Infants with fetal (intrauterine) growth restriction

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INTRODUCTION

Infants with fetal growth restriction (FGR; also referred to as intrauterine growth restriction) who did not achieve full in utero growth potential because of genetic or environmental factors are at increased risk for significant morbidity and mortality compared with infants with normal in utero growth.

The clinical features, complications, and management of infants born with FGR are discussed here. The diagnosis, evaluation, and management of FGR during pregnancy are discussed separately. (See "Fetal growth restriction: Screening and diagnosis" and "Fetal growth restriction: Evaluation and management".)

DEFINITION

Several terms have been used to describe infants with low birth weights (BW) for their gestational age. These include small for gestational age (SGA) and fetal (intrauterine) growth restriction (FGR). Although many SGA infants have FGR and many FGR infants are SGA, the two terms are not synonymous.

Fetal growth restriction — Fetal or intrauterine growth restriction (FGR/IUGR) refers to the fetus who does not achieve the expected in utero growth potential due to genetic or environmental factors (table 1). It is defined as an estimated fetal weight <10th percentile (see "Fetal growth restriction: Screening and diagnosis", section on 'Definition and classification of FGR'). Clinically, most infants with FGR are identified because they are born SGA with a BW

below the 10th percentile for gestational age (table 2 and figure 1). Moderate FGR is defined as BW in the 3rd to 10th percentile, and severe FGR as less than the 3rd percentile.

However, there are concerns that the above definition may not accurately reflect all infants who were affected by fetal growth restriction. As a result, a definition based on a survey of expert opinion was published that defines growth restriction in the newborn as one of the following [1]. However, it remains to be seen whether this definition will replace the previous definitions.

- BW less than the 3rd percentile

  or

- Three of the following criteria are met:

  - BW <10th percentile
  - Head circumference <10th percentile
  - Length <10th percentile
  - Prenatal diagnosis of fetal growth restriction (see "Fetal growth restriction: Screening and diagnosis", section on 'Definition and classification of FGR')
  - Prenatal history of conditions associated with fetal growth restriction (eg, maternal hypertension, preeclampsia, congenital infection)

Infants with FGR can be divided into:

- **Symmetric FGR** – Infants with symmetric FGR (20 to 30 percent of FGR cases) have reductions in all organ systems with the body, head, and length proportionally affected. Symmetric FGR begins early in gestation and usually is caused by intrinsic factors such as congenital infections or chromosomal abnormalities. However, decreased nutrient supply early in development can restrict growth of all organs [2].

- **Asymmetric FGR** – Infants with asymmetric FGR (70 to 80 percent of FGR cases) have disproportionate growth restriction in which head circumference is preserved, length is somewhat affected, and weight is compromised to a greater degree. As a result, the normal-sized head appears relatively large compared with the size of the trunk and extremities (picture 1). Abnormal growth typically begins in the late second or third trimesters and results from reductions in fetal nutrients that limit glycogen and fat storage, yet allow continued brain growth [2].

Ponderal index — As noted above, weight parameters at birth are not sensitive measures to detect FGR. The ponderal index (PI) is a useful tool to detect FGR, particularly in infants with asymmetric FGR [3].

PI is a ratio of body weight to length expressed as [3]:

$$PI = [\text{weight (in g)} \times 100] \div [\text{length (in cm)}]^3$$

With normal growth, the PI increases gradually from 30 to 37 weeks gestation and then remains constant. Decreased growth of adipose tissue and skeletal muscle, the major contributors to body weight, results in a reduced PI. PI of less than the 10th percentile reflects fetal malnutrition; PI of less than the 3rd percentile indicates severe wasting [4].

Other measures of body proportion ratios (eg, head circumference to weight, length, or abdominal circumference; or femur length to abdominal circumference) have also been used to detect FGR. (See "Fetal growth restriction: Screening and diagnosis", section on 'Biometric ratios'.)

Small for gestational age — Small for gestational age (SGA) is typically defined by BW below the 10th percentile for gestational age (GA) (table 2 and figure 1) [5]. However, this definition does not make a distinction among SGA infants who are constitutionally normally small from those who are growth-restricted and small. Constitutionally small infants are those with a normal BW below 10th percentile due to constitutional factors including maternal height, weight, ethnicity, and parity. These infants are not at increased risk for perinatal mortality or morbidity [5].

An alternate definition defines SGA as BW and/or length for GA that is >2 standard deviations (SD) below the mean (ie, <2.3 percentile) [6,7]. (See "Growth hormone treatment for children born small for gestational age", section on 'Definition'.)

FGR versus SGA — The substitution of SGA for FGR is imprecise. As noted above, using the SGA criteria does not distinguish the constitutionally small fetus that achieves its normal growth potential from similarly small infants with intrauterine growth restriction whose BW is lower than the expected optimal BW. In addition, using SGA as the marker for FGR will miss infants with FGR who have BWs that are greater than the 10th percentile. As a result, customized fetal growth curves based on constitutional factors have been developed to help differentiate between SGA infants who are normally small from those with FGR. The use of these curves and the ongoing challenge of distinguishing between these two groups are discussed separately. (See "Fetal growth restriction: Screening and diagnosis", section on 'Customized growth curve'.)

EPIDEMIOLOGY

The incidence of fetal growth restriction (FGR) varies among populations and increases with decreasing gestational age. In addition, it is challenging to interpret the literature as some studies use the term small for gestational age (SGA), which may include both infants who are FGR as well as those who are constitutionally normally small. Also, the reference birth weight and intrauterine growth charts will influence the classification and incidence of IUGR [8].

