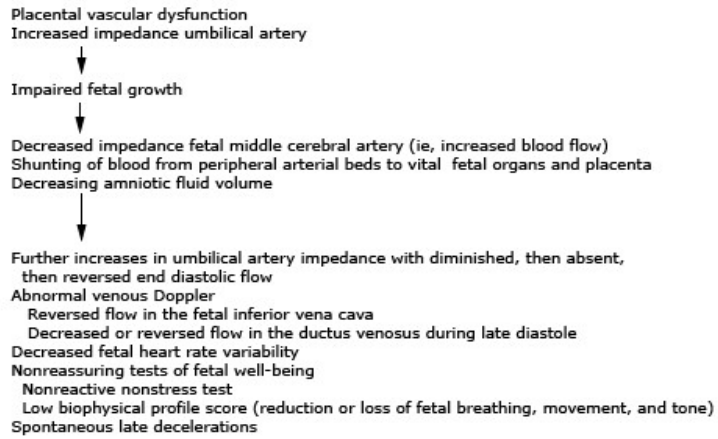
Causes of and risk factors for fetal growth restriction (FGR)	Comments
Fetal genetic abnormalities	Account for 5 to 20% of FGR. Genetic abnormalities include: aneuploidy (including triploidy), uniparental disomy, single gene mutations (eg, <i>IGF1</i> , <i>IGF2</i> , <i>IGF1R</i> ), partial deletions or duplications, ring chromosome, and aberrant genomic imprinting. The finding of symmetric FGR prior to 20 weeks of gestation suggests aneuploidy as the cause, most commonly trisomy 18. Syndromes to consider include Russell-Silver, which is characterized by asymmetric growth impairment (head size is normal) and Smith-Lemli-Opitz, which is characterized by small head size and multiple extracranial anomalies.
Fetal infection	Account for 5 to 10% of FGR. Cytomegalovirus (CMV) and toxoplasmosis are the most common infectious etiologies of FGR in developed countries. Other viruses and parasites that may cause FGR include rubella, varicella-zoster, malaria, syphilis, and herpes simplex. Malaria is a common infectious cause of FGR where the infection is endemic.
Fetal structural anomaly	Fetuses with congenital anomalies can have impaired growth, which is often related to coexistent cytogenetic disorders. The frequency of FGR is related to both the type and number of anomalies.
Multiple gestation	Fetal growth in multiple gestations is directly related to the number of fetuses. The lower weight of fetuses from multiple gestations is thought to be due to an inability of the environment to meet the nutritional needs of multiple fetuses and to pregnancy complications more common in multiple gestations (eg, preeclampsia, twin-to-twin transfusion). Placental and umbilical cord anomalies potentially associated with underperfusion are also more common in multiple gestations (eg, velamentous cord insertion).
Confined placental mosaicism	Confined placental mosaicism (CPM) refers to chromosomal mosaicism in the placenta, but not in the fetus. It usually involves a trisomy and is strongly associated with FGR. CPM has been identified after birth in approximately 10% of otherwise idiopathic FGR and in one-third of FGR associated with placental infarction and decidual vasculopathy. By comparison, the rate of CPM in placentas of women undergoing chorionic villus sampling (CVS) is about 1%.  The severity of FGR associated with CPM depends upon the chromosomes involved, the proportion of mosaic cells, and the presence of uniparental disomy.
Ischemic placental disease	Ischemic placental disease can manifest clinically as FGR, preeclampsia, abruptio placenta, or a combination of these disorders, and is often recurrent.
Gross cord and placental abnormalities	Gross cord and placental structural anomalies possibly associated with FGR include single umbilical artery, velamentous umbilical cord insertion, marginal cord insertion, bilobate placenta, circumvallate placenta, and placental hemangioma. If an association between these entities and FGR exists, it is at most weak.  Placental mesenchymal dysplasia is a rare placental abnormality characterised by placentomegaly and grape-like vesicles resembling a partial mole. The euploid fetus is at increased risk for intrauterine growth restriction, perinatal death, and Beckwith-Wiedemann syndrome.
Maternal genetic factors	In epidemiologic studies, women who were growth-restricted at birth have a twofold increase in risk of FGR in their offspring. In addition, women who give birth to a growth restricted fetus are at high risk of recurrence, and the risk increases with increasing numbers of FGR deliveries.
Maternal medical and obstetrical conditions	Maternal conditions that can be associated with diminished utero-placental-fetal blood flow and/or oxygen delivery have been associated with FGR. These conditions include, but are not limited to: <ul style="list-style-type: none"> <li>▪ Preeclampsia</li> <li>▪ Abruptio placenta</li> <li>▪ Chronic hypertension</li> <li>▪ Chronic kidney disease</li> <li>▪ Pregestational diabetes mellitus</li> <li>▪ Systemic lupus erythematosus and antiphospholipid syndrome</li> <li>▪ Cyanotic heart disease</li> <li>▪ Chronic pulmonary disease</li> <li>▪ Severe chronic anemia</li> <li>▪ Sickle cell disease</li> <li>▪ Uterine malformations</li> <li>▪ Misuse of alcohol, cigarettes, and/or drugs (eg, heroin, cocaine)</li> <li>▪ Prepregnancy radiation therapy to the pelvis</li> </ul>
Teratogens and other environmental factors	Exposures to various teratogens, including medications such as warfarin, anticonvulsants (eg, valproic acid), antineoplastic agents, and folic acid antagonists, can cause FGR with specific dysmorphic features. Exposure to alcohol, tobacco, and air pollution can also impair fetal

