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Intrauterine Growth Restriction: How to Manage and When to Deliver

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Abstract: Intrauterine growth restriction secondary to placental insufficiency is a major cause of perinatal morbidity and mortality in the United States. Once intrauterine growth restriction is identified, obstetrical management is focused on assuring safety while the fetus continues to mature within a potentially hostile intrauterine environment. In the United States, the approach to management and delivery of the premature growth-restricted fetus is often based on serial biophysical profile evaluations, whereas in Europe it is usually based on the results of cardiotocography. However, there is no single test that seems superior to the other available tests for timing the delivery of the growth-restricted fetus. Therefore, the decision to deliver a fetus, especially at < 32 weeks, remains mostly on the basis of empirical management.
Key words: IUGR, Doppler, biophysical profile, cardiotocography, delivery

Intrauterine growth restriction (IUGR) has been defined as failure to attain optimal intrauterine growth. Although scientifically correct, this definition is difficult to apply in practice because "optimal growth" cannot be easily determined. The American College of Obstetricians and Gynecologists has chosen to define IUGR as "a fetus with an estimated weight below the tenth percentile for gestational age,"[1] because perinatal mortality and morbidity increase when the birth weight is below that percentile.[2,3] With approximately 4 million births per year in the United States, 400,000 neonates will have a birth weight below the 10th percentile, but not all are at risk for an adverse outcome; some are constitutionally small, but otherwise normal infants.[3]

The consequences of in utero growth deficiency do not end at birth or in infancy but rather continue into childhood and adult life.[4] Barker and Osmond[4] have described an association between birth weight below the 10th percentile and the development later in life of hypertension, hypercholesterolemia, coronary heart disease, impaired glucose tolerance, and diabetes. Therefore, the growth-restricted fetus represents an enormous burden for both the affected individual and for society.

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Ensuring fetal well-being and determining the optimal timing for delivery of the growth-restricted fetus is a primary goal of fetal specialists. However, the timing of delivery of these fetuses, especially at less than 32 weeks, is controversial. The optimal method of fetal testing is also controversial; in the United States, the most frequently used test is the biophysical profile (BPP), whereas in Europe, cardiotocography is the preferred method.[5]

Most of the studies, which report on IUGR have not differentiated between constitutionally and pathologically small fetuses. Additionally, studies on the pathogenesis of IUGR have been limited by the concept that IUGR fetuses represent a homogeneous group. This has created some confusion and has hampered our understanding of the mechanisms that are at the basis of IUGR.

Small for Gestational Age and IUGR Fetuses

Small for gestational age (SGA) fetuses are those fetuses with an estimated weight <10th percentile. SGA fetuses include both constitutionally and pathologically "small" fetuses (IUGR). We use the term SGA for those small fetuses with no maternal pathology and with normal umbilical artery and middle cerebral artery (MCA) Doppler studies. Growth-restricted fetuses are small fetuses with a recognizable maternal pathology or an abnormal umbilical or MCA Doppler. When no maternal pathology is present but there is an abnormal fetal Doppler, we define the small fetuses as idiopathic IUGR fetuses.

Placental Insufficiency and Idiopathic IUGR Fetuses

Placental insufficiency is characterized either by a lack of the expected physiologic change resulting from trophoblastic invasion of the spiral arteries or by abnormal development of the villous vascular tree.[6] This lack of physiologic change causes decreased blood flow to the placenta. As the fetal oxygen demand increases, or the perfusion decreases, oxygen delivery to fetal blood in the placenta falls below a critical point and the fetus compensates by redistributing its blood flow from the body to the brain, adrenal glands, and heart.[7] These events can be detected by blood flow velocity studies in the fetus.[8,9] Worsening of the process will manifest first as an elevated systolic/diastolic ratio, then an absence of diastolic velocity, and finally by reversed diastolic velocity in the umbilical artery.[10] The fetal cardiac performance then becomes compromised; this is detected by changes in the venous flow to the heart (eg, absence or reversed diastolic flow of the ductus venosus). If all these Doppler abnormalities are present, the fetus is at an increased risk of death.[5,11–14]

