FETAL GROWTH RESTRICTION (FGR)

(also known as Intrauterine Growth Restriction - IUGR)

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DEFINITION

By definition, ten percent of infants in any population will have birth weights at or below the 10th percentile. This is the usual definition of fetal growth restriction as made by ultrasonographic determination of fetal weight. Perinatal morbidity and mortality however do not usually begin to rise until birth weights are below the 3rd to the 5th percentile for gestational age. For practical clinical purposes, in order to avoid the sequelae of severe FGR, it is therefore prudent to address the problem when presented with an estimated fetal weight below the 10th percentile. By convention, the term "small for gestational age" (SGA) should be used to refer to the infant after birth, and the term "intrauterine growth restriction" (IUGR), or better, "fetal growth restriction" (FGR), should be used to refer to the fetus before birth. The latter really refers to a fetus that fails to achieve its inherent growth potential as a consequence of either intrinsic genetic factors or extrinsic environmental influences. It is best to avoid the term "growth retardation" as many parents will wrongly infer that you are referring to their child's future intellectual performance. Fetal growth is also somewhat population and ethnicity dependent, as not all ethnic groups will conform to "California sea-level" standards. Notably, many North American Native American and Mexican-American groups will have larger babies and many Central American and Southeast Asian women will have constitutionally smaller offspring. Accurate pregnancy dating is also of paramount importance in making the diagnosis and is perhaps the most common confounder in clinical practice.

SIGNIFICANCE

As noted above, growth restricted fetuses are at risk for increased perinatal mortality and morbidity. They are at significantly increased risk of intrauterine fetal demise (IUFD), especially if post term. They may have up to a 30% incidence of fetal intolerance of labor as a result of placental insufficiency and may develop hypoxemia and acidemia when stressed by uterine contractions. SGA newborns may have problems with low Apgar scores, hypoglycemia, hypothermia, hypocalcemia, polycythemia, apneic episodes, seizures, and feeding difficulties. The combination of prematurity and growth restriction is especially pejorative for the neonate. The birthplace of such infants should be in a facility equipped to manage their special requirements. Long-term effects have been more difficult to quantify, but there is a definite increase in neurological sequelae, prominent among which are learning and behavioral disorders. SGA infants may also be more prone to adult-onset hypertension and ischemic heart disease.

ETIOLOGY

Risk factors for FGR include those due to maternal, placental, or fetal antecedents. Maternal medical disorders may contribute to poor fetal growth, especially maternal vascular disorders such as chronic hypertension, renal disease, diabetes with microvascular pathology, and systemic lupus erythematosus. Likewise maternal disorders characterized by under-oxygenation such as severe asthma or cyanotic congenital heart disease are associated with low birth weight. Maternal smoking is associated with a 3.5-fold increase in SGA infants and is clearly dose related, and may even be affected by passive smoke exposure. Likewise maternal cocaine or methamphetamine users, as well as narcotic addicted women, may have a 30 to 50 % incidence of FGR. A combination of vascular and nutritional effects may be involved in such women. There is a clear association between heavy maternal alcohol use and impaired fetal growth. The role of maternal malnutrition is a significant worldwide problem. When maternal caloric intake is

restricted to below 1500 kcal/day, as is common in many developing nations, a measurable effect on birth weight will become evident, as a result of both preterm birth as well as fetal growth restriction. Coagulation disorders, such as those that occur in women with a thrombophilic coagulopathy or the antiphospholipid antibody syndrome, may result in placental microvascular thrombi and result in impaired fetal perfusion and oxygenation and subsequent growth impairment or death. Viral or protozoal infections such as cytomegalovirus, varicella, toxoplasmosis, malaria, Chagas' disease, and syphilis may all cause severe placental villitis and result in severe FGR or IUFD as a result. Fetal aneuploidy, as well as confined placental mosaicism, are also well recognized causes of SGA infants. Multiple gestation, especially when associated with monochorionicity, may be associated with a placental reserve that is inadequate to support the growth of both fetuses or an unequal sharing of that reserve.

