Intrauterine Growth Restriction
William W. Hay, Jr, Patti J. Thureen and Marianne S. Anderson
*Neoreviews* 2001;2;e129
DOI: 10.1542/neo.2-6-e129

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://neoreviews.aappublications.org/content/2/6/e129

Data Supplement (unedited) at:
http://neoreviews.aappublications.org/content/suppl/2005/01/27/2.6.e129.DC1.html
Intrauterine Growth Restriction

William W. Hay, Jr, MD,*
Patti J. Thureen, MD,*
Marianne S. Anderson, MD*

Objectives  After completing this article, readers should be able to:
1. List the most common identifiable cause of intrauterine growth restriction (IUGR).
2. List maternal conditions that can cause both IUGR and preterm delivery.
3. Characterize the effects of IUGR on fetal water, mineral, nitrogen, protein, glycogen, adipose tissue, total energy balance, and tissue mass.
4. Describe Doppler velocimetry findings suggestive of chronic fetal distress.
5. List potential adult disorders resulting from IUGR.

Introduction
Intrauterine growth restriction (IUGR) is defined as a rate of fetal growth that is less than normal for the growth potential of a specific infant. An enormous number and variety of established and possible causes have been identified. Potentially, any aberration of biological activity in the fetus can lead to growth failure. For example, deficiency or insufficient action of any one of the factors that influence fetal growth (see “Factors Influencing Fetal Growth” in this issue), alone or in combination, could lead to IUGR. The most common identifiable cause is fetal undernutrition due to placental insufficiency. Although most placentas that have insufficient function probably have specific deficits in nutrient transport capacity (eg, decreased placental vasculature with resulting decreased uterine and/or umbilical blood flow, decreased number or function of specific nutrient transporters), a smaller-than-normal placenta alone is sufficient to limit fetal nutrient supply. Small placental size can be natural, pathologic, or simply relative. For example, a small mother generally cannot produce a large placenta because her uterus is small. Similarly, even a normal-size mother can have a relatively small uterus, and, therefore, produce a small placenta if she carries more than one fetus. Experiments of artificially decreased placental growth have shown that any such restriction leads to fetal growth delay, confirming the direct relationship between placental and fetal size and the primary causal role of the placenta in determining fetal growth. However, there is no obvious or known cause of placental growth failure in most cases of IUGR; the majority are idiopathic.

The diagnosis, pathophysiologic etiologies and aberrations, maternal management, and fetal therapy of IUGR are significant issues that are far from being resolved. Recent evidence that growth failure during fetal life may result in lifelong health disorders has added a new urgency to understanding this complex disorder.

Diagnosis
Traditionally, normal fetal growth rate was determined by comparing single anthropometric measurements of an infant shortly after birth with population-based growth curves constructed from single measurement data at birth in a large number of infants at different gestational ages. More recently, fetal growth curves have been developed from in utero serial ultrasonographic measurements of fetuses who subsequently were born at term in healthy condition and “normal” term baby anthropometric measurements according to both local and broadly based populations of newborns. Ultrasonographically derived in utero growth curves have the advantage of being based on continuous rather than cross-sectional indices of fetal growth. Serial measurements of fetal growth can more accurately determine the effects of external influences on fetal growth, such as severe
maternal illness and undernutrition. Figure 1 shows ultrasonographically derived fetal growth curves with superimposed in utero growth data for a fetus whose growth rate initially was limited by poor maternal health but then was increased by improved maternal nutrition. Fetal ultrasonographically derived growth curves also demonstrate less of the mid-gestational exponential increase in fetal growth rate that is typical of cross-sectional

growth curves derived from neonatal measurements at different gestational ages. This observation supports the view that preterm birth is not a normal outcome; the intrauterine growth of preterm infants probably was affected adversely by the same pathologic factors that led to the preterm birth (see following section). Thus, inaccurate growth curves probably would be derived from cross-sectional anthropometric measurements of preterm infants assessed at birth.

