Fetal growth restriction: Diagnosis

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INTRODUCTION — Fetal growth restriction (FGR, also called intrauterine growth restriction [IUGR]) is the term used to describe a fetus that has not reached its growth potential because of genetic or environmental factors. The origin may be fetal, placental, or maternal, with significant overlap among these entities.

A major focus of prenatal care is to determine whether a fetus is at risk for growth restriction and to identify the growth restricted fetus. This is important because these fetuses are at increased risk of adverse perinatal outcome. In addition, FGR appears to be an antecedent to some cases of hypertension, hyperlipidemia, coronary heart disease, and diabetes mellitus in the adult (Barker hypothesis). (See "Infants with fetal (intrauterine) growth restriction" and "Possible role of low birth weight in the pathogenesis of primary (essential) hypertension".)

Prenatal screening for FGR in general obstetrical populations involves identifying risk factors for impaired fetal growth and physically assessing fetal size. Clinical suspicion based upon risk factors or physical examination is followed by a detailed sonographic assessment of the fetus, placenta, and amniotic fluid. (See "Fetal growth restriction: Evaluation and management", section on 'Determine the cause'.)

The most common sonography-based definition of FGR is a weight below the 10th percentile for gestational age, although other definitions employing a variety of criteria have been advocated. When a small fetus is detected, it can be difficult to distinguish between the fetus that is constitutionally small versus growth restricted. It is also difficult to identify the fetus that is not small but growth restricted relative to its genetic potential. Making the correct diagnosis is not always possible, but is important prognostically and for estimating the risk for recurrence.

Ideally, prenatal detection of FGR will provide an opportunity to employ interventions to reduce the morbidity and mortality associated with this problem. Although stillbirth rates are higher when FGR is not detected antenatally [1], there is only low quality evidence that antenatal identification of FGR improves outcome [2]. Defining the population of growth restricted fetuses at high risk of adverse outcome, accurately identifying these fetuses in utero, and determining interventions to improve outcome remains a challenge. These issues need to be addressed by large multicenter studies employing consistent definitions, randomly assigned interventions, and with long-term follow-up.

The diagnosis of FGR will be reviewed here. The etiology, management, and prognosis of this disorder are discussed separately. (See "Fetal growth restriction: Evaluation and management" and "Infants with fetal (intrauterine) growth restriction".)

DEFINITION — The most common definition of FGR refers to a weight below the 10th percentile for gestational age [3], although other definitions employing a variety of criteria have been advocated (eg, <5th percentile, <3rd percentile) [4,5]. This definition is problematic because it does not make a distinction among fetuses who are (1) constitutionally small, (2) small because a pathologic process has kept them from achieving their genetic growth potential, and (3) not small but a pathologic process has kept them from achieving their genetic growth potential. It also requires an appropriate reference standard. Whether this standard should be based on birth weights across gestation, ultrasound-estimated fetal weights across gestation, or a customized standard, is also controversial [6]. The major criticism of the birth weight reference is that before term it is flawed because babies born preterm are often growth restricted. The ultrasound-based approach is limited by the inaccuracy and imprecision of ultrasound estimated fetal weight.

A small for gestational age (SGA) infant may be growth restricted or constitutionally small. (See "Infants with fetal (intrauterine) growth restriction".) As many as 70 percent of fetuses who are estimated to weigh below the 10th percentile for gestational age are small simply due to constitutional factors such as female sex (table 1) or maternal ethnicity, parity, or body mass index; they are not at high risk of perinatal mortality and morbidity [7]. There is a real possibility of misclassifying these normally nourished, healthy, but constitutionally small, fetuses as growth restricted. By comparison, a malnourished fetus whose estimated weight is slightly greater than the 10th percentile may be misclassified as appropriately grown and at low risk of adverse perinatal outcome, even though its weight may be far below its genetic potential.

Numerous approaches to differentiate the fetus or infant with growth restriction from the small, but otherwise healthy, baby have been proposed. Some criteria pertain to the fetus, others can only be employed in the neonate (eg, ponderal index, skin fold thickness, presence of nucleated red blood cells [8]).

NORMAL AND ABNORMAL FETAL GROWTH — Normal fetal growth reflects the interaction of the fetus's genetically predetermined growth potential and its modulation by the health of the fetus, placenta and the mother.

Population-based intergenerational studies of birth weight have reported that genetic factors contribute 30 to 50 percent of the variation in birth weight, with the remainder due to environmental factors [9-12]. Maternal genes influence birth weight more than paternal genes, but both have an effect.

Normal growth — The process of fetal growth comprises three consecutive and somewhat overlapping phases. The first phase is the phase of cellular hyperplasia and encompasses the first 16 weeks of gestation. The second phase, known as the phase of concomitant hyperplasia and hypertrophy, occurs between the 16th and 32nd weeks and involves increases in cell size and number. The third and final phase, called the phase of cellular hypertrophy, occurs between the 32nd week and term and is characterized by a rapid increase in cell size.

