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Intrauterine Growth Retardation

A patient information handout on intrauterine growth retardation, written by the authors of this article, is provided on page 1393.

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Intrauterine growth retardation (IUGR), which is defined as less than 10 percent of predicted fetal weight for gestational age, may result in significant fetal morbidity and mortality if not properly diagnosed. The condition is most commonly caused by inadequate maternal-fetal circulation, with a resultant decrease in fetal growth. Less common causes include intrauterine infections such as cytomegalovirus and rubella, and congenital anomalies such as trisomy 21 and trisomy 18. When IUGR is recognized, it is important to attempt to correct reversible causes, although many of the conditions responsible for IUGR are not amenable to antenatal therapy. Close fetal surveillance with delivery before 38 weeks of gestation is usually recommended. Some infants born with IUGR have cognitive and medical problems, although for most infants the long-term prognosis is good.

References in the medical literature to underweight infants date back to 1919, when it was suggested[1] that all newborns weighing less than 2,500 g (5 lb, 8 oz) should be classified as "premature." However, it was not until 1961 that the World Health Organization (WHO) acknowledged that many infants defined as "premature" were not born early but were simply of "low birth weight."[2] The current WHO criterion for low birth weight is a weight less than 2,500 g (5 lb, 8 oz) or below the 10th percentile for gestational age.

Low birth weight includes two pathologic conditions and one normal condition. The normal condition refers to the healthy but constitutionally small baby. The pathologic conditions include preterm delivery and intrauterine growth retardation (IUGR). Synonymous terms found in the literature to describe infants with IUGR include intrauterine growth restriction and fetal growth retardation. In the United States, IUGR

is linked to an increase of six to 10 times in perinatal mortality.[1,3]

Epidemiology

According to the common definition of IUGR as a birth weight under the 10th percentile, the expected incidence of IUGR should be 10 percent. The actual incidence, however, is only about 4 to 7 percent. About one fourth of infants who are below the 10th percentile have a normalized birth weight when it is corrected for low maternal weight, paternal phenotype or residence at higher altitudes.[4] Some regional variations in birth weight may exist within the United States and Canada. Previously published standards found variations of 100 to 200 g (3.5 to 7 oz) when comparing 10th-percentile infants of the same gestational age who were born in Canada with those born in Denver or California.[3]

The approximately 3.5 million annual births in the United States translate to about 350,000 infants who are born weighing less than 2,500 g (5 lb, 8 oz).[1] Approximately one third of these infants (about 100,000) have true IUGR, and the remaining two thirds (about 250,000) are constitutionally small.[3] Some authors apply the term "small for gestational age" to the latter group of infants.

Most authorities prefer to maintain the strict and more inclusive definition of IUGR as less than 10 percent of predicted fetal weight for gestational age. Using the 10th percentile as a standard results in overdiagnosis of IUGR. Other authors, however, have suggested using the 5th percentile to define IUGR infants.[1] The counter argument in favor of a strict definition is that birth weight is probably the single most important factor affecting neonatal morbidity and mortality and should be aggressively screened for.[5] A lack of consensus among perinatologists makes it difficult to fully define the extent of IUGR and the subsequent effectiveness of interventions.

Etiology

Many different factors cause IUGR, but they may be divided into two large categories, based on etiology. These categories include fetoplacental factors and maternal factors. Within the categories of maternal and fetoplacental factors are many specific causes (*Table 1*).

TABLE 1
Conditions Associated with Intrauterine Growth Retardation

Medical	Maternal	Infectious
Chronic hypertension	Smoking	Syphilis
Preeclampsia early in gestation	Alcohol use	Cytomegalovirus
Diabetes mellitus	Cocaine use	Toxoplasmosis
Systemic lupus erythematosus	Warfarin (Coumadin, Panwarfin)	Rubella
Chronic renal disease	Phenytoin (Dilantin)	Hepatitis B
	Malnutrition	HSV-1 or HSV-2
	Prior history of pregnancy with	HIV-1

Inflammatory bowel disease Severe hypoxic lung disease	intratuterine growth retardation Residing at altitude above 5,000 feet	**Congenital** Trisomy 21 Trisomy 18 Trisomy 13 Turner's syndrome

HSV=herpes simplex virus; HIV=human immunodeficiency virus.

Information from references 1 and 3.

Historically, IUGR has been categorized as symmetric or asymmetric. Symmetric IUGR refers to fetuses with equally poor growth velocity of the head, the abdomen and the long bones. Asymmetric IUGR refers to infants whose head and long bones are spared compared with their abdomen and viscera. It is now believed that most IUGR is a continuum from asymmetry (early stages) to symmetry (late stages).

