Integrated Testing and Management in Fetal Growth Restriction

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Growth-restricted fetuses are at higher risk for poor perinatal and long-term outcome than those who are appropriately grown. Multiple antenatal testing modalities can help document the sequence of fetal deterioration. The full extent of this compromise is best identified by a combination of fetal biometry, biophysical profile scoring, and arterial and venous Doppler. In the preterm growth-restricted fetus, timing of delivery is critically determined by the balance of fetal versus neonatal risks. In the near-term fetus, accurate diagnosis continues to be a challenge as unrecognized growth restriction contributes to a significant proportion of unexplained stillbirths. In this review, we present an integrated diagnostic and surveillance approach that accounts for these factors.

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Evaluation of fetal growth is common obstetric practice. Fetal growth restriction (FGR) affects 15% of pregnancies and is associated with significant morbidity and mortality in perinatal and adult life.1 Clinical suspicion of FGR requires further investigation as growth delay may be the physical manifestation of many possible conditions. When FGR is established early in pregnancy, the diagnosis is readily made. In these patients, safe prolongation of pregnancy and timing of delivery are critical issues. As gestational age at delivery has an independent effect on outcomes, early delivery can result in neonatal complications, whereas delayed delivery can increase stillbirth risk.2 When FGR presents in the third trimester, clinical manifestations and signs of deterioration may be more subtle. In these patients, accurate identification of FGR provides a challenge. Failure to recognize clinically significant FGR may contribute to over 50% of unexplained stillbirths near term.3

Antenatal surveillance modalities can provide insight into many aspects of fetal well-being. Available tests are the non-stress test (NST), computerized cardiotocography (cCTG), biophysical profile score (BPS), and multi-vessel arterial and venous Doppler. Each modality independently evaluates behavioral or cardiovascular responses to hypoxemia, but when used in isolation may have limitations in the management of FGR. Integration of antenatal assessment modalities concurrently evaluates physical, behavioral, and cardiovascular manifestations of FGR. This approach can bypass the limitations of individual tests and therefore provide the most comprehensive insight into the fetal condition to guide management.

Antenatal Surveillance Tests

Progression of fetal hypoxemia to acidemia is an important antecedent to adverse short- and long-term outcome. Therefore, antenatal surveillance aims to detect fetal responses that accompany such deterioration. These responses include changes in fetal heart rate pattern, dynamic variables (tone, movement, breathing activity), amniotic fluid volume, placental Doppler studies, and fetal arterial and venous Doppler parameters.

Fetal Heart Rate Analysis

Fetal heart rate analysis in the form of the NST is one of the first surveillance tests introduced into obstetric practice. The NST can be used to assess central and autonomic control of intrinsic cardiac activity by applying visual analysis according to criteria that have recently been updated by the American College of Obstetricians and Gynecologists.4 However, heart rate variables such as the baseline, magnitude, and du-
rati on of accelerations as well as decelerations are influenced by many factors, including the maturational state of the fetal central nervous system, gestational age, behavioral state, amniotic fluid volume, maternal status, and medications. In addition, there is significant intraobserver and interobserver variability in the interpretation of key heart rate variables, even when strict interpretative guidelines are applied. Accordingly, a “normal” reactive NST provides strong evidence of fetal well-being and absence of hypoxemia. However, a “nonreactive” NST is a nonspecific finding, particularly in the setting of FGR where delayed maturation of central fetal heart rate control contributes to a higher incidence of nonreactive NSTs.1

The cCTG was developed to compensate for the limitations of visual fetal heart rate analysis. It is not widely used in the United States, but decreases inconsistencies of visual NST analysis by providing an objective interpretation of the fetal heart rate. In addition, computer-generated variables, such as the short-term variation (STV), are derived.6 The STV expresses the variance in beat-to-beat intervals during a fixed time period in milliseconds. A decrease in the short-term variation below 3.5 milliseconds has been suggested as an optimal cutoff to identify prelabor acidemia in FGR, providing superior prediction compared with the traditional NST.7 An additional advantage of the cCTG is the ability to evaluate longitudinal trends of multiple fetal heart rate variables that cannot be assessed with the traditional NST.8