Nevertheless, it appears that FGR is more prevalent in resource-limited countries. Approximately 10 percent of term infants in developed countries are SGA, compared with 20 percent of term infants in resource-limited countries [2,9,10]. In 2012, data from the Child Health Epidemiology Reference Group (CHERG) based on 14 birth cohorts and using International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) birth weight (BW) standard (table 3) showed that SGA was observed in 19.3 percent of live births in low and middle income countries [9]. In this report, 22 percent of neonatal deaths occurred in infants born SGA.

For preterm infants, the incidence varies depending upon whether data collection is based on BW and/or gestational age. In the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network database, 22 percent of 4438 infants with BW 500 to 1500 g were classified as SGA [11]. In a larger series of 20,000 very low birth weight (VLBW) infants (BW below 1500 g) in which the gestational age was restricted to 25 to 30 weeks, the incidence of SGA was only 9 percent [12]. (See "Fetal growth restriction: Evaluation and management".)

PATHOPHYSIOLOGY AND ETIOLOGY

In FGR, the nutrient supply to the fetus is compromised. The fetus, in order to increase its chance of survival, responds by reducing its overall size, preserving brain growth, accelerating lung maturation, and increasing red blood cell production [13]. The fetus redirects blood flow from less vital organs to the brain, heart, adrenal glands, and placenta. Total body fat, lean mass, and bone mineral content are reduced, resulting in a wasted appearance in infants with severe FGR (picture 2) [14]. Nitrogen and protein content are lower because of reduced muscle mass [2]. Glycogen content is decreased in skeletal muscle and liver because of lower fetal plasma glucose and insulin concentrations [2].

Fetal growth restriction (FGR) may be caused by fetal, placental, and maternal factors (table 1). However, no underlying etiology is identified in at least 40 percent of infants with FGR. In those infants where an underlying cause is identified, FGR is caused by genetic disease in approximately one-third of infants, and is related to the fetal environment in two-thirds [15].

CLINICAL PRESENTATION

Antenatal detection — The antenatal detection of fetal growth restriction (FGR) has increased with a greater emphasis by obstetricians on identifying fetuses with poor intrauterine growth. However, antenatal diagnosis based on sonographic evaluation of the fetus, placenta, and amniotic fluid remains challenging and is discussed separately. (See "Fetal growth restriction: Screening and diagnosis".)

Neonatal findings — Classically, newborn infants with FGR appeared thin with loose, peeling skin, and decreased skeletal muscle mass and subcutaneous fat tissue. However, this presentation is less common, in part due to increased antenatal surveillance and the avoidance of postterm gestation (see "Postterm infant" and "Postterm infant", section on 'Fetal growth restriction'). Nevertheless, this classic presentation may still be seen when growth restriction persists despite antenatal intervention. The face of severely affected infants has a typical shrunken or "wizened" appearance (picture 2), and the umbilical cord often is thin [2]. Cranial sutures may be widened, and the anterior fontanelle is larger than expected due to diminished membranous bone formation. Meconium staining may be present (picture 1). In newborns with asymmetric FGR, the head appears relatively large compared with the size of the trunk and extremities (picture 1). These infants usually have a low ponderal index (PI). (See 'Ponderal index' above.)

DIAGNOSIS

Antenatal diagnosis — Most infants are diagnosed antenatally by sonographic evaluation. The antenatal diagnosis is discussed separately. (See "Fetal growth restriction: Screening and diagnosis", section on 'Diagnosis'.)

Postnatal diagnosis — The postnatal diagnosis of fetal growth restriction (FGR) is most commonly made when the birth weight (BW) is below the 10th percentile for gestational age (ie, the definition of small for gestational age [SGA]). As noted above, there are pitfalls in this approach as it does not distinguish SGA infants who are constitutionally normally small from those with FGR, and it fails to identify infants with FGR who have BWs above the 10th percentile but who still had abnormally poor in utero growth. In addition, it is important to accurately determine the gestational age (GA) of the infant, which can be challenging in the setting of FGR.

Further support for the diagnosis of FGR is made by identifying other clinical features suggestive of poor intrauterine growth. These include a significant discrepancy between the actual weight and the expected optimal weight based on maternal stature, ethnicity, and parity;

physical findings of malnourishment (eg, decreased skeletal muscle mass and subcutaneous fat tissue, and excessive skin desquamation); or evidence of asymmetric growth with a low ponderal index (PI). (See 'Neonatal findings' above and 'Ponderal index' above.)

Gestational age assessment — The most reliable method of determining GA is the knowing with certainty the last menstrual period or date of in-vitro fertilization and measurements from antenatal ultrasound performed before 22 weeks gestation (see "Prenatal assessment of gestational age, date of delivery, and fetal weight"). In clinical settings in which accurate menstrual dating and results from early antenatal ultrasounds are not available, GA is determined postnatally based on neonatal physical examination and neuromuscular assessment. However, many of the physical criteria used to assess GA are altered in infants with FGR [2]. As an example, infants with FGR have increased desquamation and enhanced wrinkling (and more mature appearance) of the soles of the feet. However, in FGR infants without an underlying disorder that affects the nervous system the neurologic assessment remains consistent with the GA. In addition, the disappearance of the anterior vascular capsule of the lens, which occurs in an orderly sequence between 27 and 34 weeks gestation, is not altered by FGR. As a result, examination with a direct ophthalmoscope after dilation of the pupil can be used to accurately estimate GA, if necessary. (See "Postnatal assessment of gestational age".)

Differential diagnosis — The main consideration in the differential diagnosis of FGR is constitutional small size (or constitutional SGA). As noted above, patients who are normally constitutionally small have a BW that is consistent with the expected optimal BW, and there are no physical findings of in utero malnourishment. Normally constitutionally small infants are not at increased risk for morbidity and mortality. It remains challenging to determine whether a neonate is constitutionally small, but this diagnosis is more likely when one or both parents are also small. (See 'Neonatal findings' above and "Causes of short stature", section on 'Familial short stature' and "Diagnostic approach to children and adolescents with short stature", section on 'Are there features that suggest that this is a normal variant of short stature?'.)

