MASTER CLASS

Fetal Growth Assessment

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The assessment of fetal growth in utero is an important part of obstetrical care. In most pregnancies, fetal growth goes unimpeded and requires little attention other than the assessment of gestational age and the determination that growth correlates with our expectations. Under certain low-risk circumstances, sonographic assessment may not even become necessary and fundal height measurement is enough to assess adequate fetal growth.

On the other hand, in some pregnancies we encounter excessive fetal growth or restrictive fetal growth. Both of these conditions require careful attention, careful assessment and, sometimes, careful intervention.

Fetal growth restriction may occur under certain clinical conditions. Some of these conditions may be nutritional, some may be related to medical conditions such as diabetes or hypertension, and some may be due to a congenital cause or even an environmental cause such as smoking. Regardless of the actual etiology, if indeed fetal growth restriction is suspected or detected, it requires intense fetal surveillance because of the potential complications that can occur either in the short term or the long term. Some of these complications can result in significant comorbidities or even mortality.

It is for this reason that this month's Master Class will provide an in-depth look at fetal growth restriction and some of the diagnostic and management approaches that may be employed. I am pleased to welcome as our guest professor Dev Maulik, M.D., Ph.D., who is currently chair of obstetrics and gynecology at Winthrop University Hospital in Mineola, N.Y., and professor of obstetrics and gynecology at the State University of New York at Stony Brook.

Dr. Maulik has written extensively about low birth weight and prematurity, predicting adverse perinatal outcome, and detecting and managing fetal growth restriction. He has recently accepted a new appointment as professor and chair of obstetrics and gynecology at the University of Missouri-Kansas City.

Diagnosing and Monitoring Growth Restriction

BY DEV MAULIK, M.D., PH.D.

Fetal growth restriction is a problem that is undoubtedly underappreciated. A significant portion of growth-restricted infants are not identified before birth despite the fact that fetal growth restriction is a major complication of pregnancy—one that affects 5%-10% of all gestations and one that significantly increases the risk of perinatal mortality and morbidity.

We have known for some time that infants who are growth restricted are more prone to problems related to oxygen deprivation and have a higher chance of dying in utero, dying during labor and delivery, and dying during the first hours, weeks, and months of life.

We have learned more recently, moreover, that fetal growth restriction has long-term adverse consequences that extend into adult life. Epidemiologic studies in England in particular show that infants who were growth restricted in utero have a higher chance of developing diabetes, hypertension, stroke, and cardiovascular disease. Significant attention has been paid to the Barker hypothesis, which theorizes that the cardiovascular and endocrine systems of growth-restricted fetuses undergo a sort of intrauterine programming caused by a compromising prenatal environment.

Many aspects of the causes and pathophysiology of growth restriction remain unclear, and none of the therapeutic approaches that have been tried to improve fetal condition—from maternal oxygen administration, various nutritional interventions, and pharmacologic agents to plasma volume expansion and abdominal compression—have been consistently successful or valuable.

However, we have made advances in our understanding of the mechanisms and perinatal risks. We also have made significant progress in diagnosis and management and can today follow an evidence-based approach for managing the complications.

We are at the point today where our role as obstetricians can and should be to identify patients at risk of fetal growth restriction, to sonographically diagnose fetal growth restriction in at-risk patients, to monitor growth-restricted fetuses for in utero compromise, and to ensure a timing of delivery that will maximize gestation while minimizing the risks of continuing the pregnancy.

Identifying the Problem

Fetal growth restriction—or intrauterine growth restriction, as it is sometimes called—refers to the failure of the fetus to realize its optimal growth potential. A baby should be considered growth restricted when sonographically measured fetal dimensions—particularly the abdominal circumference or the estimated fetal weight based on head circumference or diameter, abdominal circumference, and femoral length—deviate below the 10th percentile for gestational age.

Some have advocated for a more rigorous threshold of the 5th percentile, or even the 3rd percentile, and others have suggested using the 15th percentile as a cutoff. The 10th percentile is indeed arbitrary, but for now it is the most commonly used threshold and should be considered the current standard of practice. It strikes the right balance.

Since subnormal growth is defined using gestational age–specific standards, we must establish gestational age as early in the pregnancy as possible, preferably in the first trimester. We must also be as accurate as possible, since overestimating or underestimating the gestational age by even a few days can have significant clinical implications for the discovery of fetal growth restriction.

Use of the crown-rump length presents us with a possible 4- to 5-day variation in gestational age, which is significant but still better than a 2-week variation.