**Amniotic Fluid Volume Assessment**

Ultrasound assessment of amniotic fluid volume was added to antenatal testing to improve the prediction of poor perinatal outcome.8 Regulation of amniotic fluid volume is complex, but by the second trimester primarily reflects fetal urine production. Placental dysfunction and fetal hypoxemia may both cause redistribution of renal blood flow leading to fetal oliguria and consequently oligohydramnios. However, the correlation between the total volume of amniotic fluid index (<5 cm) or a single vertical pocket (<2 cm) with the actual decline in amniotic fluid volume is limited. Although multiple studies have related oligohydramnios with increased risk for FGR, congenital abnormalities, postdates pregnancy, meconium passage, abnormal FHR patterns, and lower Apgar scores, a reliable concordance with more objective outcome measures such as fetal acidosis has not been demonstrated.10

**Dynamic Fetal Variables**

Dynamic fetal variables including tone, movement, and breathing activity are centrally regulated components of fetal behavior. Although these individual variables can be observed as early as the first trimester, their frequency and persistence is determined by central nervous system development, maternal factors, and oxygenation of the regulatory centers. When these factors are accounted for, central effects of progressive hypoxemia and acidemia produce a predictable effect on fetal behaviors.8 Fetal breathing movements cease first, but this may be observed over a wide pH range. Gross body movements and tone decrease further until they are no longer observed over extended periods of time. Loss of fetal tone and movement are typically observed at a median pH of 7.10, and therefore provide the most consistent prediction of prelabor acidemia.11 However, when dynamic fetal variables are considered in isolation, their predictive accuracy for acidemia is limited by the physiologic variation that is observed in normal pregnancies.9

**Placental Doppler**

Doppler ultrasound of the uterine and umbilical arteries assesses the integrity of the maternal and fetal vascular compartments of the placenta. In the uterine arteries, increased blood flow resistance and/or prolonged gestational persistence of an end-diastolic notch indicates abnormal trophoblast invasion. Such suboptimal maternal placental vascularization predisposes to maternal hypertensive disorders, FGR, and fetal demise. In the umbilical arteries, a decline in end-diastolic blood flow velocities correlates with the degree of abnormalities in the villous vascular tree and the risk for fetal hypoxemia, acidemia, and stillbirth.1 However, as placental Doppler studies do not directly reflect the degree of fetal compromise, they have a limited predictive accuracy for acidemia and stillbirth in FGR.12