COMPLICATIONS

Infants with fetal growth restriction (FGR) are at risk for the several complications in the perinatal period as discussed in the following sections [16].

Prematurity — Infants with FGR are at risk for preterm delivery. In some cases, early delivery is performed because the fetal risks of remaining in utero are considered to be greater than those of prematurity. (See "Fetal growth restriction: Evaluation and management", section on 'Timing of delivery'.)

Infants with FGR who are preterm are at increased risk for death and complications related to prematurity (eg, necrotizing enterocolitis, respiratory distress syndrome, bronchopulmonary dysplasia, and retinopathy of prematurity) compared with appropriate for gestational age (AGA) control infants [12,17-20].

Perinatal asphyxia — Severely affected infants with FGR may have a difficult transition at delivery with the additional hypoxic stress of uterine contractions. This is particular an issue for fetuses with FGR due to placental pathology. (See "Placental pathology: Findings potentially associated with neurologic impairment in children".)

Impaired placental function results in hypoxia and metabolic acidosis and increases the risk of multiple organ dysfunction such as hypoxic-ischemic encephalopathy, ischemic heart failure, meconium aspiration, persistent pulmonary hypertension, and acute gastrointestinal and kidney injury. (See "Clinical features, diagnosis, and treatment of neonatal encephalopathy" and "Perinatal asphyxia in term and late preterm infants" and "Meconium aspiration syndrome: Pathophysiology, clinical manifestations, and diagnosis" and "Persistent pulmonary hypertension of the newborn".)

Impaired thermoregulation — FGR infants are at risk for hypothermia compared with AGA controls [21]. Hypothermia is due to the small for gestational age (SGA) infants' increased heat loss due to reduced subcutaneous fat, and reduced heat production due to poor nutrient reserves and depletion of catecholamines (needed for thermogenesis by brown fat) as a result of intrauterine stress [2]. Infants with FGR should be cared for in a neutral thermal environment to avoid episodes of hypothermia (eg, use of an incubator).

Hypoglycemia — Glucose must be monitored in infants with FGR because hypoglycemia is common [21-23]. The risk of hypoglycemia increases with increasing severity of growth restriction that results in decreasing reserves of fat, protein, and glycogen.

The predisposition to hypoglycemia begins in utero as low intrauterine insulin concentrations result in decreased glycogen synthesis and reduced glycogen stores. After delivery, a poorly coordinated response of counterregulatory hormones and peripheral insensitivity to these hormones may contribute to hypoglycemia [24]. Hypoglycemia typically occurs within the first 10 hours after birth. (See "Pathogenesis, screening, and diagnosis of neonatal hypoglycemia".)

Polycythemia and hyperviscosity — Polycythemia and hyperviscosity occur more frequently in infants with FGR and the risk increases with severity of growth restriction [22]. In one study, hyperviscosity was detected with a microviscometer in 18 percent of SGA infants; most had hematocrits greater than 64 percent [25]. Increased erythropoietin production resulting from fetal hypoxia is thought to be responsible [26].

Impaired immune function — Cellular immunity can be impaired in FGR infants in the newborn period and through childhood. In a cross-sectional study, T and B peripheral lymphocytes were decreased at birth; T lymphocyte numbers became normal in later childhood, but their proliferative capacity was reduced [27]. Delayed cutaneous hypersensitivity to phytohemagglutinin was reduced in both newborns and children.

Hypocalcemia — Infants with FGR who are preterm or have birth asphyxia are at risk for early hypocalcemia, which occurs in the first two to three days after birth. The risk appears to increase with the severity of growth failure [22,28]. (See "Neonatal hypocalcemia", section on 'Early hypocalcemia'.)

INITIAL MANAGEMENT

The initial management of a neonate with fetal growth restriction (FGR) is supportive and is focused on preventing or addressing any associated complications. For infants in whom there is no identified cause, further evaluation can be initiated after the infant is stabilized. (See 'Further evaluation' below.)

Delivery room management — If a fetus is known to be severely growth restricted, delivery should be planned at a perinatal center with experienced pediatric staffing. For severely affected cases, the pediatric delivery team should be prepared to manage any infant with the following possible complications:

- Perinatal asphyxia and neonatal encephalopathy (see "Clinical features, diagnosis, and treatment of neonatal encephalopathy", section on 'Treatment' and "Perinatal asphyxia in term and late preterm infants")
- Meconium aspiration (see "Meconium aspiration syndrome: Prevention and management")
- Hypoglycemia (see "Management and outcome of neonatal hypoglycemia")
- Pulmonary hypertension (see "Persistent pulmonary hypertension of the newborn")
- Hypoxia (see "Overview of neonatal respiratory distress and disorders of transition")

Because infants with FGR have impaired thermoregulation, heat loss should be avoided by immediate drying and placement of the infant under a radiant warmer. Prompt resuscitation, including clearing the airway of meconium if needed, should be instituted. (See "Neonatal resuscitation in the delivery room".)

Many of these infants are admitted to a neonatal intensive care unit (NICU) as they require more extensive care and monitoring than is routinely available in the normal nursery. (See

"Neonatal resuscitation in the delivery room", section on 'Postresuscitation' and "Overview of the routine management of the healthy newborn infant", section on 'Transitional period' and "Overview of the routine management of the healthy newborn infant", section on 'Delivery room care'.)

Nursery management — For term infants with FGR who are admitted to the normal newborn nursery, their management entails the following (table 2 and figure 1):

- Physical examination – The examination should identify any abnormality that would alter the normal newborn course or identify a medical condition that should be addressed (eg, anomalies, birth injuries, jaundice, or cardiopulmonary disorders. (See "Assessment of the newborn infant".)