The concept that placental insufficiency is *the* cause of IUGR is a source of confusion. We believe that placental insufficiency is not "*the* cause" of the problem but is rather the *consequence* of a disease process that often we do not understand. We agree with Assali, who defined placental insufficiency as "an umbrella that covers our ignorance in terms of etiology and pathogenesis of the utero-placental chronic dysfunction." Placental insufficiency is a "symptom" and it can be compared with the fever seen in patients with bacterial pneumonia. As with pneumonia there are many agents that could cause it; similarly with placental insufficiency there may be many underlying causes. If we use an antipyretic in patients with bacterial pneumonia, the fever will temporarily subside; however, to treat the entire condition it is necessary to use antibiotics to target the specific etiologic factor. Similarly, with IUGR, we often view the

problem from the wrong direction, as a consequence of placental insufficiency, and we therefore believe that we should treat the placental insufficiency. In reality, we should find and treat the specific cause of placental insufficiency. The optimal management, however, would be the prevention of IUGR fetuses.

In many IUGR fetuses, there is an underlying maternal pathology, for example, chronic hypertension or advanced stage diabetes mellitus, at the basis of placental insufficiency. In other IUGR cases, there is not an identifiable cause of placental insufficiency; these are the cases that we define as "idiopathic" IUGR fetuses.

Tests Used to Monitor the Growth-restricted Fetus

BPP

The fetal BPP is the most frequently used modality in the United States for monitoring IUGR. The BPP includes 5 parameters: breathing, movements, tone, amniotic fluid, and fetal heart rate,[15] each assigned a value of either 2 or 0, yielding a maximum score of 10. Manning[3] considered a score of 10, or 8 with normal amniotic fluid, to be normal. Any score of 6 or less is managed with delivery or intensified fetal surveillance depending upon the gestational age.

Although the false negative death rate of the BPP (defined as the occurrence of stillbirth within 1 wk of a normal BPP) determined at 2 institutions was 0.71 and 2.29 per 1000 tested fetuses, respectively,[3] another study reported that the BPP is a poor predictive test of abnormal outcome, defined as intrauterine death or umbilical cord pH 2 standard deviations below the mean.[16]

The BPP is highly correlated with umbilical venous cord pH[17] but may not become abnormal until the fetus has become acidotic. This is of major concern, as fetal acidemia is associated with an increased risk of impaired neurodevelopment. Because of these limitations of the BPP, alternative technologies have been proposed to improve assessment of the growth-restricted fetus—principally computerized cardiotocography (CTG) and Doppler ultrasonography.

CARDIOTOCOGRAPHY

Antenatal fetal heart rate monitoring in the United States is largely based on the visual assessment of fetal heart rate tracings [non-stress-test (NST)]. The accuracy of such subjective assessments are impaired by substantial interobserver and intraobserver variability, and can lead to intervention when it is not required or, conversely, lack of intervention when it is necessary. A review of 45 studies involving 49,403 NST readings from 24,407 fetuses identified 21 different definitions of reactivity, and indicated that 52% of fetal heart rate interpretations with subsequent abnormal outcomes were determined to be reactive by visual assessment, whereas 62% of fetal heart rate readings that were determined to be nonreactive by visual assessment had a subsequent normal outcome.[18]

In 1978, Dawes et al[19] developed a computerized system to analyze the human fetal heart pattern. The advantages of computerized CTG are the objective interpretation of the fetal heart rate tracing and analysis of the short-term variability (STV), which cannot be evaluated visually.[19] Subsequently, the US FDA approved use of the current version, marketed as Sonicaid Fetal Care, starting at 32 weeks gestation. Several studies have compared the Sonicaid system interpretation against visual assessment and concluded that the computer analysis interpretation reduces the number of additional tests normally

required and is superior to visual assessment in predicting abnormal outcome.[20] In a study of this system in which 60-minute recordings were obtained in growth-restricted fetuses immediately before cordocentesis, a long-term variability of less than 20 ms was always associated with severe fetal hypoxemia and acidemia.[21] Furthermore, other studies have shown that no intrauterine deaths occurred when the fetal heart rate STV was 3.0 ms or more, whereas a STV below 2.6 ms was associated with intrauterine death (4/5), or metabolic acidemia (3/11) at delivery.[22]

From the above studies, it seems that computerized CTG is better than visual interpretation of fetal heart rate monitoring. However, a limitation of the CTG is that the FDA has not approved it for clinical practice before 32 weeks gestation because it believes that more studies are needed.