Menstrual history in general is not very reliable, but if there is good concordance between gestational age based on menstrual history and that based on crown-rump length, then one can use the menstrual age. If there is more than a 1-week difference, then I advise using the crown-rump length.

One of the major issues we face in dealing with fetal growth restriction is, of course, that not all babies who are small are abnormal; some are just constitutionally small. Similarly, some babies appear to be normal—and may even be of an appropriate weight for their gestational age—but in reality are facing uteroplacental insufficiency and are not realizing their growth potential. There is, therefore, a definite "gray area" in distinguishing those babies who are truly growth restricted.

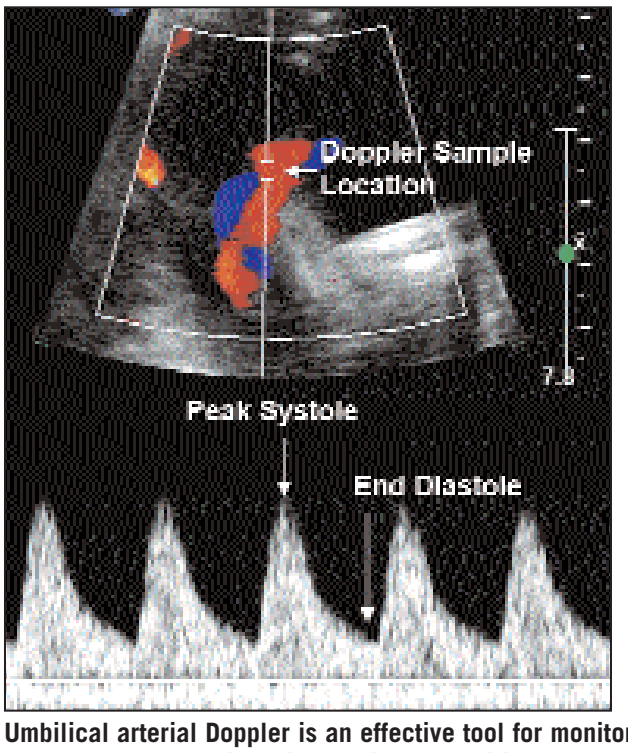
This is one reason why the best diagnostic test for fetal growth restriction is serial ultrasonography. Once we identify patients at risk for fetal growth restriction—from those who have preeclampsia and other hypertensive conditions to those with perinatal infection and smoking or substance-abuse problems—we can follow that patient and fetus to get a better sense, for instance, of whether the fetus is small but growing normally or small with progressively declining growth. We can also apply the 10th percentile threshold.

In general, routine growth scans in at-risk patients should start at around 28 weeks and be done every 3-4 weeks unless a diagnosis of growth restriction is made. If a problem such as preeclampsia becomes evident at another time, then serial ultrasonography should commence.

Recognizing the Risks

There is a host of disorders—various maternal, fetal, and placental factors—that can interfere with the mechanisms that regulate fetal growth.

Studies show that hypertensive disorders, for one, are present in 30%-40% of pregnancies that involve fetal growth restriction, and that even without proteinuria, elevated diastolic blood pressure in pregnancy is associat-



PHOTOS COURTESY DR. DEV MAULIK

Umbilical arterial Doppler is an effective tool for monitoring fetal growth restriction. The image on the left shows normal end-diastolic flow in the umbilical artery; the image on the right shows absent end-diastolic flow.

ed with small-for-gestational-age infants. Preeclampsia is associated with a fourfold increase in the risk of having a small-for-gestational-age infant.

Maternal autoimmune disorders (lupus and antiphospholipid syndrome, for instance), various medications (including certain anticonvulsants, particular β-blockers, cancer chemotherapy, and steroids), cigarette smoking, and even moderate alcohol use, have also been implicated in causing fetal growth restriction. Treatment of some of these conditions, such as the hypertensive conditions, is necessary for the health of the mother but, unfortunately, will not necessarily improve fetal growth.

Treatment of other conditions, such as those involving maternal lifestyle, will definitely lower the severity of the complication. If the mother is a smoker, for instance, a smoking cessation program is absolutely critical. Her fetus's drop in birth weight will be significantly less if smoking is stopped after the first trimester than if it continues throughout the pregnancy.

Fetal chromosomal abnormalities and congenital malformations are also significantly associated with fetal growth restriction, as is perinatal infection. Malaria may be one of the most significant causes of growth restriction in many countries where this disease is endemic. Even in the United States about 5%-10% of all cases of fetal growth restriction can be attributed to viral or protozoan infections in utero.

Bacterial infections have not traditionally been implicated as causes, but there is emerging evidence that subclinical infection and inflammation, as well as extragenital infection, may be associated with growth restriction.