Maternal causes of IUGR account for most uteroplacental cases. Chronic hypertension is the most common cause of IUGR. Moreover, the infants of hypertensive mothers have a three-fold increase in perinatal mortality compared with infants with IUGR who are born of normotensive mothers. Because of their significant risk, one author[6] recommends delivering these infants by 37 weeks of gestational age.

Preeclampsia causes placental damage that results in uteroplacental insufficiency. The pathogenic mechanism is thought to be a failure of trophoblastic invasion by maternal spiral arterioles by 20 to 22 weeks of gestation.[1] This failure causes luminal narrowing and medial degeneration, leading to diminished blood flow to the developing infant. Consequently, these infants fail to grow normally.

Infectious causes of fetal growth delay account for about 10 percent of all cases of IUGR. These causes include the "TORCH" group: Toxoplasma gondii, rubella, cytomegalovirus and herpes simplex virus types 1 and 2. Other potential pathogens include hepatitis A and hepatitis B, parvovirus B19, human immunodeficiency virus (HIV) and Treponema pallidum (syphilis).

Maternal prepregnancy weight and weight gain during pregnancy are considered strong indicators of birth weight.[7] During World War II, a population of women in Leningrad who underwent prolonged malnutrition delivered infants with an average birth weight of 400 to 600 g (14 to 21 oz) less than expected.[5] In a later study of Guatemalan Indians,[8] it was found that protein malnutrition occurring before 26 weeks of gestation resulted in IUGR. The current consensus is that a maternal weight gain of less than 10 kg (22 lb) by 40 weeks of gestation is clearly a risk factor for IUGR.[3]

Head circumference that does not change over a four-week period is worrisome and may be an indication for prompt delivery.

Maternal smoking may be the cause of 30 to 40 percent of U.S. cases of IUGR. One study[9] found a dose-dependent decrease in fetal weight with an increasing number of cigarettes smoked each day (a 7.4 g [0.26 oz] decrease for each cigarette smoked per day). Another study[10] found that women who smoked 11 or more cigarettes daily had infants weighing 330 g (11.5 oz) less than predicted and measuring 1.2 cm shorter than control subjects.

Early use of alcohol by the pregnant mother may lead to fetal alcohol syndrome, while second- or third-trimester use may result in IUGR. As little as one to two drinks per day have been shown to result in a growth-delayed child.[11] Not surprisingly, maternal cocaine use has been linked to IUGR, as well as to reduced head circumference. Other drugs associated with IUGR include steroids, warfarin (Coumadin, Panwarfin) and phenytoin (Dilantin).

Intrauterine growth retardation occurs 10 times more frequently in twin deliveries than in single gestations. The incidence of IUGR in twins is about 15 to 25 percent.[5] Decreased birth weight is second only to respiratory distress syndrome as a cause of infant mortality in twins. Reasons for IUGR in twin pregnancies include poor placental implantation, placental crowding and twin-to-twin transfusion.

Diagnosis

Before the development of ultrasonography, delayed fetal growth was indicated by low maternal weight gain, Leopold maneuvers and fundal height measurement. Currently, IUGR is still often suspected on the basis of fundal height measurements. A significant lag in fundal height is a 4-cm or greater difference than expected for gestational age. However, even carefully performed fundal height measurements only have a 26 to 76 percent sensitivity in predicting IUGR.[12] IUGR is frequently detected in a pregnancy with a less-than-expected third-trimester weight gain (100 to 200 g [3.5 to 7 oz] per week) or as an incidental finding on ultrasound examination when fetal measurements are smaller than expected for gestational age.

The main prerequisite for determining IUGR is precise dating. The most accurate dating method uses ultrasound examination at eight to 13 weeks. Later ultrasound examinations are helpful, but the margin of error is increased. The date of the last menstrual period, early uterine sizing and detection of fetal heart tones are helpful ways to accurately date the pregnancy. Most cases of IUGR present during the third trimester, which makes them difficult to accurately diagnose. This is especially true if the patient has presented for prenatal care at a late stage. The physician must determine if the dating is incorrect and the fetal size is actually normal or if the mother truly needs further evaluation for IUGR.

When the suspicion of IUGR is strong, a complete assessment of maternal risk factors should be undertaken. This includes past medical and obstetric history, medication use, recent infections, occupational or toxic exposures, and a history of tobacco, alcohol or illicit drug use.

Ultrasonography is normally the first study done to assess IUGR. This test loses its accuracy as the pregnancy progresses, but the sensitivity and positive predictive

value can be improved if several variables are combined.[13] These variables include estimated fetal weight, head circumference and abdominal circumference.