  It includes:
  - Accurate measurement of length, weight, and head circumference.
  - Accurate assessment of gestational age. (See "Postnatal assessment of gestational age".)

- Thermoregulation – Maintenance of a neutral thermal environment that may require the use of an incubator or radiant heater versus an open crib.

- Glucose surveillance – Monitoring for hypoglycemia is initiated within one to two hours after birth. Samples are obtained before feedings. Surveillance is continued in infants with low plasma glucose concentrations (less than 40 mg/dL, 2.2 mmol/L) until feedings are well established and glucose values have normalized. The management of hypoglycemia is discussed separately. (See "Pathogenesis, screening, and diagnosis of neonatal hypoglycemia".)

- Calcium monitoring – SGA infants who are preterm or have birth asphyxia are at risk for hypocalcemia. Ionized calcium concentrations should be monitored starting at 12 hours after birth, and adequate calcium intake should be provided. (See "Neonatal hypocalcemia".)

- Monitoring for polycythemia – A hematocrit or hemoglobin should be obtained in infants who have signs or symptoms that may be due to polycythemia, such as cyanosis, tachypnea, poor feeding, and vomiting. (See "Neonatal polycythemia", section on 'Which infants should be screened?'.)

- Nutrition – Enteral feeding should be started early in infants at volumes appropriate for the infant's weight [29,30]. It is not certain what the most optimal caloric intake is for

infants with FGR [13]. Our goal is to provide enough nutrients to achieve postnatal growth similar to a normal fetus of the same gestational age or infant with the same postmenstrual age. Mother's breast milk is preferred as it meets most of the nutritional requirements and provides both short-term and long-term benefits over formula. (See "Infant benefits of breastfeeding".)

Infants who are unable to feed enterally require parenteral nutrition, which is provided in a more intensive care setting. (See "Parenteral nutrition in premature infants" and "Parenteral nutrition in infants and children".)

FURTHER EVALUATION

Once the infant is stabilized, further evaluation to determine the cause of fetal growth restriction (FGR) should be performed for infants in whom the underlying etiology remains unknown (table 1). However, in a large portion of cases, no underlying cause is identified. Management is directed, if possible, to treat the underlying cause and to monitor for long-term complications such as growth abnormalities and impaired neurodevelopmental outcome.

- Detailed assessment of maternal history and pregnancy history may yield the reason for the growth failure.
- Pathological examination of the placenta for evidence of infarction or infection may be useful.
- Comprehensive physical examination should be performed to detect dysmorphic features that may be indicative of an underlying chromosomal abnormality or syndrome. In some cases, genetic consultation may be helpful as well as chromosomal studies.
- Prenatal drug or toxin exposure (eg, alcohol) should be considered. A diagnosis may be made based on an assessment and work up. (See "Fetal alcohol spectrum disorder: Clinical features and diagnosis", section on 'Clinical features'.)
- Congenital infection could be the reason for FGR even if clinical signs are not obvious (eg, cytomegalovirus), and blood serologic testing or urine studies for congenital infection may be helpful. (See "Congenital cytomegalovirus infection: Clinical features and diagnosis", section on 'Clinical manifestations'.)

OUTCOMES

The risk of mortality and long-term morbidity is increased in infants with FGR because of the compromised growth and reduced energy reserves that increase the vulnerability of these infants during the stressful perinatal period with the transition from intrauterine to extrauterine life. (See "Physiologic transition from intrauterine to extrauterine life".)

Mortality — Perinatal mortality is increased in infants with FGR (small for gestational age, SGA) compared with to those born appropriate for gestational age (AGA) infants in both term and preterm infants [17,31-38]. Perinatal mortality increases as growth restriction becomes more severe, rising abruptly when birth weight (BW) is below the 6th percentile (figure 2) [39]. In a population-based study from Ontario, Canada, the highest mortality was observed in infants with severe SGA (BW <5th percentile) in both preterm and term infants [38]. In resource-limited areas, 22 percent of reported neonatal deaths occur in infants who are SGA, while overall 19 percent of infants were born SGA [9].

Term infants — Several studies have demonstrated that SGA is a risk factor for mortality in term infants [31-35]. In a systematic review of the literature, absolute BW correlated with neonatal mortality, with a BW below 1.5 kg in term infants associated with the greatest risk of mortality (odds ratio [OR] 48.6, 95% CI 28.6-82.5) [35]. Congenital malformations, perinatal asphyxia, and transitional cardiorespiratory disorders contribute to the high mortality rate in term infants.

Preterm infants — Mortality rates increase with decreasing GA and decreasing birth percentiles [17,20,37,38,40,41]. In the French EPIPAGE study that prospectively followed preterm live births born in 1997, the mortality for infants born between 24 and 28 weeks gestation was 62, 42, and 30 percent for infants who were SGA (BW <10th percentile), mildly SGA (BW between 10th and <20th percentile), and AGA (BW ≥20th percentile), respectively [40]. For infants born between 29 and 32 weeks gestation, the mortality was 10.5, 4.8, and 4.24 percent for infants born SGA, mild SGA, and AGA.

Long-term morbidity

Physical growth — Infants with FGR have different patterns of growth depending upon the etiology and the severity of growth restriction. In moderately affected infants, growth during the first 6 to 12 months after birth may be accelerated, resulting in attainment of normal size in most children [42,43]. In one study, for example, 87 percent of 3650 term infants with birth length more than two standard deviations (SDs) below the mean had normal height at one year of age [43]. However, in a report of national survey data, SGA infants appeared to catch up in weight in the first six months, but maintained a deficit in height of approximately 0.75 standard deviation units through 47 months compared with AGA infants [44]. In contrast, a prospective

study of children at 12.5 years of age born with FGR to mothers with severe early-onset hypertensive disorders during pregnancy reported that these children had comparable height and weight to age-matched controls [45].