**The Association of IUGR and Preterm Birth**

Most cases of fetal growth restriction represent only minimal growth delay. They are relatively natural, reproductively successful (though not perfect) adaptations to a modest reduction in nutrient supply to the fetus. Accordingly, IUGR generally is not a major cause of preterm delivery, and fetal growth rate and length of gestation are not related. However, the pathophysiologic processes causing severe IUGR can lead to preterm labor and preterm delivery. Thus, IUGR frequently occurs with a variety of maternal conditions that are associated with preterm delivery (Table). It is not surprising, therefore, and important to note, that the frequency of IUGR is inversely proportional to gestational age. Recent reports suggest that in many neonatal intensive care units, more than 50% of infants born at fewer than 26 weeks’ gestation demonstrate significant fetal growth restriction.

Established maternal conditions that cause both IUGR and preterm delivery include direct effects of very low maternal prepregnancy weight, prior preterm delivery, and cigarette smoking and indirect effects of very young or advanced maternal age and lower maternal socioeconomic status. IUGR related to maternal smoking and substance abuse may be due to reduced placental blood flow, inhibition of uteroplacental vascular development, or direct fetal toxicity. Nutritional, uterine, and vascular mechanisms may be common factors in very young and very old women who produce IUGR infants who often are also born preterm. Young, still-growing adolescent women appear less capable of mobilizing fat reserves in late pregnancy, apparently reserving them for their own continued development. Failure to mobilize such reserves can limit nutrient supply to the fetus and the rate of fetal growth.

Racial differences in rates of growth restriction and preterm delivery have been well established. African-American women who were born in the United States have a two-fold greater incidence of both preterm birth and IUGR than do Caucasian United States women or African-American women who emigrated from Africa. Reasons for this are multifactorial and include nearly all of the generally associated risks and causes of IUGR and preterm delivery.

In cases of multiple gestation, uterine and placental space-occupying anomalies (eg, fibroids), and polyhydramnios, stretch-activated mechanisms of uterine contractions probably induce preterm labor, leading to preterm delivery. These conditions also are associated with insufficient endometrial surface area for placental invasion and growth plus abnormal placental perfusion, which combine to restrict nutrient delivery to the fetus, thereby producing IUGR. In addition, poor placental growth and function limit placental supply of growth-promoting hormones to the fetus (eg, placental lactogen, steroid hormones, insulin-like growth factor [IGF]-1) and, because of abnormal rates and patterns of blood flow, limit effective maternal-fetal nutrient exchange. In cases of polyhydramnios, IUGR often is related to a primary fetal pathologic process such as fetal infection, anemia, cardiac failure, or neuromuscular disorder.

Intrauterine fetal infections can limit fetal growth by directly damaging the fetal brain and neuroendocrine axis that support fetal growth via IGFs and insulin and by damaging the fetal heart, leading to diminished cardiac output, poor placental perfusion, and inadequate nutrient substrate uptake. Fetal infections and ascending infections of the membranes from the vagina also are associated with preterm delivery, most likely related to enhanced fetal supply of prostaglandins, which causes

---

**Table. Maternal Conditions Associated With Both IUGR and Preterm Delivery**

- Both young and advanced maternal age
- Maternal prepregnancy short stature and thinness
- Poor maternal weight gain during the latter third of pregnancy
- Maternal illness during pregnancy
- Nulliparity
- Failure to obtain normal medical care during pregnancy
- Lower socioeconomic status
- African-American ethnicity (in the United States)
- Multiple gestation
- Uterine and placental anomalies
- Polyhydramnios
- Preeclampsia
- Diabetes
- Intrauterine infections
- Cigarette smoking, cocaine use, and other substance abuse
fetal and uterine production of various cytokines that are associated with or cause the onset of labor. Chronic placental and fetal infections also limit placental perfusion, in some cases by inhibiting nitric oxide production, which leads to uteroplacental vasoconstriction, placental insufficiency, and IUGR.

Preeclampsia limits endometrial vascular support for growth of the placenta, leading to placental growth failure, fetal nutrient insufficiency, and IUGR. Fetal hypoglycemia, hypoxemia, and acidosis are usually present in such cases of poor placental development and perfusion. These factors lead to increased production of prostaglandins and the activation of labor-promoting cytokines, leading to preterm delivery. Many affected fetuses are delivered preterm to protect the mother from eclampsia or the fetus from hypoxic-ischemic injury.