DOPPLER ULTRASONOGRAPHY

Doppler ultrasonography of the umbilical and MCA, in combination with biometry provides the best tool to identify small fetuses at risk for adverse outcome.[8,10] Moreover, Doppler studies of the fetal cardiovascular system allow assessment of the blood flow redistribution observed in IUGR.[8] This process is mainly characterized by an increased umbilical artery, and a decreased MCA-pulsatility index (PI),[8] which suggests increased vascular resistance of the umbilical artery and cerebral vasodilatation.

Of importance is that randomized trials have demonstrated a lower number of stillbirths in high-risk pregnancies when the information of umbilical artery Doppler is made available to the obstetrician.[23] A randomized, controlled clinical trial also demonstrated that umbilical artery Doppler, as a screening test for fetal well-being in a high-risk population, was associated with a decreased incidence of cesarean delivery for fetal distress compared with the nonstress testing, with no increase in neonatal morbidity.[24]

Dubinsky et al[25] assessed the sensitivity for predicting poor outcome in a group of fetuses with estimated weights below the 10th percentile. They defined poor outcome as the following: cesarean delivery for fetal distress without labor, fetal death, intraventricular hemorrhage, cerebral infarction, admission to the neonatal intensive care unit (NICU) for more than 10 days, NICU admission at term, or preterm delivery. Abnormal umbilical artery Doppler had a sensitivity of 64%, whereas oligohydramnios, BPP, and fetal heart rate monitoring had sensitivities of 32%, 18%, and 14%, respectively.

Meta-analyses of randomized controlled trials[26] have shown that the use of umbilical artery Doppler velocimetry can improve perinatal outcome in high-risk pregnancies. Thus, many clinicians consider reversed umbilical-end diastolic flow velocities after 32 weeks of gestation and absent end-diastolic flow velocities at 34 weeks or more as an indication for prompt delivery if it occurs in a tertiary center with a NICU.[27] However, in cases of reversed diastolic flow in the umbilical artery before 32 weeks, management is less straightforward.

Doppler Changes in IUGR

Several studies have provided recommendations as to the timing of delivery for IUGR fetuses. The loss of the "brain sparing effect" was initially considered a parameter to guide timing the delivery of a growth-restricted fetus.[28] In another study, it was reported that there is a temporal sequence of Doppler changes preceding the onset of late decelerations.[29] Another preliminary study has shown that in growth-restricted fetuses monitored longitudinally with Doppler ultrasound, the last premorbid

changes that occur in the cardiovascular system of these fetuses are right-followed by left-sided cardiac failure. (Mari et al, abstract presented at the ISUOG, 2006).

More recently, 3 studies have emphasized that there is a temporal sequence of Doppler and biophysical changes that precede the peripheral and central circulatory changes of the severely growth-restricted fetus.[5,11,12] Hecher et al[5] evaluated 93 growth-restricted fetuses with at least 3 Doppler studies after the diagnosis of fetal growth restriction, the last measurements being taken within 24 hours of delivery or intrauterine death. The amniotic fluid index and umbilical artery PI were the first variables to become abnormal, followed by the changes in STV of the fetal heart rate, MCA-PI, aortic PI, and ductus venosus S/a ratio. In fetuses delivered before 32 weeks, the perinatal mortality was higher if both STV and ductus venosus PI were abnormal (39%) compared with only one or neither being abnormal (7%). The median time interval between the occurrence of the first persistently abnormal finding and delivery was 3 days (range, 0 to 19 d) if STV was the first abnormal sign and 7 days (range, 0 to 43 d if the ductus venosus PI was the first variable to become abnormal. The authors did not perform BPPs in their population.

Baschat et al[11] studied growth-restricted fetuses with an umbilical artery PI > 2 standard deviations above the mean for gestational age, and serially assessed fetal well-being using BPP scoring and additional Doppler studies. In 42 fetuses, Doppler studies revealed deterioration of the umbilical artery and ductus venosus parameters at a median of 4 days before delivery, whereas 2 to 3 days before delivery, fetal breathing movement began to decline, followed by a drop in amniotic fluid volume the next day. A loss of fetal movement and tone were findings that prompted delivery. The authors did not perform CTG in their population.

Ferrazzi et al[12] conducted a longitudinal study of 26 growth-restricted fetuses that had abnormal uterine and umbilical artery Doppler velocimetry, and based the decision to deliver the fetus on a nonreactive NST defined as the absence of accelerations of at least 10 beats/min for > 10 seconds, with a short-term variation < 2.2 seconds for > 120 minutes. The authors reported that an abnormal ductus venosus and also decreased aortic and pulmonary outflow tract velocities, were associated with perinatal death and occurred in 50% of patients 4 to 5 days before delivery. Interestingly, the authors observed that more than 50% of fetuses that were delivered because of an abnormal fetal heart rate did not have venous Doppler abnormalities. The authors likewise did not perform BPPs in their population.