In comparison, severely affected SGA infants frequently weigh less and are shorter than AGA infants throughout childhood and adolescence. In one report, the average height at age 17 years in adolescents who had BW less than the 3rd percentile was less than that of AGA controls (169 versus 175 cm in boys, and 159 versus 163 cm in girls, respectively) [46]. In addition, the adolescent height of SGA adolescents was more likely to be less than the 10th percentile (OR 4.13 for boys and OR 3.32 for girls).

The pathophysiology of growth restriction in SGA children and the efficacy of growth hormone therapy are discussed separately. (See "Growth hormone treatment for children born small for gestational age".)

Neurodevelopment — Children who were born with FGR are at increased risk for neurodevelopmental abnormalities and decreased cognitive performance [40,47-50].

- This was best illustrated by a systematic review of the literature that showed children with FGR compared with those born AGA were more likely to have lower scores on cognitive testing during the first 12 years of life [47]. In this study, data consistently demonstrated poorer cognitive outcomes for children born with FGR compared with AGA controls based on 60 studies that included over 50,000 children, including children born preterm (standard mean difference of test scores [SMD] -0.27, 95% CI -0.17 to -0.38) or at term (SMD -0.39, 95% -0.28 to -0.50).

- Another systematic review that identified 16 studies that evaluated early childhood neurodevelopment (six months to three years of age) reported poorer neurodevelopmental outcome including motor, cognitive, and language delay [48].

- There are also data that adolescents and young adults who were SGA due to FGR (particularly severe FGR) had lower intelligence and cognitive test scores, are more likely to have learning difficulties, and are at greater risk for developing cerebral palsy [51-55].

Preterm infants — Cognitive and neurodevelopmental abnormalities are more common in survivors who were growth restricted preterm infants compared with those who were AGA and born at the same GA.

A report from the EPIPAGE study of preterm infants (GA 26 to 32 weeks) showed survivors with symmetric growth restriction, defined as a BW and head circumference both <20th percentile,

were more likely to have cognitive difficulties at five years of age and poor school performance at eight years of age than AGA survivors born at the same GA [56].

In addition, the Extremely Low Gestational Age Newborns Cohort Study reported that children at 10 years of age born extremely preterm (gestational age <28 weeks) with severe FGR were at increased risk of multiple cognitive and behavioral dysfunctions compared to children born extremely preterm who were AGA [57]. In this analysis, increasing severity of FGR corresponded to lower levels of function on cognitive and academic achievement assessments.

Other studies have shown that children who were preterm and growth restricted compared with AGA controls are more likely to have:

- Lower scores on cognitive testing [19,34,40,58,59]
- School difficulties or require special education [34,40]
- Gross motor and minor neurologic dysfunction [19,34,59]
- Behavioral problems (attention deficit hyperactivity disorder [ADHD]) [40]
- Growth failure [19]

Adult chronic disorders — FGR appears to be a contributing factor for adult chronic diseases including coronary heart disease and hyperlipidemia, hypertension, and chronic kidney disease (CKD) (Barker hypothesis).

- **Coronary artery disease** — Adults who were infants with FGR may be at increased risk for ischemic heart disease and related disorders. This proposed association between FGR and adult coronary and vascular disease is based upon the assumption (fetal origins of adult disease theory or Barker hypothesis) that fetal undernutrition results in changes in vascular development that predisposes to adult disease, such as hypertension, stroke, diabetes, and hypercholesterolemia (Barker hypothesis) [60-62].

  The association with SGA and adult ischemic heart disease was best illustrated in a cohort study of 6425 subjects born SGA or preterm at four major Swedish delivery units between 1925 and 1949 [63]. At follow-up during the time period from 1987 to 2002, the risk of ischemic heart disease was greater in subjects who were born SGA compared with age- and sex-matched controls who were born AGA with GAs greater than 35 weeks (adjusted hazard ratio 1.64, 95% CI 1.23-2.18). The negative association between poor fetal growth and risk of ischemic heart disease was independent of GA.

  Other studies demonstrated an increase in aortic wall thickness (a marker of early atherosclerosis) by ultrasonography in infants with FGR compared with infants with normal intrauterine growth [64,65], and increased aortic stiffness [66]. In addition, one

postmortem study in children between 1 and 13 years of age demonstrated an inverse relationship between BW and the extent and severity of aortic lesions [67]. Although these findings are suggestive of a fetal contribution to later cardiovascular risk, long-term longitudinal studies are needed to more fully understand the clinical significance of these changes and whether they contribute to atherosclerosis [68]. (See "Possible role of low birth weight in the pathogenesis of primary (essential) hypertension".)

However, this hypothesis (fetal origins of the adult disease theory) is not universally accepted [69-72]. In a smaller case cohort study, no significant differences in health quality outcomes were noted between 50-year-old adults who were born full term with a BW below the 10th percentile (defined as FGR) compared with controls with BWs greater than the 10th percentile [69].

- **Hypertension** — The association between BW and adult blood pressure is discussed separately. (See "Possible role of low birth weight in the pathogenesis of primary (essential) hypertension".)

- **Chronic kidney disease** — There are data that suggest individuals who are born SGA are at risk for chronic kidney disease (CKD) including end-stage renal disease (ESRD) [73]. This was illustrated in a large population-based study from Norway of individuals born between 1967 and 2004 that reported individuals with a weight for GA that was <10th percentile were more likely to develop ESRD than those born AGA after adjusting for confounding variables such as congenital malformations, multiple delivery, maternal age, and prenatal eclampsia (relative risk [RR] 1.5, 95% CI 1.2-1.9) [74]. A systematic review also reported an association between low BW and CKD [75].