Experts have long recognized a strong association between fetal growth restriction and prematurity, though it's unclear whether there is a true casual relationship.

Monitoring the Growth-Restricted Baby

When a diagnosis of fetal growth restriction is made, our role then focuses on fetal surveillance and the recognition of fetal stress and compromise.

Ultrasonography, first of all, should be done every 2-4 weeks after the diagnosis is made. Of all the additional modalities that we can use for fetal surveillance, umbilical arterial Doppler, which measures blood-flow impedance in the placenta, is one of the most effective tests we have for detecting a fetus who is getting into trouble. It should be used as our primary test. We now have compelling evidence from more than 20 randomized trials that fetal Doppler surveillance significantly improves outcomes (deaths in utero and other medical outcomes) in well-defined, high-risk pregnancies—most notably those involving fetal growth restriction and preeclampsia.

We can supplement Doppler with traditional tests of fetal heart rate monitoring, namely the nonstress test (NST), and evaluation of amniotic fluid volume. Both nonreactive NST and oligohydramnios have been associated with adverse perinatal outcome.

We also can use the biophysical profile (BPP), which incorporates parameters relating to the heart rate pattern, the fluid levels, umbilical artery Doppler, and examination of growth via ultrasound.

Just as the nonstress test does, the BPP has a low false-negative rate but a high false-positive rate. None of these additional tests is backed by the "level 1" evidence (randomized controlled trials) that Doppler carries, but they have essentially become standards of care. When used once a week, the tests are a valuable part of management, and I have incorporated them into my own evidence-based management guidelines. (See chart below.)

Usually, ominous changes in the fetal heart rate pattern or the BPP will follow nonreassuing Doppler indices—a fact that is indicative not only of the value of umbilical arterial Doppler but the value of these other tests in helping us to assess fetal distress and compromise, and the need for delivery, as completely as possible.

If our umbilical arterial Doppler shows an absence of flow at the end of the cardiac cycle and the other tests are normal, we can—if the pregnancy hasn't reached 34 weeks—step up the frequency of our other tests and attempt to carry the gestation through a bit further. If the end-diastolic flow is reversed, however, we need to intervene promptly. Reversed end-diastolic flow is an ominous sign.

Other ominous signs are a BPP score of 4 or less; an amniotic fluid index of 5 cm or less or a single deepest pocket less than 2 cm; and nonreassuring fetal heart rate patterns such as persistent nonreactive NSTs, continuous deceleration, and poor heart rate variability from one cardiac cycle to another.

The use of venous Doppler sonography is getting more attention today as another back-up test for evaluating fetal well-being when the umbilical arterial Doppler shows absent end-diastolic flow.

Doppler assessment of flow patterns through the inferior vena cava, umbilical vein, and the ductus venosus have all been suggested as supplementary tests—experimentation is underway particularly in Europe—but it is flow through the ductus venosus that may warrant the most attention at this point in time in institutions that have appropriately trained personnel. When flow during atrial contraction is absent or reversed in the ductus venosus, urgent intervention is usually necessary.

Our decisions to deliver, of course, should always be highly individualized, taking into account gestational age, the progression of change, institutional resources and expertise, and other issues. In general, though, once we're at or beyond 34 weeks of gestation, there is no benefit to prolonging the pregnancy if we have any ominous findings.