The authors of the above longitudinal studies deserve credit for providing novel insights into the disease process of the growth-restricted fetus. Although they suggest that there may be a common sequence of biophysical changes that indicate progressive fetal compromise in IUGR, a careful review reveals that there are some differences among the studies. The involvement of the fetal brain and heart, as detected by an abnormal fetal heart rate/BPP or DV Doppler indices is highly variable among fetuses and does not follow a predictable pattern. Also, amniotic fluid was among the first parameter to become abnormal in Hecher's study but was among the last in Baschat's study. Although Ferrazzi et al[12] and Hecher et al[5] based their interventions on CTG, which is not used in the United States, Baschat et al[11] used the abnormal BPP, which is not used in Europe.

It is likely that differences found among the above studies can be attributed

to differences in the growth-restricted fetuses studied. We believe the most useful information would be provided if authors differentiated between idiopathic IUGR as here defined and IUGR secondary to maternal diseases. However, even if we posit idiopathic IUGR as a homogeneous group, differences are found. A recent longitudinal study including only idiopathic IUGR fetuses reported that, on the basis of Doppler results, there are in fact 2 idiopathic IUGR groups. One group included 33% of the study population; in this group, all fetuses had absent/reversed ductus venosus velocities at the time a cesarean delivery was performed, because of a nonreassuring fetal testing. In the second group, most IUGR fetuses had normal ductus venosus waveforms at the time the diagnosis of a nonreassuring fetal testing was made.[30]

A randomized trial has been published by the Growth Restriction Intervention Trial (GRIT) group. It compared the 2 management strategies concerning the indication for immediate versus delayed delivery in high-risk pregnancies when clinical uncertainty prevailed; immediate delivery outcomes were compared with delayed delivery outcomes when the obstetrician was no longer "uncertain."[31] The results demonstrated that the perinatal morbidity and mortality, and also the neurologic outcome 2 years after birth, were not statistically significant between the 2 groups.[32] However, BPP and Doppler (with the exception of the umbilical artery) were not used for fetal surveillance in all cases in either arm of the GRIT study. In addition, the growth-restricted fetuses included in the study represented a heterogeneous population because, in this study, one-fourth of the fetuses had normal umbilical artery flow velocity waveforms indicating they may simply have been SGA.

Because of the variability in the findings of the above studies, a new randomized trial evaluating the timing of delivery based on early (abnormal ductus venosus with presence of umbilical artery end-diastolic velocity) and late fetal Doppler venous changes (absent/reversed flow of the ductus venosus) versus CTG has been designed in Europe (Trial of Umbilical and Fetal Flow in Europe-TRUFFLE). The study does not include the BPP for fetal surveillance.

Are Additional Randomized Trials to Determine the Optimal Timing of Delivery of the Growth-restricted Fetus Indicated at This Time?

We believe that the undertaking of a randomized study to determine the optimal timing of delivery of the growth-restricted fetus is premature at the current time because there is no observational study that has longitudinally evaluated the BPP, CTG, and Doppler velocimetry in the same population. On the basis of the existing data, a randomized trial in IUGR that excludes the BPP has limitations because CTG and/or Doppler have not (clearly) been shown to be preferable to the BPP. Odibo et al[33] recently reported that the BPP represents the best test to guide physicians in the timing of delivery of the preterm growth-restricted fetus. In addition, there is no study that has longitudinally evaluated in IUGR the changes occurring in the velocity of many fetal vascular vessels.

Recently, we have performed a cross-sectional and a longitudinal assessment of the MCA-PI and MCA-peak systolic velocity (PSV) in growth-restricted fetuses. Our data show that although the MCA waveforms change in growth-restricted fetuses, the MCA-PSV predicts perinatal mortality more accurately than the MCA-PI. This finding can be explained in the following way; initially,

the MCA-PI is abnormal in most of the fetuses, but subsequently the MCA-PI increased and a tendency toward normalization occurred before delivery. The MCA-PSV, conversely, progressively increased with advancing gestation in all fetuses, with a tendency to decrease slightly, just before delivery or the occurrence of fetal demise. However, despite this decrease, the MCA-PSV value remained above the upper limit of normal (ie, abnormal) until a few hours from delivery or fetal demise.[34] Figures 1 and 2 report the MCA-PI and MCA-PSV plotted over their reference ranges in a group of severely growth-restricted fetuses.