Quantitatively, normal singleton fetal growth increases from approximately 5 g/day at 14 to 15 weeks of gestation to 10 g/day at 20 weeks and 30 to 35 g/day at 32 to 34 weeks, after which the growth rate decreases [13]. The median growth rate in multiple gestations is lower than that of singletons during the third trimester (see topic reviews on twin and triplet pregnancy).

Symmetric and asymmetric growth restriction — The pattern of normal growth described above forms the basis for the clinical classification of FGR:

- Symmetric FGR, which comprises 20 to 30 percent of growth restricted fetuses, refers to a growth pattern in which all fetal organs are decreased proportionally due to global impairment of early fetal cellular hyperplasia.
- Asymmetric FGR is characterized by a relatively greater decrease in abdominal size (eg, liver volume and subcutaneous fat tissue) than head circumference and is found in the remaining 70 to 80 percent of the FGR population. Asymmetric fetal growth is thought to result from the capacity of the fetus to adapt to a hostile environment by redistributing blood flow in favor of vital organs (eg, brain, heart, placenta) at the expense of nonvital fetal organs (eg, abdominal viscera, lungs, skin, kidneys) [14,15].

CLINICAL ASSESSMENT — Clinical assessment is a reasonable screening tool for FGR in low risk pregnancies, as there is no high quality evidence that alternative approaches, such as routine ultrasound examination, improve outcome over clinical assessment alone [16,17]. Clinical assessment is based on assessment of past and present risk factors, physical examination, and ultrasound studies. (See "Fetal growth restriction: Evaluation and management", section on 'Determine the cause' and "Routine prenatal ultrasonography as a screening tool".)

Accurate assessment of gestational age — Accurate knowledge of gestational age (GA) is critical to the diagnosis of FGR, given that normal and abnormal fetal size are defined, in part, by comparing the fetal weight of the index fetus to that of other fetuses of the same gestational age. A detailed discussion of determination of GA can be found separately. (See "Prenatal assessment of gestational age and estimated date of delivery".)

In a subgroup of fetuses, growth delay can be identified as early as the first trimester. (See "Diagnosis and outcome of first-trimester growth delay".)

Symphysis-fundal height measurement — Measurement of the distance between the upper edge of the pubic symphysis and the top of the uterine fundus using a tape measure is a simple, inexpensive, and widespread procedure performed during antenatal care to detect fetuses that are poorly grown. The first suspicion of FGR often arises when this length is noted to be discordant with the expected size for dates. Discordancy has been defined in various ways, the most common criteria is a fundal height in centimeters that is at least three centimeters below the GA in weeks (eg, fundal height 32 cm at 36 weeks of gestation) [18].

The accuracy of fundal height measurements for screening for and diagnosis of FGR is controversial. A systematic review concluded evidence was inadequate (one randomized trial) to evaluate the effectiveness of this technique versus abdominal palpation for detecting abnormal fetal growth [19]. Observational studies using symphysis-fundal height measurements have reported a wide range of sensitivities: 13 to 86 percent of small fetuses were detected [18,20-27]. The method performs best when all of the measurements are done by the same clinician using the unmarked side of the tape (to reduce bias [28]) and are plotted to reflect fetal growth for the individual patient (“customized”), rather than against a standardized norm [29,30]. Other factors which may affect sensitivity include maternal body mass index, bladder volume, parity, and ethnic group [25,26,31,32].

The INTERGROWTH-21st Project International published printable symphysis-fundal height measurement standards for the 3rd, 50th, and 97th centiles using the eight urban populations of healthy, well-nourished women [33].

Abdominal palpation — Clinical assessment of fetal size by abdominal palpation does not perform well as a test for detecting FGR: sensitivities range from 30 to 50 percent [22,34,35].

SONOGRAPHIC SCREENING — (See "Routine prenatal ultrasonography as a screening tool", section on 'Better diagnosis of deficient growth and improvement in perinatal outcome'.)

SONOGRAPHIC DIAGNOSIS — There is a general consensus that once the suspicion of FGR has arisen because of risk factors or physical examination, sonographic techniques should be used to try to confirm or exclude the diagnosis [36-38]. Clinical assessment alone is not adequate in pregnancies at high risk for FGR, given the low sensitivity and specificity. Risk factors that should prompt an ultrasound examination include significant lag of the fundal height on physical examination, suboptimal growth on a prior ultrasound, history of a prior birth of a small for gestational age infant, poor maternal weight gain, preeclampsia, or maternal conditions (eg, lupus erythematosus, hypertension) associated with suboptimal fetal growth. (See "Fetal growth restriction: Evaluation and management".)

A variety of sonographic parameters have been used to diagnose FGR. The procedures for measuring these parameters can be found separately. (See "Ultrasound examination in obstetrics and gynecology".)

A major limitation in interpreting the predictive value of sonography for diagnosing FGR and comparing predictive values derived from different studies is that these values depend upon the prevalence of FGR in the population studied. Thus, ultrasound results need to be interpreted in terms of pretest risk of FGR and take into account whether the subject population was at low, moderate, or high risk of fetal growth abnormality [39-41].