LONG-TERM FOLLOW-UP

As noted above, there is a great deal of variability in the long-term outcome for individuals with fetal growth restriction (FGR), ranging from patients with severe growth failure and neurodevelopment impairment to those without any evidence of disability. As a result, guidelines outlining long-term care for children and adults with FGR are not feasible.

Our clinical practice is affiliated with a strong network of primary care pediatricians who are able to provide high level care to infants with complex medical issues who are discharged from the neonatal intensive care unit (NICU). As a result, most infants with FGR who are discharged from our hospital are followed by their primary care provider. During these routine visits, growth parameters (height, weight, and head circumference) are measured. In cases in which

there is suboptimal growth, further interventions include nutrient supplementation and possible referral to a feeding specialist. In addition, routine neurodevelopmental screening may identify at-risk infants for neurodevelopmental impairment, who should be referred by their primary care providers for further evaluation and/or early intervention services. (See "Care of the neonatal intensive care unit graduate", section on 'Neurodevelopment' and "Care of the neonatal intensive care unit graduate", section on 'Growth and nutrition' and "Growth management in preterm infants", section on 'After discharge'.)

In our discharge planning, a neurodevelopmental assessment that is more comprehensive than the screening performed during routine pediatric care is recommended for infants with one or more of the following (see "Long-term neurodevelopmental impairment in infants born preterm: Risk assessment, follow-up care, and early intervention", section on 'Approach for follow-up care'):

- Severe growth restriction defined as birth weight less than the 3rd percentile for gestational age
- Poor growth during the NICU hospitalization with suboptimal gains in weight, length, and/or head circumference
- Diagnoses of an underlying syndrome and/or chromosomal abnormality
- Maternal substance use that resulted in FGR
- Poor oral feeding
- Evidence of absent or reversed end diastolic flow in the umbilical artery before delivery, which is a sign of fetal cardiovascular and metabolic deterioration

SUMMARY AND RECOMMENDATIONS

- **Definitions** – Fetal growth restriction (FGR) refers to the fetus who fails to maintain its expected in utero growth potential due to genetic or environmental factors (table 1). Infants with FGR are at increased risk for significant morbidity and mortality compared with infants with normal intrauterine growth. FGR is defined as an estimated fetal weight <10th percentile. (See "Fetal growth restriction: Screening and diagnosis", section on 'Definition and classification of FGR' and 'Fetal growth restriction' above.)

- **Clinical presentation** – Most infants with FGR are identified antenatally by sonographic evaluation. Newborn infants with the most severe form of FGR typically appear thin with loose, peeling skin, and decreased skeletal muscle mass and subcutaneous fat tissue. The face generally has a shrunken or "wizened" appearance, and the umbilical cord often is thin (picture 2). However, with early fetal detection of FGR and close follow-up of fetal

wellbeing, severe cases have become more uncommon, and the appearance of FGR could be modified and the clinician may not see the typical somatic signs of severe FGR. (See 'Clinical presentation' above.)

- **Diagnosis** – The diagnosis of FGR is most commonly made when the birth weight (BW) is below the 10th percentile for gestational age (ie, the definition of small for gestational age [SGA]) (table 2 and figure 1). However, there are pitfalls in this approach as it does not distinguish SGA infants who are constitutionally normally small (who are not at increased risk for perinatal mortality or morbidity) from those with FGR, and it fails to identify infants with FGR who have BW that is above the 10th percentile. As a result, it is important for the clinician to confirm the diagnosis of FGR by identifying other clinical features suggestive of poor intrauterine growth. (See 'Diagnosis' above.)

- **Complications** – Neonatal complications associated with FGR include prematurity, perinatal asphyxia, poor thermoregulation, hypoglycemia, polycythemia resulting in hyperviscosity, and impaired immune function. (See 'Complications' above.)

- **Management**

  - **Delivery room** – Management in the delivery room is supportive and is focused on preventing or addressing the associated complications. (See 'Delivery room management' above.)

    - If a fetus is known to be severely growth restricted, we suggest that delivery should be planned at a perinatal center with experienced pediatric staffing (**Grade 2C**). For severely affected cases, the pediatric delivery team should be prepared to manage any infant with perinatal depression, meconium aspiration, hypoglycemia, myocardial dysfunction, and hypoxia.

    - All infants with FGR should be immediately dried and placed under a radiant heat warmer to prevent hypothermia.

    - Depending on the clinical status, the infant can be admitted to the neonatal intensive care unit if the patient requires more extensive care or monitoring than the routine care provided in the normal nursery.

  - **Nursery** – For infants with FGR admitted to the normal nursery, routine care includes:

    - Blood glucose monitoring initiated within one to two hours after birth. Surveillance is continued in infants with low plasma glucose concentrations (less than 40 mg/dL, 2.2 mmol/L) until feedings are well established and glucose values have

normalized. (See "Pathogenesis, screening, and diagnosis of neonatal hypoglycemia".)

- Measurement of ionized calcium level for infants who are preterm or who experienced birth asphyxia starting at 12 hours after birth. These infants are at risk for hypocalcemia, and ionized calcium levels should be monitored. (See "Neonatal hypocalcemia".)

- Measurement of a hematocrit or hemoglobin level in any infant with symptoms suggestive of polycythemia (cyanosis, tachypnea, poor feeding, and vomiting). (See "Neonatal polycythemia", section on 'Which infants should be screened?'.)

- Enteral feeding should be started early at volumes appropriate for the infant's weight. Mother's breast milk is preferred over formula because of its additional short-term and long-term benefits. (See 'Nursery management' above.)