The results of a randomized study could lead to the adoption of a test to determine the optimal timing for delivery of the growth-restricted fetus. However, we do not wish to make the mistake of possibly adopting a test determined to be "the best" in such a trial before the full range of observational and randomized studies to evaluate all tests in normal and "at risk and diseased" pregnancies has been completed. To do so would duplicate the history and ensuing controversies of adoption of fetal heart rate monitoring for fetal surveillance. This could occur if observational studies are not performed before randomized trials are initiated and, as a result, future randomized studies are conducted without including potentially important diagnostic tests, such as the BPP, or other parameters, such as the MCA-PSV.

A review of the literature allows us to conclude that in IUGR secondary to placental insufficiency (abnormal umbilical artery Doppler) the following occurs: initially, a low MCA-PI might reflect a decreased brain vascular resistance and a slight increase in blood flow. With increased severity, the MCA-PSV increases, as a consequence of an increased left cardiac output. When the process becomes more severe, a portion of the blood ejected from the right ventricle is shifted to the brain through the aortic isthmus because of a high descending aorta vascular resistance.[35] Although the MCA-PSV may decrease

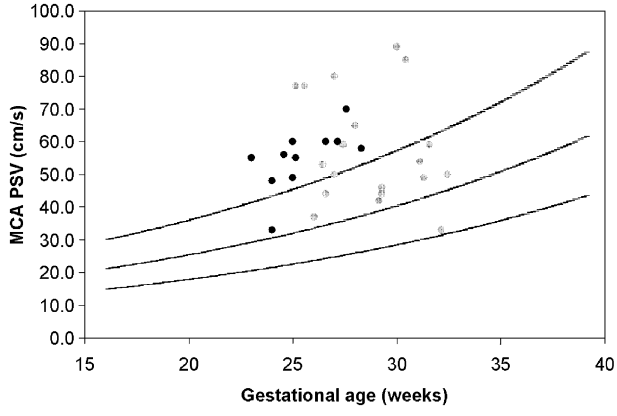

FIGURE 1. MCA-PSV values in 30 IUGR fetuses plotted over the normal reference range. The black circles represent the velocity values in 11 fetuses that died. The gray circles represent the velocity values in the remaining fetuses (With permission from *Ultrasound Obstet Gynecol.* 2007;29:310–316).

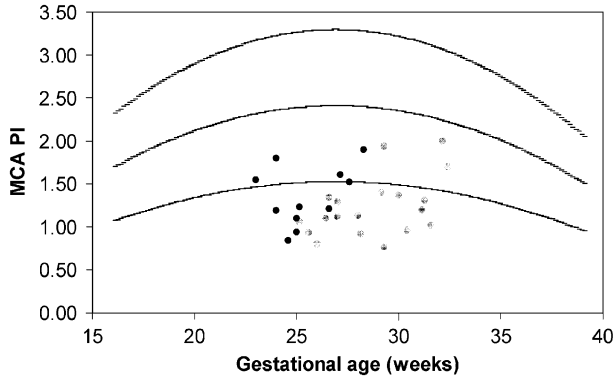

FIGURE 2. MCA-PI values in 30 IUGR fetuses plotted over the normal reference range. The black circles represent the PI values in 11 fetuses that died. The gray circles represent the PI values in the remaining fetuses (With permission from *Ultrasound Obstet Gynecol.* 2007;29:310–316).

before an intra-uterine-fetal demise, the MCA-PSV remains above the normal range. This might be the consequence of either an exaggerated cerebral vascular vasodilatation or vasoconstriction that occurs in the over-stressed fetus. The last changes that occur in the cardiovascular system of the growth-restricted fetus before demise or delivery because of nonreassuring testing are right cardiac failure followed by left cardiac failure (Mari et al. SMFM 2007). In Figures 3 to 5, we report the pathologic Doppler changes that occur in growth-restricted