Sonographic estimation of fetal weight is the single best morphometric test to screen for and diagnose FGR (see 'Estimated fetal weight (EFW)' below). Customized and individualized growth curves may improve diagnostic performance (see 'Customized growth curves' below). The other morphometric tests discussed below are more likely to overlook fetuses with symmetric FGR, but can be used as confirmatory tests of suspected asymmetric FGR. As discussed above, symmetric FGR comprises 20 to 30 percent of growth restricted fetuses and asymmetric FGR occurs in the remaining 70 to 80 percent of the FGR population.

When ultrasound examination suggests a diagnosis of FGR, further evaluation to look for maternal, placental, or fetal disorders associated with impaired fetal growth is indicated. This evaluation helps to (1) distinguish the growth impaired fetus from the constitutionally small fetus, and (2) guide further management of the pregnancy. (See "Fetal growth restriction: Evaluation and management", section on 'Confirm the diagnosis'.)

Abdominal circumference — When fetal growth is compromised, the fetal abdominal circumference (AC) is smaller than expected because of depletion of abdominal adipose tissue and decreased hepatic size related to reduced glycogen storage in the liver. Although the size of the fetal liver may be reduced as a result of fetal malnutrition, this is a less sensitive marker for FGR than AC [42,43].

Most studies report reduced AC is the most sensitive single morphometric indicator of FGR [44-49]. The performance of AC measurement was illustrated by a study of 3616 pregnancies over 25 weeks of gestation that had a single ultrasound examination performed within two weeks of delivery [48]. AC measurement predicted small for gestational age (SGA) infants (ie, birth weight below the 10th percentile for GA) with sensitivity, specificity, positive and negative predictive values of 61, 95, 86, and 83 percent, respectively. Measurement of AC was more predictive of FGR than measurement of either head circumference (HC) or biparietal diameter (BPD) or the combination of AC with either one of these two variables. The optimal time to screen for FGR was at approximately 34 weeks of gestation.

The following factors affect the sensitivity of the AC measurement:

- Symmetric versus asymmetric growth abnormality. AC is more sensitive in asymmetric FGR. As an example, a study of 151 SGA infants reported the sensitivity of AC was 73 percent in the asymmetrical group, 59 percent in the symmetrical group, and 64 percent for the entire population [39].
- Gestational age. AC is more sensitive later in gestation. As an example, the sensitivity and positive predictive value of AC measurement at 29 to 31 weeks for prediction of FGR were 41 and 51 percent, respectively; however, these values increased at term to 88 and 71 percent, respectively [50].
- Time interval between AC measurements. AC is more sensitive when the interval between measurements is more than two weeks. This was illustrated by a study that showed that the false positive rates for inter-examination intervals of one, two, and four weeks were 31, 17, and 3 percent, respectively [51].

Small AC also correlates with parameters of morbidity associated with FGR. Biochemical markers of hypoxia and acidemia are more common when the AC is below the 5th percentile for GA [52].

Estimated fetal weight (EFW) — AC alone can be used for predicting weight in normally growing fetuses at term and in low-risk populations; however, this method has limitations when used in preterm or growth restricted fetuses [37,53,54]. Therefore, additional sonographic variables have been incorporated into models for predicting fetal growth abnormalities. Fetal weight estimation has become one of the most common methods of identifying the growth restricted fetus since pediatricians use birth weight as their primary variable for defining growth restriction in the infant. Examples of fetal weight distribution by gestational age are provided in the tables (table 2 and table 1); several such tables exist and are slightly different depending on the population studied and methods used. The Fetal Growth Longitudinal Study developed an international growth and size standard by prospectively assessing fetal growth in over 4000 healthy, well-nourished women with well-dated pregnancies at

low risk of fetal growth restriction who had no major pregnancy complications and delivered live nonanomalous singletons [55]. Ultrasound examinations were obtained every five weeks from 14 weeks to 42 weeks of gestation and biometric measurements were used to derive the best fitting curves for the 3rd, 50th, and 97th centiles. Standards for newborn birthweight were also developed (table 3) [56]. The World Health Organization has published charts for fetal growth and common ultrasound biometric measurements based on longitudinal data derived from 10 countries [57]. (See "Infants with fetal (intrauterine) growth restriction".)

In 1975, Campbell and Wilkin first published a regression equation for estimating fetal weight based upon sonographic measurement of the AC and HC [58]. Other equations have been published subsequently using two or more morphometric body measurements (eg, BPD, AC, HC, occipital frontal diameter, abdominal diameter, transthoracic circumference, and femur length [FL]) to improve sonographic accuracy [59-62]. Equations that incorporate AC, BPD, and FL seem to provide the most accurate estimates of fetal weight [63]. (See "Prenatal sonographic assessment of fetal weight".)

In one study, EFW assessments within one week of delivery were within 10 percent of the actual birth weight in 75 percent of patients in whom there was a clinical suspicion of FGR [63]. The sensitivity, specificity, positive and negative predictive values of EFW for FGR <10th percentile are approximately 90, 85, 80, and 90 percent, respectively, when performed proximate to delivery [64-67]. EFW performed within one to two weeks of delivery is more predictive than when performed earlier in gestation.