DIAGNOSIS

Once the diagnosis is established, a work-up for the above noted conditions may be begun and can be directed by historical factors and the clinical setting. Nevertheless, a specific etiology is only found in about half the cases. How is the diagnosis best established? The World Health Organization has found that simple sequential measurements of fundal height are perhaps the best screening tool to assess adequate fetal growth, although their sensitivity is only 50 to 80 percent. Lagging fundal growth may be due to a small fetus and/or oligohydramnios and it may be variable as a result of maternal habitus. Ultrasound is currently the mainstay of diagnosing FGR.

Critical to the diagnosis FGR is **accurate early pregnancy dating**. A first trimester ultrasound is predictably more accurate than menstrual dating because of the variability in the length of the follicular phase. If the discrepancy between the crown-rump length and the menstrual dates is greater than 7 days, dating preference should be given to sonography. In the second trimester the head circumference is the most accurate parameter, but the composite of multiple parameters will slightly improve accuracy. There are 38 published regression equations to which an ultrasound machine may be programmed, and all are able to give comparably accurate predictions. If the discrepancy is greater than 7-10 days when compared to the LMP, give preference to the biometric prediction. How about the third trimester where most of the FGR cases usually come to attention? Here ultrasound is no longer accurate to within one week.

If the patient presents for her first evaluation in the third trimester and you have no other clinical data to use for dating, use the **sonographic estimate of gestational age** to date the pregnancy. Subsequently, the strategy must be to evaluate the adequacy of serial fetal growth. The various biometric parameters cannot very accurately be compared at less than 3-week intervals. Therefore repeat the scan in 2-4 weeks to see whether or not the fetus is growing along its growth percentile curve or it is "falling off" its curve. Remember that ultrasound-derived estimated fetal weight (EFW) is obtained from the volume of the structures measured; it cannot take into account the variable of tissue density. Thus, in late gestation the EFW may vary by as much as 10 to 20 percent from the actual weight obtained at birth. Occasionally, in the situation of a suspected near term growth restricted fetus versus a wrongly dated premature fetus, amniocentesis may be useful in documenting fetal lung maturity.

It is unclear whether the distinction between **"symmetric" and "asymmetric" FGR** has any prognostic significance, but classically, symmetric growth restriction is associated with an early intrinsic insult to the fetus that is usually not amenable to intervention. Yet is the fetus in question symmetrically growth restricted, or just at a younger gestational age and growing appropriately? It is difficult to discern if you only have one third-trimester scan. On the other hand, asymmetric growth restriction, where the abdominal circumference is smaller than the head circumference (elevated HC/AC ratio), is associated with extrinsic, potentially remediable, factors and its presence should facilitate the diagnosis of actual growth impairment. It is theorized to be the

result of utilization of fetal hepatic glycogen stores and fetal intra-abdominal fat stores with a subsequent reduction in liver/abdominal volume.

The other important clue to the ultrasound diagnosis of FGR is the presence of **oligohydramnios**. Amniotic fluid volume is gestational-age dependent as well, so a nomogram should be consulted at the earlier gestational ages. The familiar criteria for the amniotic fluid index (AFI) of < 5 cm for severe oligohydramnios and < 8 cm for "borderline" oligohydramnios are derived from the study of term fetuses. "Oligo" will usually only develop in the more severely affected cases however. It is hypothesized to be a result of brain shunting causing relative splanchnic ischemia with resultant decreased renal blood flow and decreased fetal urine production. The AFI is subject to considerable inter- and intra-observer variability, so repeat measurements are usually appropriate before making a clinical decision on this parameter alone.

Altered fetal hemodynamics can be fairly well assessed by Doppler velocimetry of various fetal vessels. This less-used ultrasound modality has become very helpful in the contemporary strategy for the diagnosis and management of FGR. An increased systolic to diastolic ratio (S/D) in the umbilical artery is thought to estimate downstream increased placental resistance reflecting placental insufficiency. Nomograms are available as values are also gestational age-dependent. At term, values >3.0 are thought to be abnormal. By itself, the actual S/D ratio has been less useful than the presence of absent- or reverse-end diastolic flow in the umbilical artery. Both of these findings may reflect severe, life-threatening FGR and require some clinical action. Prior to the development of these advanced disease findings, however, evaluation of the middle cerebral artery (MCA) may allow a better early assessment of the situation. As placental insufficiency and resistance increases, the fetus will shunt blood to its central nervous system, the "brain-sparing effect," and the pulsatility index (PI) of the MCA will decrease (a fall in cerebral resistance to allow enhanced flow). The combination of a high umbilical artery PI and a low PI in the MCA will allow the identification of a compromised fetus prior to end-stage disease. Growth-restricted fetuses with a normal "cerebroplacental ratio" have perinatal outcomes not different from AGA babies. Altered waveforms in various fetal venous structures (umbilical vein, ductus venosus, inferior vena cava) also have prognostic significance. An understanding of how to interpret these studies and knowing when to order them can improve management of these pregnancies. *