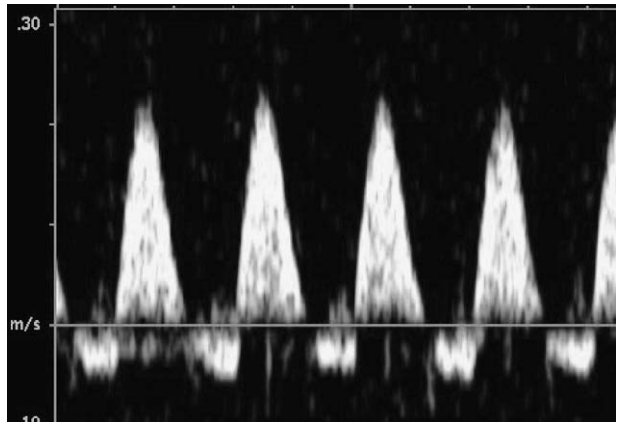

FIGURE 3. Umbilical artery reversed flow in an IUGR fetus early in the third trimester. This finding is not an indication for delivery in IUGR fetuses before 34 weeks' gestation.

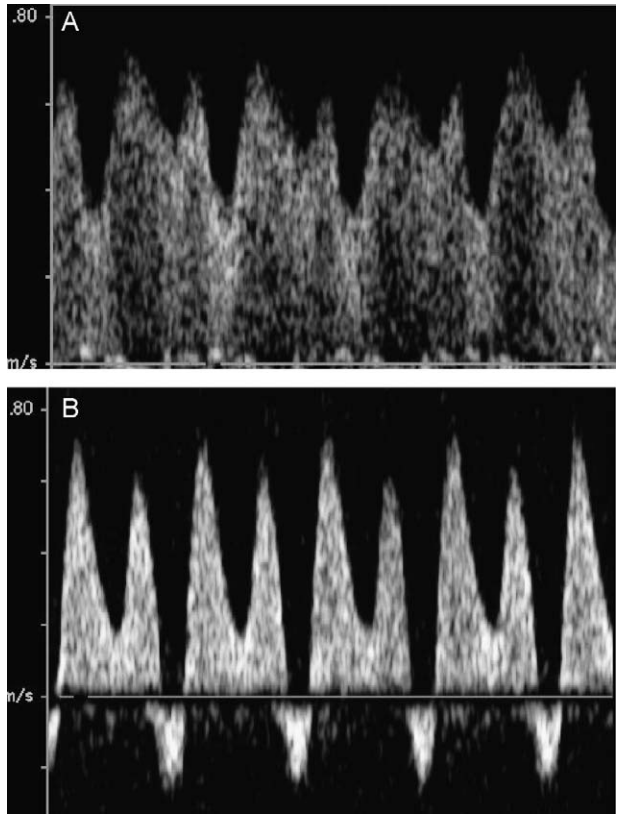

FIGURE 4. A, Normal ductus venosus flow velocity waveforms. B, Reversed flow of the ductus venosus.

fetuses at the umbilical artery, MCA, ductus venosus, and maternal uterine arteries.

What is the Best Test for Determining the Optimal Timing of Delivery for Very Premature Growth-restricted Fetuses?

At the current time this question is unanswerable. In the United States, most physicians make the decision to deliver a growth-restricted fetus on the basis of an abnormal BPP or a nonreassuring NST. In terms of survival rate, the growth-restricted fetuses delivered at >25 and <30 weeks' gestation is the most problematic. In our experience, growth-restricted fetuses delivered at <25 weeks' gestation, do not survive; at the other extreme, all growth-restricted fetuses survived when delivered at >30 weeks' gestation.[34]

As can be noted, there is an absence of robust data to rely on to determine the optimal timing of delivery for very premature growth-restricted fetuses. We manage our growth-restricted fetuses in the following manner: if the patient does not desire any intervention, she is enrolled in research protocols and followed as an outpatient. If, after 25 weeks' gestation, a patient is carrying a growth-restricted fetus with absent or reversed flow of the umbilical artery and (a) understands the risk of an early