The sensitivity of EFW for predicting FGR and adverse outcome associated with FGR is highest for infants with severe growth restriction (birth weight <3rd percentile) [64,68]. In one study, all infants with birth weight <3rd percentile were identified prenatally [64]. In another study including 1116 consecutive fetuses with EFW <10th percentile, all 8 mortalities occurred among the 826 fetuses with EFW <3rd percentile [69]. EFW <3rd percentile was the only sonographic weight-related definition consistently associated with adverse outcome.

Customized growth curves — EFW is typically classified using population-based birth weight centiles; however, multiple variables affect fetal weight and can be incorporated into individualized or customized centiles. These variables include fetal gender and maternal parity, ethnicity, height, weight, and age [70,71]; maternal characteristics have greater fetal effects than paternal characteristics. A potentially better approach is to utilize large population-based data sets that account for these variables and exclude the effects of pathologic variables such as maternal smoking, hypertension, diabetes, and preterm birth. Using these data, the optimal birth weight and range of normal around this weight for a specific fetus can be estimated at term and can be determined for each gestational age to create an ultrasound-based, customized, optimal growth curve. The actual EFW is then plotted on this optimized customized curve to create the individual fetus' growth curve across gestation. Free software for calculating customized fetal weight centiles can be downloaded from the internet site www.gestation.net.

Although no randomized trials are available [72], several studies have compared the use of population-based birth weight centiles to customized centiles for prediction of SGA and perinatal morbidity. These studies have generally concluded that using a customized birth weight standard improves the identification of fetuses at risk of perinatal death and neonatal morbidity [73-81], but this remains controversial. One large study found that neither the population-based nor the customized reference did well in predicting adverse perinatal outcomes, and was only useful at ≤5th centile [5]. However, the small for gestational age fetus by population-based standards that is normal in size on a customized growth standard did not appear to be at risk of adverse outcome. Another large study concluded that birth weight ≤25th or ≥85th centile was associated with greater risk of adverse outcomes, but customized growth curves did not identify more fetuses at risk of death than noncustomized growth curves [82].

This improvement in prediction of outcome may be related to better identification of the constitutionally small fetus through adjustment for maternal characteristics, or to use of an intrauterine (ultrasound) growth standard rather than a birth weight standard for classification of FGR. Since fetuses who are born preterm tend to have lower birth weights that fetuses of the same gestational age who remain in utero, using an intrauterine weight standard increases identification of FGR remote from term [83]. The higher perinatal mortality among infants classified as FGR by the customized reference is largely due to the inclusion of more preterm births in this group [78,84,85]. When adjusted for preterm birth, the use of customized fetal growth curves rather than population based growth curves does not clearly improve identification of pregnancies at increased risk of neonatal morbidity and mortality [85].

A long-term study suggested that none of the current standards predict long-term neurodevelopmental outcome well, although the customized standard performed slightly better than other standards [86].

Growth velocity — As discussed above, the use of any parameter (eg, AC, EFW) in the prediction of FGR is based upon accurate assessment of GA. If dates are unknown, serial sonographic examinations at two-week intervals should be performed to evaluate the rate of interval growth (ie, growth velocity). Irrespective of GA, there is a significantly lower rate of change over time of AC or EFW in FGR fetuses compared with those fetuses whose growth is appropriate for GA [87]. In one study, as an example, a change in fetal AC of less than 10 mm over a two-week period had a sensitivity of 85 percent and specificity of 74 percent for identifying FGR [88]. Fetuses with normal growth velocity, amniotic fluid volume, and Doppler velocimetry are at low risk of complications associated with FGR.

Body proportions — The HC/AC ratio, FL/AC ratio, and ponderal index have also been used to identify the growth restricted fetus, particularly in the setting of asymmetric FGR.

HC/AC ratio — The HC/AC ratio has been proposed for evaluating fetuses with asymmetric FGR [89]. In these infants, the size of the liver tends to be disproportionately small compared to the circumference of the head or length of the femur, which are initially spared from the effects of nutritional deficiency (see 'Fetal cerebral arteries' below).

The HC/AC ratio decreases linearly throughout pregnancy and a ratio greater than 2 standard deviations (SD) above the mean for GA is considered abnormal. One prospective study of the HC/AC ratio for detecting asymmetric FGR due to uteroplacental insufficiency reported normal ratios in 79 percent of fetuses, none of whom were SGA; the remaining 21 percent had abnormal ratios and were diagnosed correctly as FGR [90]. In contrast, the sensitivity, specificity, positive and negative predictive values of an abnormal HC/AC in a population with FGR of mixed etiologies were 36, 90, 67, and 72 percent, respectively [65].

These findings demonstrate that an abnormal HC/AC ratio is more accurate in predicting FGR related to uteroplacental insufficiency (often asymmetric) than FGR from other etiologies (often symmetric). However, not all fetuses with an elevated HC/AC ratio have FGR. As an example, macrocephaly could also be associated with an abnormal HC/AC, which would be unrelated to FGR.