**Fetal Growth in Normal and IUGR Fetuses**

Fetal growth restriction can occur during any or all periods of gestation. During the embryonic period, growth occurs primarily by increased cell number (hyperplasia); in the middle of gestation, cell size also increases (hypertrophy) and the rate of cell division stabilizes. In later gestation, the rate of cell division declines, but cell size continues to increase. Thus, insults that limit fetal growth in early gestation result in global reduction in fetal growth. Insults in later gestation usually limit growth of specific tissues, such as adipose tissue and skeletal muscle, that primarily develop during this period and spare other organs and tissues, such as the brain and heart, whose growth rate already has slowed.

**Water**

Total body water content in the normal fetus increases over gestation, but fetal total body water content as a fraction of body weight decreases due to relative increases in protein, mineral, and fat accretion. Extracellular water also decreases more than intracellular water as gestation advances, primarily because of increasing cell number and size. In fetuses that exhibit mild-to-moderate IUGR, measurements of extracellular fluid are usually normal for gestational age because adipose tissue, skeletal muscle, and mineral accretion all are decreased to about the same extent. In contrast, severe IUGR with markedly decreased fat content is characterized by higher fractional contents of body water.

**Minerals**

Mineral content per body mass and bone mass in IUGR fetuses does not differ from that in normally grown fetuses. For example, fetal calcium content in IUGR fetuses increases exponentially with a linear increase in length because bone density, area, and circumference increase exponentially in relation to linear growth. Accretion of other minerals varies more directly with body weight and according to the distribution of the minerals into extracellular (eg, sodium) or intracellular (eg, potassium) spaces.

**Nitrogen and Protein**

Data from the very few available chemical composition studies of normal human infants show that nonfat dry weight and nitrogen content (predictors of protein content) have a linear relationship with fetal weight and an exponential relationship with gestational age (Fig. 2). Approximately 80% of fetal nitrogen content is found in protein; the remainder is in urea, ammonia, and free amino acids. Among IUGR infants, nitrogen and protein
contents are reduced for body weight, primarily due to deficient muscle growth.

**Glycogen**

Glycogen synthetic rates are low in the human fetus, accounting for less than 5% of fetal glucose utilization. Insulin acts synergistically with glucose to increase hepatic glycogen stores, with cortisol, epinephrine, and glucagon developing the capacity to promote glycogenolysis and glucose release into the plasma close to term. Most tissues in the fetus, including brain, liver, lung, heart, and skeletal muscle, produce glycogen over the second half of gestation. Liver glycogen content, which increases with gestation (Fig. 3), is the most important store of carbohydrate for systemic glucose needs because only the liver contains sufficient glucose-6-phosphate for release of glucose into the circulation. Skeletal muscle glycogen content increases during late gestation and forms a readily available source of glucose-6-phosphate for glycolysis within the myocytes. Lung glycogen content decreases in late gestation with change in cell type, leading to loss of glycogen-containing alveolar epithelium, development of type II pneumocytes, and onset of surfactant production. Cardiac glycogen concentration decreases with gestation owing to cellular hypertrophy, but cardiac glycogen appears essential for postnatal cardiac energy metabolism and contractile function.

Glycogen content is markedly reduced in IUGR infants, both in the liver and in the skeletal muscles (Fig. 3), due to lower fetal plasma concentrations of glucose and insulin, which are the principal regulators of glycogen synthesis. Repeated episodes of hypoxemia in severe IUGR can stimulate epinephrine secretion, which will deplete glycogen further by activating glycogen phosphorylase and increasing glycogenolysis.

**Adipose Tissue**

The fat content of human newborns at term is about 15% to 20%, which is considerably greater than the 1% to 3% found in most other land mammals (Fig. 4). Human fat accretion begins in the late second to early third trimester of gestation. In the first half of gestation, nonfat and fat components contribute equally to the carbon content of the fetal body. Subsequently, fat accumulation exceeds that of the nonfat components such that between 36 and 40 weeks’ gestation, the rate of fat accretion is approxi-
mately linear and accounts for more than 90% of the carbon accumulated by the fetus.