Estimated fetal weight is the most common screen. It is based on the measurements of head circumference, abdominal circumference and femur length. These measurements are plotted on a preexisting standardized chart. In about 95 percent of cases, ultrasound examination allows an estimation of fetal weight with a 15 to 18 percent variance.[13] An estimated fetal weight of less than the sixth percentile strongly correlates with growth retardation, and an estimated fetal weight of greater than the 20th percentile virtually rules out IUGR. An estimated fetal weight at the 15th percentile or less, or a decreasing estimated fetal weight as determined by serial ultrasound examination, is suggestive of IUGR.

In all growth-retarded fetuses, the abdominal circumference is the first biometric measure to change. This translates to an increased ratio of head circumference to abdominal circumference. The ratio of head circumference to abdominal circumference is normally one at 32 to 34 weeks and falls below one after 34 weeks. A ratio of greater than one detects about 85 percent of growth-restricted fetuses.[14]

The first radiographic sign of IUGR may be decreased amniotic fluid volume. About 85 percent of IUGR infants have oligohydramnios.[15] This condition occurs because blood flow from peripheral organs (kidneys) is diverted to the brain. Renal perfusion and urinary flow rates are commonly reduced in infants with IUGR.[16] An amniotic fluid index of less than 5 cm increases the risk of IUGR. A vertical pocket of amniotic fluid less than 1 cm, regardless of gestational age, is found in about 39 percent of cases of IUGR.[14]

Maternal arterial umbilical blood flow increases from 50 mL per minute early in pregnancy to about 700 mL per minute at term. The increase is secondary to a gradual decrease in vessel resistance to blood flow throughout the pregnancy. Doppler velocimetry uses ultrasound to measure peak-systolic and end-diastolic blood flow through the umbilical artery. Three measurements are averaged as the systolic/ diastolic ratio. As the pregnancy progresses, diastolic flow increases, and the systolic/diastolic ratio should

TABLE 2
Indications for Delivery Based on the Biophysical Profile

BPP<2
BPP=4 at >32 weeks
BPP=4<32 weeks; repeat same day; induce if <6
BPP=6 with normal AFI, >36 weeks with favorable cervix
BPP=8 with oligohydramnios
BPP=6 at <36 weeks and cervix unfavorable; repeat in 24 hours; induce if <6; follow if >6

BPP=biophysical profile; AFI=amniotic fluid index.

NOTE: The biophysical profile consists of five components, including fetal breathing movements, gross body movements, tone,

gradually decrease. In a large number of IUGR pregnancies, an alteration in placental blood flow occurs. As a result, researchers have correlated an increased systolic/diastolic ratio with IUGR. The ratio is increased in about 80 percent of cases of IUGR diagnosed by ultrasound examination.[17] An average systolic/ diastolic ratio greater than three at 30 or more weeks of gestation has a sensitivity of 78 percent and a specificity of 85 percent in predicting IUGR.[18]

amniotic fluid index and a nonstress test. Each component is scored as either zero or 2, with a maximum score of 10.

Information from reference 21.

Ultrasonographic placental grading has been studied with respect to IUGR. Normally, a grade 3, or mature, placenta would not be detected before 36 weeks of gestation. The presence of a grade 3 placenta before 36 weeks, along with an estimated fetal weight of less than 2,700 g (5 lb, 14 oz), carries a four-fold risk of IUGR.[19]

Antenatal Surveillance

When the diagnosis of IUGR has been established, it is helpful to determine a specific etiology. Therapy may be nonspecific but should try to address the underlying cause. Many infants thought to be growth-retarded are, in retrospect, found to be constitutionally small. The key management issues are the gestational age of the pregnancy at the time of diagnosis and the urgency to expedite delivery. Most fetal deaths involving IUGR occur after 36 weeks of gestation and before labor begins.[1] The clinician must balance the risk of delivering a premature infant against the potential for intrauterine demise.

Ultrasonography at three- to four-week intervals is recommended to assess fetal growth.[1,5] It is important that the physician communicate with the ultrasonographer, indicating that suspected IUGR is the reason for the serial examinations. Appropriate attention must be given to estimated fetal weight, biparietal diameter, head circumference, abdominal circumference and amniotic fluid volume. Third-trimester fetal weight gain should be 100 to 200 g (3 lb, 8 oz to 7 lb) per week. Head circumference that does not change over a four-week period is worrisome and may be an indication for prompt delivery.[1]

Twice-weekly nonstress testing (NST) is an appropriate surveillance method in following a fetus with IUGR. A reactive NST (two accelerations in fetal heart rate of more than 15 beats per minute lasting for more than 15 seconds in a 20-minute span) has been shown to correlate with fetal well-being.[1] Spontaneous variable decelerations in fetal heart rate on the NST may indicate oligohydramnios and an increased risk of perinatal

TABLE 3
Diagnostic Studies for Evaluation of Possible Intrauterine Growth Retardation

Chemistry panel

mortality.[20] A nonreactive NST indicates possible fetal hypoxemia and should be followed by a contraction stress test or a biophysical profile. The biophysical profile includes an NST, fetal breathing movements, gross body movements, fetal tone and amniotic fluid index. Two large studies[21,22] found the biophysical profile to be predictive of fetal well-being, fetal distress and ultimate perinatal mortality. Guidelines for antepartum management are based on biophysical profile scoring (*Table 2*).