FL/AC ratio — The FL/AC ratio uses sonographic elements that relate to both weight and length in the prediction of FGR. An FL/AC ratio greater than 23.5 percent has a sensitivity of 56 to 64 percent and specificity of 74 to 90 percent for identification of asymmetric FGR [91,92]. This ratio is independent of GA in normally grown fetuses in the last half of pregnancy. However, an abnormal FL/AC ratio does not accurately diagnose symmetric FGR. The sensitivity, specificity, positive and negative predictive values of the 90th percentile of FL/AC ratio in a mixed population of FGR fetuses were 30, 91,14, and 96 percent, respectively [93].

Therefore, the FL/AC ratio is unsuitable for screening for FGR in the general population, but can be used as a GA independent parameter in high-risk pregnancies in which asymmetric FGR is suspected.

Ponderal index — Pediatricians often use an abnormal ponderal index (ie, PI = [weight (in g) x 100] ÷ [length (in cm)](3)) to define growth restriction [94]. A fetal PI has been calculated based upon a sonographically derived EFW and measurement of the FL. One study reported sensitivity, specificity, and positive predictive value of the fetal PI for FGR of 77, 82, and 36 percent, respectively; however, there was a poor correlation between fetal and neonatal PI [95].

Transverse cerebellar diameter — Growth of the transverse cerebellar diameter (TCD) is not affected in FGR, thus TCD may serve as an independent indicator of GA against which other potential deviations of growth may be compared [96]. The TCD/AC ratio is constant (0.14+0.01; mean+SD) during pregnancy [97,98], and a TCD/AC ratio exceeding 2 SD above the mean is predictive of asymmetrical growth restriction [98]. A prospective study of the TCD/AC ratio for identifying growth restricted fetuses in pregnancies at risk reported sensitivity, specificity, positive and negative predictive values of 71, 77, 79, and 68 percent, respectively [99]. Fourteen FGR fetuses were missed by this ratio, eight of whom were severely growth restricted.

The status of the TCD/AC ratio as a predictor of FGR remains controversial due to limited data from large and controlled studies [100,101].

Amniotic fluid volume — Oligohydramnios refers to amniotic fluid volume that is less than expected for gestational age. It is typically diagnosed by ultrasound examination and may be described qualitatively or quantitatively by various methods. These are discussed separately. (See "Assessment of amniotic fluid volume" and "Oligohydramnios".)

Oligohydramnios is one of the sequelae of FGR. The proposed mechanism is diminished fetal urine production due to hypoxia-induced redistribution of blood flow to vital organs at the expense of less vital organs, such as the kidney [102,103]. The presence of oligohydramnios has been evaluated as a diagnostic tool to predict both the presence of FGR and the level of associated fetal compromise.

Oligohydramnios is difficult to assess accurately (as determined by dye-dilution studies) and commonly occurs with complications of pregnancy other than FGR. In addition, a significant proportion (approximately 15 to 80 percent) of fetuses with FGR do not have decreased amniotic fluid volume. Therefore, oligohydramnios is a poor screening modality for suboptimal growth [47,88,104,105]. However, if it is present in the absence of ruptured membranes, congenital genitourinary anomalies, or prolonged pregnancy, FGR is the most likely etiology.

Using the oligohydramnios definition of largest vertical fluid pocket less than 1 cm, Manning reported sensitivity, specificity, positive and negative predictive values for prediction of FGR of 84, 97, 90, and 95 percent, respectively [106]. However, other investigators have not confirmed these results. In one such study, this criterion was highly diagnostic of FGR, but had poor sensitivity (27 percent), and thus was inadequate as a screening test [105]. Changing the definition of oligohydramnios to a vertical amniotic fluid pocket of less than 2 cm still resulted in poor sensitivity (16 percent), with specificity and positive predictive value of 98 and 78 percent, respectively [88].

Other studies using single and serial estimates of amniotic fluid volume by amniotic fluid index (AFI) in low risk pregnancies found that neither the rate of the change of AFI nor the final AFI measurement prior to delivery predicted any of the anthropometric criteria of FGR [47].

In general, pregnancies with the most severe oligohydramnios have the highest perinatal mortality rate, incidence of congenital anomalies (especially of the urinary tract), and incidence of FGR [107]. Oligohydramnios combined with EFW <3rd percentile is predictive of adverse outcome [69].

Oligohydramnios is abnormal at any GA, therefore the observation of low amniotic fluid volume when GA is unknown suggests FGR is present (if rupture of membranes and urinary tract anomalies have been excluded) and that fetal biometric measurements may underestimate the true GA.

Soft tissue measurements — FGR results in a decrease in both adipose tissue and muscle mass. Measurement of fetal soft tissue is probably predictive of FGR; however, there are inadequate data for defining the best site for measurement or the sensitivity and specificity of this parameter.

Measurement of the fetal thigh circumference incorporates the contributions of both adipose and muscle. In one study, a thigh circumference measuring 2 SD below the mean had a sensitivity of 78 percent and a positive predictive value of 85 percent in the prediction of FGR [108].