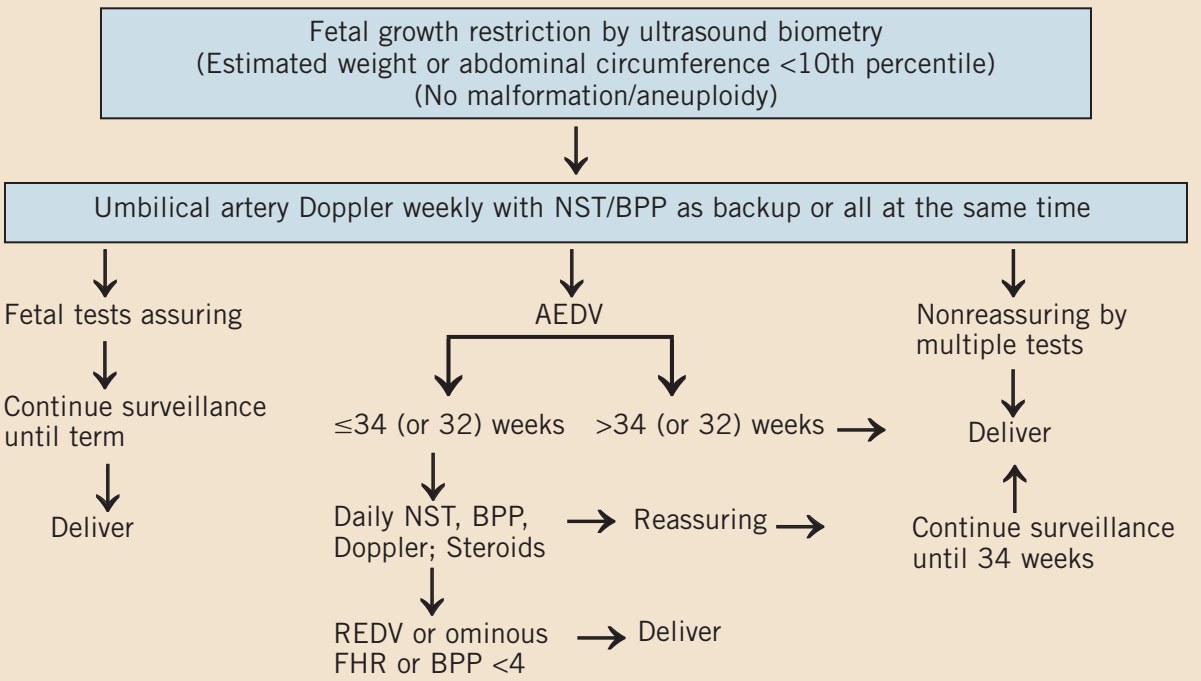
The absence of end-diastolic flow on the umbilical arterial Doppler, for instance, should prompt delivery once we've reached 34 weeks, whereas before 34 weeks we could instead intensify surveillance and watch for additional ominous findings. (Many, however, would use a cutoff of 32 completed weeks based on outcomes in the intensive care nursery of their institution).

We also should not allow pregnancies involving growth restriction to become postdated. There are no clear-cut guidelines addressing the question of whether we should induce babies who have come to term, but if the baby is in jeopardy—if there are multiple signs of compromise or distress—the baby will have a limited ability to tolerate labor, and a cesarean section is best.

Our most difficult decisions come with gestations of less than 28 weeks. Unfortunately, a recent randomized controlled trial of delivering early vs. delaying delivery (the Growth Restriction Invention Trial) brought us no clear answers.

This means that we have to continue utilizing our clinical judgment about the respective risks of a hostile intrauterine environment and the risk of pulmonary immaturity, and have a compassionate, nonpatronizing discussion with the parents. In general, if multiple parameters are abnormal, too much waiting will deprive the fetus of any chance of survival. ■

Fetal Growth Restriction: Fetal Surveillance Guidelines



Note: NST = nonstress test; BPP = biophysical profile; AEDV = absent end-diastolic velocity; REDV = reverse end-diastolic velocity.
Source: Dr. Maulik

Elsevier Global Medical News

Delaying Umbilical Cord Clamping Precludes Iron Deficiency

BY JOHN R. BELL
Associate Editor

Waiting up to 2 minutes after delivery to cut the umbilical cord led to increased iron status at 6 months, with no adverse associations for mothers or infants, and could be valuable in preventing developmental delays associated with iron deficiencies, according to findings from a large randomized controlled trial.

Dr. Camila M. Chaparro of the University of California, Davis, and colleagues reported results from 358 mother-and-singleton infant pairs delivered at a large obstetric hospital in Mexico City. The primary outcomes were infant blood and iron status at age 6 months—the longest follow-up to date in any trial of delayed cord clamping (Lancet 2006;367:1997-2004).

The investigators randomized mothers to one of two groups: In one group, the umbilical cord was clamped after 10 seconds. In the other group, it was clamped after 2 minutes—coinciding roughly with the usual cessation of cord pulsations—unless the physician determined earlier cord removal was necessary. Ultimately, the mean clamping time for the early-clamping group was roughly 17 seconds, compared with about 94 seconds for the delayed-clamping group—a difference of just over 1 minute.

At 6 months of age, the delayed-clamping infants had significantly higher levels than the early-clamping infants in several measures (adjusted for maternal factors): stored iron (58 mg vs. 31 mg), body iron (343 mg vs. 316 mg), mean corpuscular volume (81.0 fL vs. 79.5 fL), and ferritin (50.7 mcg/L vs. 34.4 mcg/L). Moreover, the incidence of iron deficiency (less than 9 mcg/L) in the early-clamping infants was 7%, compared with 1% in the delayed-clamping group, and unadjusted incidence of iron-deficiency anemia was 4% in early-clamping infants vs. 0% in the delayed-clamping group, the investigators noted. ■