MANAGEMENT

Because the growth-restricted fetus is at risk of hypoxia, acidosis, and death, once FGR has been diagnosed, heightened surveillance of fetal well-being is indicated. **Delivery** may be appropriate regardless of gestational age if reassuring fetal surveillance cannot be obtained. What is the best strategy to assure that the fetus is not in jeopardy? Is there any evidence that antenatal surveillance in pregnancies complicated by FGR improves outcomes?

The best strategy initially would include a **high-resolution ultrasound fetal anatomic survey** to rule out anomalies and assess amniotic fluid volume. Other diagnostic studies will depend on the maternal history of intercurrent exposure to possible infectious etiologies. Obtaining fetal karyotype and "TORCH" titers may then be appropriate in selected cases, but the etiology in most cases will remain elusive. Non-stress testing has been the mainstay of surveillance, but it has poor sensitivity and often may not become abnormal until late in the course of this disorder. There are no studies addressing the optimal time interval between tests.

At present there is also not enough evidence from randomized trials to evaluate the use of the **biophysical profile** as a test of fetal well-being. **Doppler ultrasound** however has been shown to be useful in this disorder. There is a temporal sequence in the deterioration of the various Doppler parameters in FGR prior to the onset of fetal distress. This onset of abnormal Doppler findings usually follows a predictable sequence: elevated umbilical artery PI, decreased middle cerebral artery PI, absent end diastolic flow in the umbilical artery, increased resistance to flow in the ductus venosus, reversed flow in the umbilical artery, eventually followed by an abnormal

non-stress test. These findings are thought to evolve over a course of approximately 2 weeks, but are variable. The optimum timing of repeat testing is unknown, and remains dependent on the assessment of the severity of the FGR. The best evidence is that a normal umbilical artery to middle cerebral artery PI ratio has a 98 per cent negative predictive value as regards IUFD, and allows continued expectant management if the fetus is preterm. *

Unfortunately, there is **insufficient evidence from randomized trials of the benefit** of any intervention for FGR other than smoking cessation and treatment of malaria in infected women. Interventions of questionable or no efficacy include bed rest, nutritional supplementation, micronutrient supplementation, oxygen therapy, plasma volume expansion, and low dose aspirin. Therefore, delivery is the best treatment for the mature fetus but it may be problematic for the preterm fetus. It is important to put together the whole clinical picture and not just react to one abnormal ultrasound finding, but rather to decide if this fetus is actually at risk of IUFD and would do better in the nursery. If fetal surveillance is persistently non-reassuring however, corticosteroid therapy for promotion of fetal lung maturation is appropriate, followed by delivery. Many of these severely affected fetuses will not tolerate labor and a high rate of cesarean delivery may be anticipated. A positive contraction stress test may or may not predict which fetuses will tolerate labor. If oligohydramnios is present, variable decelerations may be anticipated, and amnioinfusion may be an appropriate strategy. Late decelerations reflect diminished placental function and are more difficult to remedy. Be sure oxygen delivery to the fetus is maximized. Optimizing maternal cardiac output through adequate hydration and lateralization, enabling her to have enough volume to best perfuse the placenta, can most physiologically effect this. Remember that maternal oxygen saturation is usually over 95 per cent on room air, so don't count on supplemental oxygen to be able to significantly improve her oxygenation on this part of the curve or to enable her to transfer more oxygen to the fetus. Growth-restricted infants should be born in a facility with a nursery staff able to handle their various postnatal problems. *

For more information on management consult the selected references shown below:

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CASE STUDY

Evangeline Agimuk is a 36 y/o G5P3 who presents for her first prenatal visit at 32 weeks by her last period, which fell on Christmas day. She has a history of essential hypertension and is taking atenolol 25 mg daily. She smokes 10-15 cigarettes a day but denies use of any other recreational drugs. She says that all her babies have been small but doesn't recall their birth weights. Her weight today is 121 pounds, and this represents a total weight gain for the pregnancy of 6 pounds as calculated from a weight obtained during an urgent care visit shortly before the pregnancy. Her BP is 153/93 and her urine dipstick is negative for protein. The uterine fundal height measures 27 cm and a nonstress test is reactive. Composite ultrasound biometry gives an estimated gestational age of 29 weeks 5 days $\pm$ 17 days and calculates an estimated fetal weight of 1191 g, which is at the 12^{th} percentile for her menstrual dates. Measurements give the following gestational age estimates: BPD-30 weeks 3 days, HC-31 wks 6 days, AC-27 weeks 4 days, FL-28 weeks 5 days. The AFI is 9.9 and the fetus appears to be structurally normal.

1. While the ultrasound values are discordant, the BEST estimate of her gestational age at this time is:

   a. 32 weeks
   b. 29 weeks
   c. 27 weeks
   d. 25 weeks

2. The factor which MOST led you to chose this gestational age is

   a. the very decreased abdominal circumference suggests asymmetric FGR
   b. oligohydramnios is present
   c. one should rely on composite ultrasound biometric parameters
   d. the fundal height measures 26 cm

3. Because this fetus is premature you would like to defer delivery if possible. The current evidence supports which ONE of the following as the most reliable test to assure on-going fetal well-being:

   a. the non-stress test
   b. the biophysical profile
   c. the systolic/diastolic ratio of the umbilical artery
   d. the umbilical artery/middle cerebral artery pulsatility index ratio

4. If the fetus does not appear to be in jeopardy, the pregnancy can be managed expectantly with on-going fetal surveillance. To most accurately assess fetal growth a follow-up ultrasound is best obtained in:

   a. one week
   b. 2-4 weeks
   c. 4-6 weeks
   d. 6-8 weeks

Answers:

1)a; 2) a; 3) d; 4) b

Discussion:

Questions #1. and #2.

Ms Agimuk is a set up for fetal growth restriction. She has several risk factors for FGR: she is a chronic hypertensive, she is taking a beta-blocker, she is a heavy smoker, she has a suboptimal pregnancy weight gain, and she may be underweight pre-pregnancy. Her dates are fairly certain but her fundal height is considerably smaller than her dates. While we have no prior dating criteria and ordinarily would use the composite ultrasound-derived gestational age, there is a marked discordance between the head and abdominal measurements, with the head biometry reasonably close to her dates. This finding in combination with mild oligohydramnios in this clinical setting is highly suggestive of asymmetric FGR. Therefore her most likely gestational age is 32 weeks, with FGR.

Question #3. and #4.

While all the testing modalities listed may be appropriate to follow this pregnancy, we have noted that the non-stress test often does not become abnormal until the problem is fairly far advanced. Further, the biophysical profile has not been confirmed as an effective surveillance tool by randomized controlled trials. Umbilical artery Doppler velocimetry alone is usually not sensitive or specific enough to guide clinical management unless absent or reversed diastolic flow is observed. The evidence does suggest, however, that the "cerebroplacental index", the comparison of the pulsatility index (PI) in the umbilical artery and the middle cerebral artery, which is able to demonstrate the absence of shunting of fetal blood flow to the central nervous system, is highly predictive of fetal well-being. It therefore is currently thought to be the optimal method for fetal surveillance in FGR. Because of the variability in fetal ultrasonographic measurements noted in the text, it is difficult to discern meaningful change in growth over a short interval. The minimal timing of repeat measurements is at 2-4 week intervals. Longer intervals might miss a significant change. Remember to put together the whole clinical and ultrasound picture and, if the fetus is immature, not react to one abnormal finding unless it is confirmed. At-risk pregnancies remote from term like this one would hopefully be managed at the tertiary care center where the fetus would be delivered. *