Other measurements of fetal adipose tissue include subcutaneous tissue thickness at the level of the fetal midcalf, midthigh, or abdominal wall, and cheek-to-cheek diameter [109,110]. A prospective study of 137 unselected pregnancies, in which serial sonographic measurement of fetal subcutaneous abdominal fat were made, found that fetuses with subcutaneous fat of less than 5 mm at 38 weeks of gestation were approximately five-fold more likely to be SGA [111]. The sensitivity and specificity for diagnosis of FGR were 76 and 67 percent, respectively. In addition, the frequency of neonatal morbidity (eg, meconium aspiration, hypoglycemia, hypothermia, poor feeding, and jaundice) was significantly higher in infants with adipose tissue depletion.

Doppler velocimetry — Doppler ultrasound is a noninvasive technique commonly used to evaluate maternal and fetal hemodynamics. Continuous, adequate perfusion of the maternal and fetal sides of the placenta is necessary for normal fetal growth. FGR is associated with diminished flow and abnormal Doppler waveforms in both maternal and fetal vessels. Assessment of Doppler flow with appropriate intervention can reduce perinatal mortality in pregnancies complicated by FGR [112]. (See "Doppler ultrasound of the umbilical artery for fetal surveillance".) Although useful for monitoring pregnancies complicated by FGR, Doppler of any vessel is not useful as a screening tool for identifying these pregnancies [113].

Arteries, particularly the umbilical artery, are the vessels most commonly insonated. Venous Doppler assessment has been studied less extensively, and is used for monitoring, rather than diagnosis, of FGR.

Uterine artery — Uterine artery Doppler flow velocimetry has limited diagnostic accuracy for prediction of FGR and is not useful as a screening tool.

Trophoblast invasion into the uterine vessels occurs in the first half of pregnancy and results in dilated spiral arteries, thereby creating a 10- to 12-fold increase in uterine perfusion, and providing nutrient supply and gas exchange for the fetus. The shape of the uterine artery velocity waveform is unique: it is characterized by high end-diastolic velocities with continuous forward blood flow throughout diastole. As GA advances, the degree of end-diastolic flow typically increases; however, failure of normal endovascular trophoblastic invasion of the spiral arteries results in increased uterine artery vascular resistance and decreased perfusion of the placenta [114,115]. Preeclampsia and/or FGR often subsequently develop [116].

The systolic/diastolic (S/D) ratio of the uterine artery in normal pregnancies should be less than 2.7 after the 26th week of gestation. If the end-diastolic flow does not increase throughout pregnancy or a small uterine artery notch is detected at the end of systole, the fetus is at high risk for developing FGR [117]. Diastolic blood flow may be absent or even reversed with extreme degrees of placental dysfunction. Such findings are ominous and may precede fetal death or signal a high risk of abnormal fetal neurologic outcome [118].

Doppler studies of the uterine artery in early pregnancy have been evaluated as a screening tool for pregnancies destined to develop preeclampsia or FGR. The predictive value of an abnormal test is low, although the association with these adverse outcomes is statistically significant [119-121]. As an example, a review of 27 uterine artery Doppler studies for the prediction of preeclampsia and associated complications (eg, FGR, perinatal death) included 12,994 pregnancies stratified into low or high risk for developing these problems [120]. In low-risk women the pooled likelihood ratio for developing FGR was 3.6 (95% CI 3.2-4.0) for a positive test result and 0.8 (95% CI 0.8-0.9) for a negative test result. In the high-risk population, a positive test result predicted FGR with a pooled likelihood ratio of 2.7 (95% CI 2.1-3.4), whereas the likelihood ratio for a negative test was 0.7 (95% CI 0.6-0.9).

Umbilical artery — Doppler umbilical artery studies are not useful for screening and diagnosis of FGR. Comparative studies are scarce, but support this conclusion. A prospective study examined whether Doppler velocimetry of the umbilical artery yielded better or earlier prediction of FGR than sonographic estimates of fetal weight [122]. One hundred sixty-eight women at

high risk for FGR were evaluated for growth restriction with Doppler and gray-scale ultrasound; 42 delivered an SGA infant. Sensitivity of the S/D ratio of the umbilical artery was lower than for sonographic estimates of fetal weight (55 versus 76 percent); however, the Doppler had higher specificity (92 versus 80 percent) and higher positive predictive value (73 versus 58 percent). The two techniques used together further improved the positive predictive value for diagnosis of FGR to 77 percent, with a negative predictive value of 93 percent [123].

Doppler has been useful in evaluation and management of pregnancies suspected of FGR [124,125]. Not all infants whose birth weight is below the 10th percentile have been exposed to a pathological process. Most small newborns are constitutionally small and healthy. Differentiating the fetus with pathological growth restriction who is at risk for perinatal complications from the constitutionally small, but healthy, fetus has been an ongoing challenge in obstetrics. This is the setting in which Doppler is useful because it can distinguish between these two groups [67,126-128] and guide timing of interventions (eg, intensive monitoring, antenatal glucocorticoids, early delivery) that reduce perinatal mortality. (See "Doppler ultrasound of the umbilical artery for fetal surveillance".)

Fetal descending aorta — As with other Doppler tests, the pulsatility index (ie, peak systolic minus minimal diastolic velocity divided by the mean velocity or S-D/mean) of the fetal descending aorta is not useful for screening and diagnosis of FGR in the general obstetric population. It performs best for predicting the FGR fetus who is beginning to decompensate from chronic hypoxia and malnutrition.