In human IUGR fetuses at term, fat content may be less than 10% of body weight. Causes include decreased fatty acid, triglyceride, and glucose supplies from the smaller placenta as well as a simultaneous insulin deficiency that limits fat synthesis because of decreased stimulation of fatty acid synthase in adipocytes. Because fat has a high energy content of 9.5 kcal/g and a very high carbon content of approximately 78%, decreased fat content in IUGR fetuses leads to large decreases in energy and carbon accretion rates.

**Total Energy Balance and Tissue Mass**

The relative mass of all tissue components, not just fat and glycogen stores, depends on energy supply, particularly for protein deposition. For example, chronic selective restriction of glucose delivery to the fetal sheep leads to increased protein breakdown as well as to lower rates of fetal growth and lipid content. Although most studies suggest that the greatest relative decrease in tissue mass occurs in the fat compartment in human IUGR fetuses, others have shown that muscle mass can be markedly deficient, even more than fat.

**Clinical Approach**

**Diagnosis**

It is difficult to diagnose IUGR antenatally. Serial maternal physical examinations are the most common clinical means of assessing fetal growth, but this is very insensitive. Despite recent significant advances, serial fetal ultrasonography is not universally available, and the accuracy of size assessment can vary highly, depending on available equipment and operator experience. Additionally, prenatal gestational dating by maternal history may not be accurate. Not surprisingly, therefore, more than 50% of infants who have IUGR are not identified before birth.

Once a decrease in fetal growth rate is suspected, the current diagnostic approach to determining the severity of IUGR includes serial ultrasonographic evaluation of fetal growth rate and body proportions combined with Doppler velocimetry of the uterine, placental, and fetal
circulations. Doppler velocimetry measurements particularly have provided increasingly accurate prognostic evidence of deteriorating fetal condition and impending death. Chronic fetal distress resulting from placental insufficiency, hypoxia, and ischemia (with or without acidosis) is associated with increased systolic-to-diastolic arterial flow velocity (amplitude) waveforms, indicating vascular resistance and reduced systemic flow in the fetal descending aorta and umbilical artery. Various ratios of systolic-to-diastolic flow velocity waveforms have been used, including the systolic-to-diastolic ratio, the systolic-diastolic/systolic ratio (resistance index), and the systolic-diastolic/mean ratio (pulsatility index). Ratios or indices greater than two standard deviations from the mean are associated with IUGR; reversed or absent diastolic waveforms represent severe fetal hypoxia and increased risk of fetal death. The most severely affected IUGR fetuses that have the greatest risk of death demonstrate absent or reversed diastolic flow in systemic fetal arteries plus increased umbilical venous pulsation and reversed flow in the abdominal vena cava. Interestingly, these same fetuses often have decreased cerebral (internal carotid artery) flow velocities, indicating increased cerebral blood flow. This flow pattern has been interpreted as one way in which brain growth is spared as body growth rate slows following placental ischemia and/or placental growth failure. Doppler waveform abnormalities usually precede less specific signs of fetal distress, such as abnormal changes in fetal heart rate that are spontaneous or in response to oxytocin challenge.

The fetus also should be examined ultrasonographically for anatomic abnormalities that indicate congenital malformations, genetic syndromes, and deformations. The amniotic fluid index is useful for identifying oligohydramnios (a risk factor for congenital anomalies), severe IUGR with reduced urine production, pulmonary hypoplasia, variable decelerations from cord compression, and intrauterine fetal death in as many as 5% to 10% of affected pregnancies.