- **Further evaluation** – Once the infant is stabilized, further evaluation to determine the cause of FGR should be performed for infants in whom the underlying etiology remains unknown (table 1). However, in the majority of cases, no underlying cause is identified. (See 'Further evaluation' above.)

- **Outcome** – Infants with FGR are at risk for perinatal mortality and significant long-term morbidity including growth abnormalities and impaired neurodevelopmental outcome. However, there is significant heterogeneity in long-term outcome. In addition, individuals who were FGR may be predisposed to cardiovascular disease, hypertension, and chronic kidney disease (CKD) as adults. (See 'Outcomes' above.)

- **Long-term follow-up** – Long-term management includes monitoring growth and neurodevelopmental outcome, which is typically provided by the primary care provider. (See 'Long-term follow-up' above.)

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Topic 5062 Version 49.0

GRAPHICS

Causes of and risk factors for fetal growth restriction

Causes of and risk factors for FGR	Comments
Fetal genetic abnormalities	Account for 5 to 20% of FGR. Genetic abnormalities include: aneuploidy (including triploidy), uniparental disomy, single gene mutations (eg, *IGF1*, *IGF2*, *IGF1R*), partial deletions or duplications, ring chromosome, and aberrant genomic imprinting. At least 50% of fetuses with trisomy 13 or 18 are restricted. 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 (normal head size circumference); Smith-Lemli-Opitz, which is characterized by asymmetric growth impairment (small head circumference) and multiple extracranial anomalies; and Prader-Willi, which is characterized by asymmetric growth impairment (small head circumference), polyhydramnios, genital abnormalities, and decreased fetal movement.
Fetal infection	Accounts for 5 to 10% of FGR. Cytomegalovirus 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-twin transfusion). Placental and umbilical cord anomalies potentially associated with underperfusion are also more common in multiple gestations (eg, velamentous cord insertion). Loss of one fetus of a twin gestation increases the risk for FGR in the surviving twin.
CPM	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 mothers undergoing chorionic villus sampling is approximately 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, placental abruption, stillbirth, growth restriction, 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 characterized 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, mothers who were growth-restricted at birth have a twofold increase in risk of FGR in their offspring. In addition, mothers 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 obstetric 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: ▪ Preeclampsia ▪ Placental abruption ▪ Chronic hypertension ▪ Chronic kidney disease ▪ Pregestational diabetes mellitus ▪ Systemic lupus erythematosus and antiphospholipid syndrome ▪ Cyanotic heart disease ▪ Chronic pulmonary disease ▪ Severe chronic anemia ▪ Sickle cell disease ▪ Uterine malformations ▪ Misuse of alcohol, cigarettes, and/or drugs (eg, heroin, cocaine) ▪ Prepregnancy radiation therapy to the pelvis ▪ Heavy first trimester antepartum bleeding ▪ Previous small for gestational age newborn ▪ Previous stillbirth (unless placental insufficiency was excluded)
Teratogens and other environmental factors	Exposures to various teratogens, including medications such as warfarin, antiseizure medications (eg, valproic acid), antineoplastic agents, and

	folic acid antagonists, can cause FGR with specific dysmorphic features. Exposure to alcohol, tobacco, marijuana, 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 approximately 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	
Abnormal maternal biochemical markers for Down syndrome screening	Examples include: Low pregnancy-associated plasma protein A (PAPP-A), low beta-human chorionic gonadotropin (hCG), high alpha-fetoprotein (AFP)
Discrepancy between crown-rump length measurements and accurate menstrual history by 2 to 6 days	

FGR: fetal growth restriction; CPM: confined placental mosaicism.

Graphic 99966 Version 13.0

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

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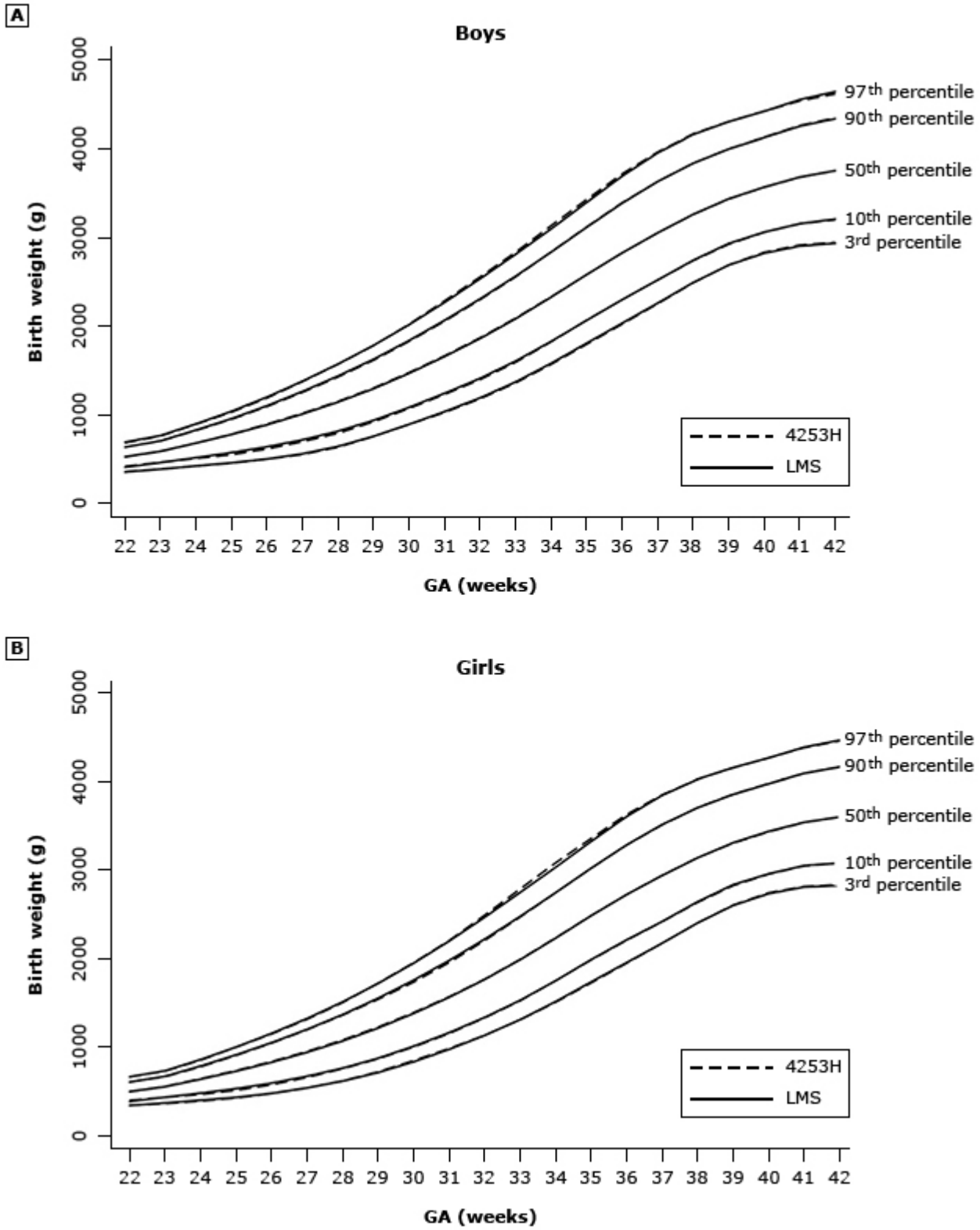
Graphic 75060 Version 4.0