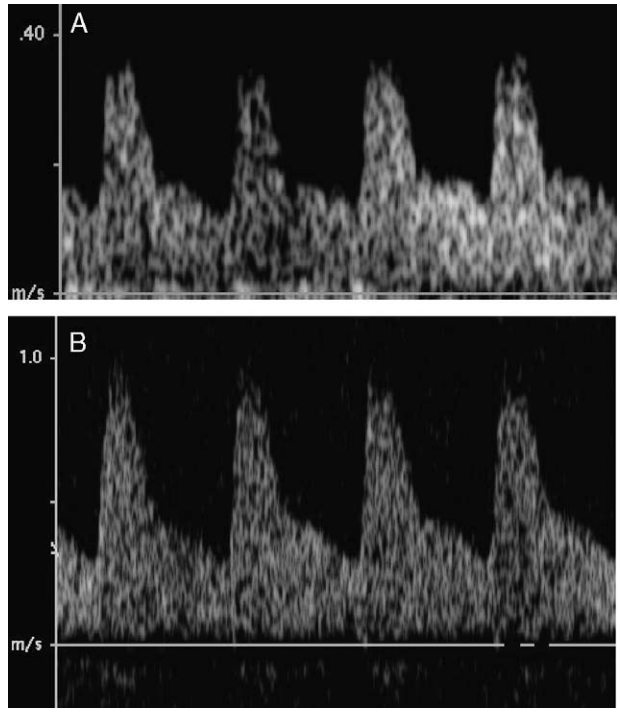

FIGURE 5. Abnormal MCA flow velocity waveforms. A, The PI is abnormal but the PSV is normal. B, Both the PI and the PSV are abnormal. These findings indicate a more severe IUGR condition compared with those cases in which the PSV is normal.

delivery and (b) opts for intervention for a nonreassuring fetal testing, she is admitted to the hospital. She receives steroids for fetal lung maturity. Her fetus is followed with a daily BPP and fetal heart rate monitoring. The latter is performed either continuously or at variable intervals. In the presence of an abnormal BPP (4/8 on 2 successive examinations or 2/8 on one single examination) or a nonreassuring fetal heart rate monitoring (continuous variable or late decelerations) a cesarean delivery is performed. A low fetal weight is not a limitation for an early delivery in our NICU. In our NICU, the "lightest" survivor with no major complications was a growth-restricted infant with a birth weight of 360 g delivered at 25.5 weeks' gestation.

Is an Abnormal Doppler Ultrasound an Indication for Delivery?

The important concept that must be emphasized is that although there are several Doppler changes seen in growth-restricted fetuses with advancing gestation, more studies are needed before concluding that an abnormal Doppler is an indication for delivery of a fetus especially at < 32 weeks. It is also

possible that we will never determine the optimal test for timing delivery of very premature IUGR fetuses because of the heterogeneity of the disease. If this occurs, the management should be individualized because subsequent to 25 weeks' gestation and at <29 weeks, perinatal mortality decreases by $>40\%$ for each week the IUGR fetus remains in utero (Mari et al. SMFM 2007 abstract).

When Should the Growth-restricted Fetus be Delivered ≥ 32 weeks' Gestation?

Even after 32 weeks' gestation, there are no data to support intervention based on an abnormal Doppler ultrasonography of the umbilical artery, MCA, and ductus venosus. When there is absent or reversed umbilical artery flow, we admit the patient to the Hospital and complete a course of steroids. The fetuses are followed with daily BPP and fetal heart rate monitoring. If these tests remain reassuring, we deliver the growth-restricted fetus at 34 weeks' gestation.

Beyond 34 weeks' gestation, we deliver growth-restricted fetuses when there is an abnormal umbilical artery Doppler study.

What is the Best Delivery Mode of IUGR Fetuses?

The data of the literature seem to support a cesarean delivery for a growth-restricted fetus when there is absent or reversed flow of the umbilical artery, as these fetuses rarely tolerate attempts at vaginal delivery. Care must be individualized, however, as the fetus ≥ 34 weeks with an abnormal umbilical artery S/D ratio but a normal BPP will not uncommonly tolerate labor.

In summary, IUGR secondary to placental insufficiency remains a major cause of perinatal morbidity and mortality in the United States. There is no single test that appears superior to the other available tests for timing the delivery of the growth-restricted fetus. Therefore, the decision to deliver a fetus, especially at <32 weeks, remains mostly based on empirical management. We believe that 2 steps are necessary to determine the optimal management of the growth-restricted fetus: (a) an observational longitudinal study performed in a few centers with experience in the management of growth-restricted fetuses. Idiopathic IUGR and IUGR secondary to other causes (chronic hypertension, preeclampsia, infection, etc) should be evaluated as 2 different groups. In these fetuses the BPP, cardiotocography, CTG, and Doppler evaluation of the fetal cardiovascular system should be assessed from the time of initial diagnosis is made until delivery of the growth-restricted fetus, (b) on the basis of the findings, decide if a randomized study of growth-restricted fetuses is indicated.

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