Future Diagnostic Modalities
Altered fetal growth rate and pathophysiology associated with IUGR usually develop insidiously. Once these conditions become clinically obvious, fetal damage already has occurred. It is important, therefore, to develop and apply diagnostic techniques to the fetus that would establish even minimal changes in growth rate and coordinated changes in physiologic function accurately and sensitively. Doppler ultrasonographic measurements of fetal cardiac output, systemic blood flow, and organ blood supply are close to achieving this goal, particularly with respect to placental circulation. Recent research trials have attempted to quantify placental transfer functions in pregnant women who are carrying severely IUGR fetuses. Stable isotopes of nutrients normally transported across the placenta (such as glucose and selected amino acids) are administered, followed by timed fetal umbilical cord blood sampling. Placental transfer characteristics of these substrates are assessed and compared with that from pregnancies that have normal placental function and fetal growth rates. Such studies have indicated decreased transplacental transport rates of selected amino acids in IUGR pregnancies.

New diagnostic techniques to assess the severity and timing of fetal pathophysiologic changes in severe IUGR hold great promise. Current examples include magnetic resonance imaging, Doppler measurements of blood flow to specific organs, cordocentesis, and neurologic and neuromuscular response to vibroacoustic stimulation. A goal of such potential studies should be to assess whether the earliest detected changes in fetal growth rate and pathophysiology associated with IUGR are, in fact, as serious and indicative of future handicap as careful postnatal follow-up studies have indicated. Such findings might encourage more aggressive diagnosis and early treatment studies to prevent the more severe forms of IUGR.

Antenatal Management for Prevention
Considerably more research is necessary to determine when and how damage to the fetus can be ameliorated or prevented. At present, there is no known successful prevention strategy for IUGR. Bed rest and treatment of acute and chronic maternal illnesses appear beneficial. Trials of low-dose aspirin therapy aimed primarily at treating preeclampsia have not consistently improved fetal growth. Correction of maternal nutritional deficiencies is useful, particularly when the mother is markedly undernourished. Maternal dietary zinc supplements have improved fetal growth when zinc deficiency was prominent. Prenatal high maternal protein intakes in women at risk for mild undernutrition have been associated with worse IUGR and perinatal morbidity and mortality. Improved protein nutrition of mothers whose diets are very protein-deficient is, however, a reasonable goal to improve overall nutritional health and possibly the supply of amino acids to the fetus.

Antenatal Management for Amelioration of Existing IUGR
Few data document effective prenatal strategies for reversing established IUGR. Maternal administration of
supplemental oxygen improves fetal oxygenation, and in a few studies of severe IUGR fetuses that had signs of chronic distress, it has been associated with improved rates of fetal growth and reduced fetal aortic blood flow velocity (increased blood flow). To date, no studies have demonstrated conclusively improved fetal growth with either maternal or fetal nutrient supplementation in IUGR pregnancies. In several animal models, glucocorticoids have been administered to both mother and fetus to increase fetal lung surfactant development. There may be some additional enhanced maturation of other fetal organs, including gut, heart, adrenals, and kidneys. Continued research is necessary to assess brain development with such treatments as well as long-term growth and development of all affected organs. More research is also required to determine the risks and potential advantages of artificially altered patterns of organ development during fetal life with exogenously administered hormones and growth factors.

Monitoring the Pregnancy With Suspected or Confirmed IUGR

Fetal surveillance techniques should be instituted to determine whether the fetal condition is beginning to fail and if delivery might result in a successful outcome. Traditional fetal surveillance techniques have included fetal activity recordings; the oxytocin challenge test, which measures fetal heart rate changes after oxytocin-induced uterine contractions; and the nonstress test (NST), which measures the acceleration and beat-to-beat variability of the fetal heart rate after spontaneous fetal movement. These tests are being replaced by Doppler velocimetry and the biophysical profile. The latter assessment combines analyses of fetal breathing movements, gross body movements, fetal heart rate, fetal heart rate reactivity to movement, and estimated amniotic fluid volume. A low biophysical profile correlates with fetal hypoxia (as determined by absent or reversed diastolic flow in the umbilical artery), abnormal fetal blood gas and acid-base measurements obtained by cordocentesis, and impending fetal demise.