	growth. Exposure to therapeutic, but not diagnostic, doses of radiation can cause permanent restriction of growth.
Assisted reproductive technologies	Singleton pregnancies conceived via assisted reproductive technologies have a higher prevalence of small for gestational age infants compared with naturally conceived pregnancies.
Low prepregnancy weight, poor gestational weight gain, malabsorption, poor nutritional status	Maternal weight at birth, prepregnancy weight, and gestational weight gain can affect the risk of FGR as these factors are responsible for about 10% of the variance in fetal weight. Macro- and micronutrients in the maternal diet also appear to play a role.
Residing at high altitude	A direct relationship between increasing altitude and lower birth weight has been demonstrated in studies performed in Denver and Leadville, Colorado (altitude 1600 and 3100 m, respectively), Tibet (altitude 3658 m), and Peru. Birth weight data from 15 areas in Peru located between sea level and 4575 m showed birth weight declined an average of 65 g for every additional 500 m in altitude above 2000 m.
Short interpregnancy interval	
Extremes of maternal age	

Graphic 99966 Version 4.0

## Progression of fetal growth restriction

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## Birth weight percentiles by gestational age

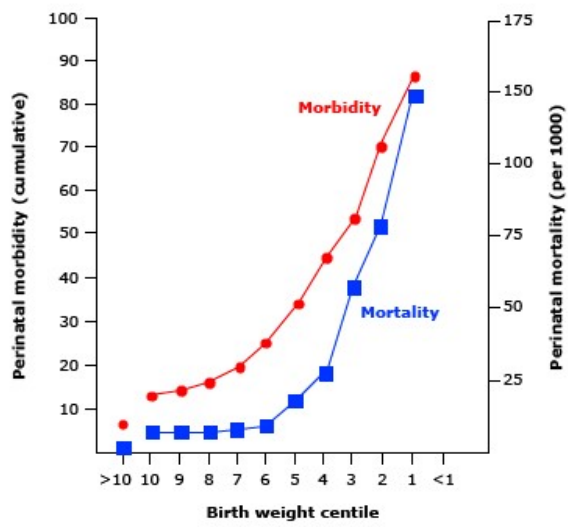
Week of gestation	5 <sup>th</sup> percentile	10 <sup>th</sup> percentile	50 <sup>th</sup> percentile	90 <sup>th</sup> percentile	95 <sup>th</sup> percentile
24	539	567	680	850	988
25	540	584	765	938	997
26	580	637	872	1080	1180
27	650	719	997	1260	1467
28	740	822	1138	1462	1787
29	841	939	1290	1672	2070
30	952	1068	1455	1883	2294
31	1080	1214	1635	2101	2483
32	1232	1380	1833	2331	2664
33	1414	1573	2053	2579	2861
34	1632	1793	2296	2846	3093
35	1871	2030	2549	3119	3345
36	2117	2270	2797	3380	3594
37	2353	2500	3025	3612	3818
38	2564	2706	3219	3799	3995
39	2737	2877	3374	3941	4125
40	2863	3005	3499	4057	4232
41	2934	3082	3600	4167	4340
42	2941	3099	3686	4290	4474

Table constructed using United States National Center for Health Statistics data from 2011 for live-born singleton neonates between 500 and 6000 grams without malformations. Gestational age was based on the obstetric estimate of gestational age included in the revised 2003 United States birth certificate, which, when available, incorporates ultrasound dating information.

From: Duryea EL, Hawkins JS, McIntire DD, et al. A revised birth weight reference for the United States. *Obstet Gynecol* 2014; 124:16. DOI: [10.1097/AOG.0000000000000345](https://doi.org/10.1097/AOG.0000000000000345). Copyright © 2014 American College of Obstetricians and Gynecologists. Reproduced with permission from Lippincott Williams & Wilkins. Unauthorized reproduction of this material is prohibited.

Graphic 56847 Version 7.0

## Perinatal morbidity and mortality in fetuses with intrauterine growth restriction



Data from: Manning FA. Intrauterine growth retardation. In: *Fetal Medicine: Principles and Practice*, Appleton & Lange, Norwalk, CT 1995. p.312.

Graphic 56263 Version 6.0



## Relationship between selected first and second pregnancy outcomes

Outcome of first pregnancy, live births only	Odds ratio for stillbirth in second pregnancy (95% CI)	Stillbirth rate per 1000 births
AGA, term	1.0	2.4
SGA, term	2.0 (1.5 to 2.6)	4.8
SGA, moderately preterm	4.0 (2.5 to 6.3)	9.5
SGA, very preterm	8.0 (4.7 to 13.7)	19.0

Analysis adjusted for factors such as cigarette smoking, maternal age, interpregnancy interval, and presence of hypertension or antepartum bleeding.

AGA: weight appropriate for gestational age; SGA: weight small for gestational age (ie, birth weight >2 standard deviations below the mean for gestational age [<2.5<sup>th</sup> percentile]); moderately preterm: 32 to 36 weeks of gestation; very preterm: <32 weeks of gestation.

*Adapted from: Surkan PS, Stephansson O, Dickman PW, Cnattingius S. Previous preterm and small-for-gestational-age births and the subsequent risk of stillbirth. N Engl J Med 2004; 350:777.*

Graphic 56032 Version 4.0

## Contributor Disclosures

**Robert Resnik, MD** Other Financial Interest (Coeditor, receive royalty payments): Elsevier Publishing [Maternal-fetal medicine (Textbook)]. **Charles J Lockwood, MD, MHCM** Consultant/Advisory Boards: Celula [Aneuploidy screening (No current products or drugs in the US)]. **Deborah Levine, MD** Nothing to disclose **Vanessa A Barss, MD, FACOG** Nothing to disclose

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