Normal blood flow in the fetal descending aorta is highly pulsatile, with a minimal end-diastolic component. This part of the aorta provides perfusion to the fetal abdominal organs, umbilical-placental circulation, and lower limbs. Increased placental impedance combined with redistribution of blood flow from nonvital to vital organs may result in changes in the aortic velocity waveforms. Assessment of these waveforms is limited to the pulsatility index because of the lack of diastolic flow.

An elevated pulsatility index is associated with both FGR and adverse outcomes, such as severe FGR, necrotizing enterocolitis, nonreassuring fetal heart rate patterns, and perinatal mortality [129-137]. In one group of 30 fetuses with absent end-diastolic flow in the descending aorta, abnormal waveforms were detected at a mean of eight days prior to the onset of fetal heart rate (FHR) abnormalities [133]. All of the neonates were SGA and 66 percent had abnormal placentas with villous fibrosis and microfibrinous deposits.

The sensitivity and specificity of absent end diastolic flow in the descending aorta for prediction of FGR with FHR abnormalities are approximately 85 and 80 percent, respectively [135-137]. These pregnancies are also characterized by higher rates of cesarean delivery, right ventricular failure, and perinatal mortality.

Fetal renal artery — Fetal renal artery Doppler is not a useful test in the initial diagnosis of FGR [103,138-140]. It may be used to corroborate other tests or evaluate renal artery perfusion when oligohydramnios is observed. The pulsatility index of renal artery velocity waveforms in FGR is significantly elevated, possibly indicating decreased renal perfusion, which may, in turn, cause oligohydramnios. There is an overall negative correlation between the increase in pulsatility index and the amniotic fluid volume [140]. In addition, umbilical blood sampling on FGR fetuses demonstrated a relationship between blood oxygen deficit and increased renal artery pulsatility index.

Fetal cerebral arteries — Doppler evaluation of fetal cerebral arteries is not useful in the initial diagnosis of FGR, but may be useful confirming the diagnosis and evaluating the FGR fetus. In the normally developing fetus, the brain is an area of low vascular impedance and is the recipient of continuous forward flow throughout the cardiac cycle. Asymmetric FGR is likely caused by redistribution of fetal blood flow to the fetal brain, at the expense of less essential areas such as subcutaneous tissue, kidneys, and liver. However, the already low cerebral resistance has to drop even further to enhance cerebral blood flow. This has been measured as increased end diastolic velocities and decreased S/D ratios in the cerebral arteries of growth restricted fetuses [15,141-145].

A study of blood flow in the internal carotid and umbilical arteries of 44 FGR fetuses reported the umbilical artery pulsatility index was increased by more than 2 SD in 80 percent of cases, whereas the internal carotid pulsatility index was reduced by more than 2 SD in only 45 percent of cases [142]. This suggests that high placental impedance precedes the onset of the redistribution reflex.

Venous Doppler — Venous Doppler has no role in diagnosis of FGR since venous Doppler abnormalities constitute a late circulatory finding. Venous Doppler assessment is used for monitoring fetal well-being; use of this technique appears to significantly improve the prediction of stillbirth and acidemia over use of umbilical artery Doppler alone. (See "Fetal growth restriction: Evaluation and management", section on 'Doppler velocimetry'.)

Three-dimensional ultrasonography — Three-dimensional ultrasound has become available in the past decade and is being evaluated for assessment of pregnancies complicated by FGR [146-156]. One study used this technique in 100 fetuses to compare birth weight predicted by calculating thigh volume to birth weight predicted by two-dimensional ultrasound using BPD, AC, and FL [152]. All infants were delivered within 48 hours of ultrasound examination. The best-fit formula for thigh volume in the prediction of birth weight was linear and was superior to commonly used two-dimensional formulas. The error in birth weight prediction by three-dimensional ultrasound, Warsof's formula, Hadlock's formula, and Thurnau's formula were 0.7, 6.2, 6.7, and 20.8 percent respectively. In addition, three-dimensional ultrasound thigh volumetry was not influenced by oligohydramnios,

fetal head engagement, or inaccurate abdominal circumference measurement. These results were confirmed in other studies that found three-dimensional thigh, femur, or humerus volume measurement was simple, and more accurate than two-dimensional ultrasound methods in the prediction of fetal weight [153-156].

Three-dimensional ultrasound appears to be highly promising in the clinical setting of FGR because it appears to provide more precise information regarding structural abnormality, organ volumetry, EFW and oligohydramnios than standard two-dimensional techniques. However, this modality is not widely available and has not been adequately assessed in large or controlled studies.