Most obstetricians avoid labor when combined fetal surveillance techniques show severe IUGR and evidence of severe chronic distress. Such signs include absent or reversed diastolic flow in the fetal aorta, increased pulsations and/or reversed flow in the umbilical veins, and a low biophysical profile score. These conditions usually are associated with nonreactive NST results and a flat baseline fetal heart rate variability pattern. Such fetuses often deteriorate rapidly during labor and quickly show signs of acute distress, with worsening fetal bradycardia patterns, loss of beat-to-beat variability, and decreased movement. Prior to emergency delivery, the mother usually is given oxygen to breathe. More recently, saline amnioinfusion has been used, particularly in the presence of oligohydramnios. Amnioinfusion may decrease the incidences of meconium-stained fluid, variable fetal heart rate decelerations, end-stage bradycardia, and acute fetal acidosis.

Generally, the mild-to-moderately affected IUGR fetus should be left in utero unless repeated evaluations show progressively worsening IUGR and signs of fetal distress. Decisions to deliver these fetuses to prevent fetal death should be tempered by the difficulties of accurately diagnosing the worsening of fetal condition and successfully managing all potential neonatal problems of a preterm infant. Frequent consultations between maternal-fetal medicine specialists and neonatologists should be standard, adding thought and data from repeated evaluations to appropriate caution regarding a decision for early delivery. This is especially true for the earliest (<30 weeks’ gestation) and smallest (<1,000 g) of these fetuses.

Possible Adult Disorders Resulting From IUGR

Recent epidemiologic evidence indicates that obesity, insulin resistance, diabetes, and cardiovascular disease are more common among adults who were smaller-than-normal at birth because of IUGR, particularly those who had a high placental-to-fetal weight ratio. A variety of animal studies support this concept, including the greater incidence of obesity, glucose intolerance, plasma lipid abnormalities, and hypertension in offspring whose mothers were fed a low-protein diet during pregnancy. These examples indicate that certain adult pathologies may be unavoidable consequences of environmentally imposed conditions, such as severe and prolonged fetal undernutrition, that lead to fetal growth restriction to ensure fetal survival. These conditions may represent examples of what Lucas refers to as metabolic “programming,” in which an insult applied at a critical or sensitive stage in development may result in a lasting effect on the structure or function of the organism. IUGR, therefore, is increasingly viewed as an adaptive physiologic process, even though it can produce adverse fetal, neonatal, and adult consequences.

Mechanisms responsible for these later life morbidities in adults whose growth was restricted in utero are not yet clearly established. There is some evidence of diminished pancreatic growth and development, which might present in later life as pancreatic insufficiency when the adult starts eating a diet rich in simple carbohydrates and
lipids. Peripheral insulin resistance may develop in the same way, and hypertension in adulthood may be the result of altered adrenal development in response to IUGR. If these epidemiologic and supportive animal data hold true, there is even more reason to focus attention on early fetal growth failure.

ACKNOWLEDGMENTS
Supported in part by NIH Grant MO1 RR00069, HD20761, and DK52138.

Suggested Reading


NeoReviews Quiz

4. The body composition of a fetus who has intrauterine growth restriction (IUGR) differs from that of a normally grown fetus. Of the following, IUGR is most likely to increase the:
   A. Energy content of adipocytes.
   B. Fractional content of body water.
   C. Glycogen content of skeletal muscle.
   D. Mineral content per bone mass.
   E. Nitrogen content per body weight.

5. Antenatal diagnosis of IUGR is important for early detection of the fetus in jeopardy and for possible intervention. Of the following, the most accurate statement regarding antenatal diagnosis is that:
   A. Amniotic fluid index provides an accurate measure of fetal lung maturity.
   B. Doppler velocimetry provides an accurate prognosis of impending fetal death.
   C. Fetal heart rate monitoring reveals specific signs of fetal distress.
   D. Fetal ultrasonography is a sensitive method of assessing intrauterine growth.
   E. More than 50% of infants who have IUGR are identified before birth.

6. Several strategies have been explored for antenatal prevention of IUGR. Of the following, the strategy for maternal treatment that has proven to be most beneficial in preventing IUGR is:
   A. Bed rest.
   C. Low-dose aspirin therapy.
   D. Oxygen administration.
   E. Protein supplementation.