Singleton United States birth weight percentile curves for boys and girls born in 2017



Comparison of smoothed BW-for-GA percentile curves for infants born in the United States in 2017 using two smoothing techniques (lambda-mu-sigma [LMS] and 4235H, a nonlinear resistant method).

BW: birth weight; GA: gestational age.

Graphic 121969 Version 3.0

Meconium-stained infant with severe intrauterine growth restriction

The infant has the characteristic appearance of an infant with intrauterine growth restriction. Note the loose, peeling skin, decreased subcutaneous tissue and muscle mass, and meconium staining.

Courtesy of George T Mandy, MD.

Graphic 78143 Version 3.0

International birth weight centiles

Boys							Girls					
	Number of observations	Centiles for birth weight (kg)						Number of observations	Centiles for b			
		3rd	10th	50th	90th	97th			3rd	10th	5	
33 weeks	34	1.18	1.43	1.95	2.52	2.82	33 weeks	17	1.20	1.41	1	
34 weeks	48	1.45	1.71	2.22	2.79	3.08	34 weeks	65	1.47	1.68	2	
35 weeks	128	1.70	1.95	2.47	3.03	3.32	35 weeks	114	1.71	1.92	2	
36 weeks	323	1.93	2.18	2.69	3.25	3.54	36 weeks	293	1.92	2.14	2	
37 weeks	857	2.13	2.38	2.89	3.45	3.74	37 weeks	803	2.11	2.33	2	
38 weeks	2045	2.32	2.57	3.07	3.63	3.92	38 weeks	1802	2.28	2.50	2	
39 weeks	3009	2.49	2.73	3.24	3.79	4.08	39 weeks	2869	2.42	2.65	3	
40 weeks	2568	2.63	2.88	3.38	3.94	4.22	40 weeks	2523	2.55	2.78	3	
41 weeks	1179	2.76	3.01	3.51	4.06	4.35	41 weeks	1195	2.65	2.89	3	
42 weeks	206	2.88	3.12	3.62	4.17	4.46	42 weeks	224	2.74	2.98	3	
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 exact gestational age.

kg: kilogram.

Reproduced from: Villar J, Cheikh Ismail L, Victoria CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet 2014; 384:857. Table used with the permission of Elsevier Inc. All rights reserved.

Graphic 96940 Version 3.0

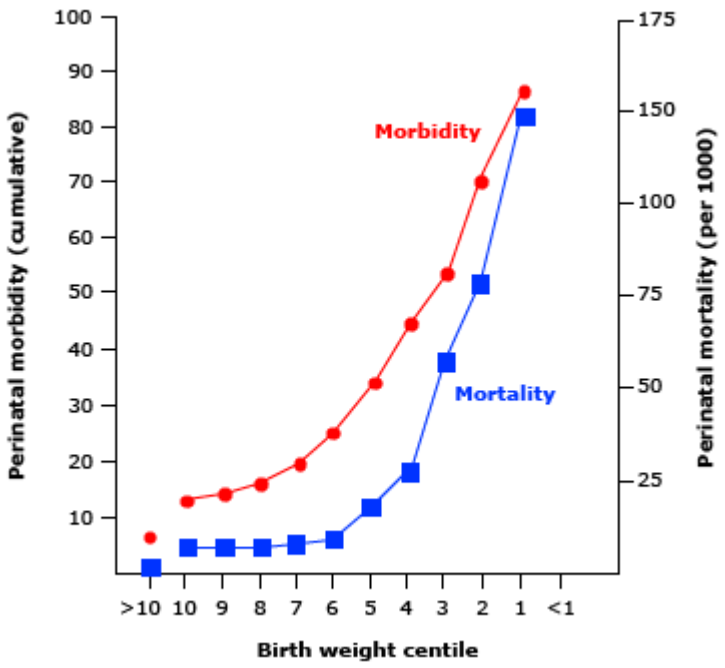
Infant with severe intrauterine growth restriction

The infant has the typical shrunken or "wizened" appearance of an infant with intrauterine growth restriction.

Courtesy of George T Mandy, MD.

Graphic 53832 Version 5.0

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

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