SUMMARY AND RECOMMENDATIONS

- The diagnostic approach to fetal growth restriction (FGR) should integrate information from maternal history and physical examination with information from sonographic evaluation of the fetus, placenta, and amniotic fluid. The combined information helps to both confirm the diagnosis and establish the etiology for the growth abnormality. (See 'Introduction' above.)
- The ultrasound diagnosis of FGR is based on discrepancies between actual and expected biometric measurements for a given gestational age. (See 'Sonographic diagnosis' above.)
- There is no high quality evidence that ultrasound screening for FGR in low risk pregnancies improves pregnancy outcome over clinical assessment alone. We suggest screening for FGR by identifying the presence of risk factors and performing serial measurements of fundal height to identify discordancy between fundal height and gestational age (**Grade 2C**). Clinical suspicion of FGR should be followed with detailed sonographic assessment to make or exclude the diagnosis. (See 'Clinical assessment' above.)
- A major limitation in interpreting the predictive value of sonography for diagnosing FGR and comparing predictive values derived from different studies is that these values depend upon the prevalence of FGR in the population studied. Thus, ultrasound results need to be interpreted in terms of pretest risk of FGR and take into account whether the subject population was at low, moderate, or high risk of fetal growth abnormality. (See 'Sonographic diagnosis' above.)
- The fetal AC is the most sensitive single morphometric measurement for diagnosis of FGR. However, it is not as predictive of FGR as sonographic estimation of fetal weight. **Sonographic estimation of fetal weight is the best method for identifying fetuses whose birth weight is likely to be below the 10th percentile for gestational age**. Estimated fetal weight <3rd percentile is consistently associated with adverse outcome. (See 'Abdominal circumference' above and 'Estimated fetal weight (EFW)' above.)
- Abnormal HC/AC or FL/AC ratios are particularly useful in the diagnosis of asymmetric fetal growth. (See 'HC/AC ratio' above and 'FL/AC ratio' above.)
- Sonographic diagnosis of oligohydramnios corroborates the diagnosis of FGR by identifying one of the major consequences of the disorder. (See 'Amniotic fluid volume' above.)
- The combination of an estimated fetal weight less than the 10th percentile for gestational age and abnormal umbilical artery Doppler velocimetry is highly predictive of FGR and is the best tool available for identifying the growth restricted fetus at risk of adverse outcome. These pregnancies require more intensive monitoring. Venous Doppler assessment is used for monitoring fetal well-being, but has no role in diagnosis of FGR since venous Doppler abnormalities constitute a late circulatory finding. (See 'Doppler velocimetry' above.)
- It is anticipated that three-dimensional volumetric fetal measurements will improve the accuracy of sonographic estimates of fetal weight, and thus our ability to identify the small fetus. (See 'Three-dimensional ultrasonography' above.)

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Topic 6752 Version 38.0

GRAPHICS

Tenth percentile of birth weight (g) for gestational age by gender: United States, 1991, single live births to resident mothers

Gestational age, weeks	Male	Female
20	270	256
21	328	310
22	388	368
23	446	426
24	504	480
25	570	535
26	644	592
27	728	662
28	828	760
29	956	889
30	1117	1047
31	1308	1234
32	1521	1447
33	1751	1675
34	1985	1901
35	2205	2109
36	2407	2300
37	2596	2484
38	2769	2657
39	2908	2796
40	2986	2872
41	3007	2891
42	2998	2884
43	2977	2868
44	2963	2853

Graphic 75060 Version 4.0

Birth weight percentiles by gestational age

Week of gestation	5th percentile	10th percentile	50th percentile	90th percentile	95th 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.

Graphic 56847 Version 7.0

International birth weight centiles

Boys							Girls						
	Number of observations	Centiles for birth weight (kg)						Number of observations	Centiles for birth weight (kg)				
		3rd	10th	50th	90th	97th			3rd	10th	50th	90th	97th
33 weeks	34	1.18	1.43	1.95	2.52	2.82	33 weeks	17	1.20	1.41	1.86	2.35	2.61
34 weeks	48	1.45	1.71	2.22	2.79	3.08	34 weeks	65	1.47	1.68	2.13	2.64	2.90
35 weeks	128	1.70	1.95	2.47	3.03	3.32	35 weeks	114	1.71	1.92	2.38	2.89	3.16
36 weeks	323	1.93	2.18	2.69	3.25	3.54	36 weeks	293	1.92	2.14	2.60	3.12	3.39
37 weeks	857	2.13	2.38	2.89	3.45	3.74	37 weeks	803	2.11	2.33	2.80	3.32	3.60
38 weeks	2045	2.32	2.57	3.07	3.63	3.92	38 weeks	1802	2.28	2.50	2.97	3.51	3.78
39 weeks	3009	2.49	2.73	3.24	3.79	4.08	39 weeks	2869	2.42	2.65	3.13	3.66	3.94
40 weeks	2568	2.63	2.88	3.38	3.94	4.22	40 weeks	2523	2.55	2.78	3.26	3.80	4.08
41 weeks	1179	2.76	3.01	3.51	4.06	4.35	41 weeks	1195	2.65	2.89	3.37	3.92	4.20
42 weeks	206	2.88	3.12	3.62	4.17	4.46	42 weeks	224	2.74	2.98	3.46	4.01	4.30
Total	10397	..	..	..	..	..	Total	9905	..	..	..	..	..

International standards for newborn weight by gestational age and sex from the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Table shows smoothed centiles for birth weight of boys and girls according to gestational age.

kg: kilogram.

Graphic 96940 Version 2.0

Contributor Disclosures

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Conflict of interest policy