Complete blood count
Maternal antibody titers ("TORCH" titers--IgM, IgG)
Ultrasound examination
Biophysical profile
Doppler velocimetry
Amniocentesis (to check fetal maturity before induction)

TORCH=Toxoplasma gondii, rubella, cytomegalovirus and herpes simplex virus types 1 and 2.

Doppler velocimetry, previously discussed as a diagnostic technique for IUGR, has not found a place in routine antenatal surveillance. It has helped physicians understand the pathophysiology of IUGR with regard to diminished blood flow. Results of this procedure correlate with increased fetal morbidity and mortality: an absent or reversed end-diastolic umbilical flow is an ominous finding and necessitates aggressive intervention. As a screening test, however, the procedure appears to be lacking in benefit; some studies[23] have shown that 40 to 60 percent of infants with IUGR had normal Doppler velocimetry results just before birth. Currently, the American College of Obstetrics and Gynecology[24] classifies fetal Doppler studies as investigational. *Table 3* summarizes diagnostic studies used in the evaluation of IUGR.

Treatment

Treatment of the mother and the growth-restricted fetus is, when possible, dictated by the etiology of the condition. As previously noted, many of the conditions responsible for IUGR are not amenable to antenatal therapy.

Prenatal Management

Maternal hyperoxygenation has been evaluated in several studies, but only limited data prove its efficacy. In one study,[25] nasal oxygen at 2.5 L per minute administered to mothers at 27 to 28 weeks of gestation improved neonatal blood gas measurements but resulted in an increased incidence of hypoglycemia and thrombocytopenia in the infants. One report[1] suggests that supplemental oxygen may have a role in short-term prolongation of pregnancy, while steroids can be administered to accelerate fetal lung maturity.

Low-dose aspirin (150 mg per day) as a treatment for IUGR has been studied over the past several years. One study[26] found that when aspirin was given to women in the third trimester who had abnormal umbilical Doppler indices, fetal weight and head circumference parameters were improved compared with a placebo group. In a second trial,[27] aspirin, given in a dosage of 150 mg per day with dipyridamole in a dosage of 225 mg per day and administered at 15 to 18 weeks of gestation in

high-risk patients, resulted in a lower incidence of still-birth, placental abruption and IUGR. Birth weight was improved, and no excess of maternal or fetal aspirin-related side effects occurred. It would seem prudent to consider low-dose aspirin therapy in selected patients with risk factors for IUGR (*Table 1*).

Labor and Delivery Management

Approximately one half of infants with IUGR have intrapartum asphyxia and lower Apgar scores than control subjects. A higher incidence of meconium aspiration has also been noted in these infants. Therefore, continuous monitoring of fetal heart rate throughout labor is recommended in cases of IUGR.[1,3] Amnioinfusion may also have a role in these cases, especially in the presence of olgihydramnios. Late decelerations are more predictive of fetal hypoxia and a resultant adverse outcome in this group of high-risk infants. A lower threshold for the choice of cesarean section is therefore recommended. Neonatal resuscitation and subsequent care of the growth-restricted infant should follow in the same manner used with other newborns. Problems to closely watch out for in infants with IUGR include hypoglycemia, hypocalcemia, polycythemia secondary to intrauterine hypoxia and hypothermia due to decreased body fat.[1,5]

Neonatal Outcomes

In most cases, infants with IUGR ultimately have good outcomes, with a reported mortality rate of only 0.2 to 1 percent.[1] These infants often exhibit fast catch-up growth in the first three months of life and attain normal growth curves by one year of age. Some early studies[28,29] have found a variety of long-term complications in infants with IUGR. These complications include hyperactivity, clumsiness and poor concentration. Other studies[30,31] have found growth-restricted infants to be at increased risk for development of hypertension, abdominal obesity and type 2 (noninsulin-dependent) diabetes as adults.

In a recent British study,[32] records of 1,576 men and women born between 1920 and 1943 for whom birth weight and anthropomorphic measurements were recorded in detail after birth were examined. No definite association was found between cognitive function (intelligence quotient and vocabulary) and birth weight, head circumference or ratio of head circumference to abdominal circumference. Collectively, developmental studies demonstrate that many factors contribute to the ultimate intellectual development of infants with IUGR, including birth weight, time of onset of IUGR, head circumference, gestational age at delivery, etiology of the IUGR and postnatal environment. Most infants with IUGR have an excellent long-term prognosis.

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