**Fetal Doppler**

Fetal cardiovascular responses to abnormal placentation can be observed in multiple vascular beds. From a practical standpoint, the cerebral and precordial venous circulations have been most widely studied in the human fetus. Increases in placental blood flow resistance and perceived fetal hypoxemia are associated with a decrease in the cerebroplacental Doppler ratio and/or increased end-diastolic velocity in the cerebral circulation.1 These responses contribute to the preferential distribution of well-oxygenated blood from the ductus venosus to the brain, upper body, and the heart. With progressive placental dysfunction, abnormalities may be observed in the venous flow velocity waveforms. An associated decline in forward velocities during atrial systole indicates abnormalities in forward cardiac function that may be related to worsening placental disease and/or cardiac impacts of metabolic compromise. The most severe venous Doppler abnormalities include absence/reversal of the ductus venosus atrial systolic forward velocity and bi-triphasic pulsations in the umbilical venous flow velocity profile. However, as vascular parameters are influenced by several variables, including gestational age, blood viscosity, and blood pressure, there is a wide range in the distribution of blood gas values associated with abnormal arterial and venous Doppler findings (Fig. 1).
Nageotte and coworkers combines the NST and the amniotic fluid index and the computerized cardiotocogram (cCTG; pH irrespective of the underlying pathology and gestational age. The modified biophysical profile score introduced by the recognition that, in the absence of overt abnormalities, individual tests have a limited ability to distinguish between physiologic and pathologic variation in fetal status. The five-component BPS demonstrates best how integration of short-term variation. Biophysical variables (AFV, amniotic fluid index and appropriate fetal body movement, FBM, fetal gross movement). The same relationships are expressed for umbilical artery absent end-diastolic velocity (AEDV) and deviation of the arterial or venous Doppler indices may be observed which will eventually reverse (UA-REDV). In this setting, a progressive rise in venous Doppler indices may be observed which will eventually escalate over a wide range. Elevated umbilical artery Doppler index, and brain sparing if placental gas exchange is affected. Chronic nutrient deprivation has multiple organ effects that are proportional to the degree of placental dysfunction. Of particular relevance to fetal surveillance are central nervous system and cardiovascular effects. Growth-restricted fetuses exhibit delayed maturation of behavioral milestones, including a delay in the development of fetal heart rate reactivity. Despite this delay in behavioral development, the responses to deteriorating acid-base status are preserved. In the cardiovascular system, development of brain sparing typically follows blood flow abnormalities in the placental vascular bed. When placental blood flow resistance is significantly increased, umbilical artery end-diastolic velocity ceases, or may reverse (UA-REDV). In this setting, a progressive rise in venous Doppler indices may be observed which will eventually escalate over a wide range.

**Clinical Features of FGR**

There are several clinical features that are unique to placenta-based fetal growth restriction that require consideration in the diagnosis and management. As one of the earliest manifestations of placental dysfunction, a reduction in umbilical venous volume flow leads to decreased nutrient delivery to the fetal liver. Accordingly, a decrease in liver size and abdominal circumference is the first fetal physical manifestation of placental dysfunction. More widespread placental disease leads to either a decrease in umbilical artery end-diastolic velocity when the villous vascular tree is abnormal or isolated brain-sparing if placental gas exchange is affected. Chronic nutrient deprivation has multiple organ effects that are proportional to the degree of placental dysfunction. Of particular relevance to fetal surveillance are central nervous system and cardiovascular effects. Growth-restricted fetuses exhibit delayed maturation of behavioral milestones, including a delay in the development of fetal heart rate reactivity. Despite this delay in behavioral development, the responses to deteriorating acid-base status are preserved. In the cardiovascular system, development of brain sparing typically follows blood flow abnormalities in the placental vascular bed. When placental blood flow resistance is significantly increased, umbilical artery end-diastolic velocity ceases, or may reverse (UA-REDV). In this setting, a progressive rise in venous Doppler indices may be observed which will eventually escalate over a wide range.

**Integrated Approaches to Fetal Surveillance**

The rationale to combine surveillance modalities is based on the recognition that, in the absence of overt abnormalities, individual tests have a limited ability to distinguish between physiologic and pathologic variation in fetal status. The five-component BPS demonstrates best how integration of short-term parameters is typically associated with a normal pH. However, elevation of venous Doppler indices, either alone or in combination with umbilical artery pulsations, predicts fetal acidemia with 70% to 90% sensitivity and specificity. Similarly, absence or reversal of the ductus venosus a wave and multiphasic umbilical venous pulsation predict subsequent stillbirth with 65% sensitivity and 95% specificity.

**Figure 1** This figure displays a diagramatic representation of pH deviation from the gestational age mean (ΔpH) with abnormal test results in various antenatal tests. These include fetal heart rate (FHR) analysis using traditional nonstress testing (NST, –react, non-reactive) and the computerized cardiotocogram (cCTG, +acc, accelerations present, +dec, obvious decelerations present, STV, short-term variation). Biophysical variables (AFV, amniotic fluid volume, FBM, fetal body movement, FGM, fetal gross movement). The same relationships are expressed for umbilical artery absent end-diastolic velocity (AEDV) and deviation of the arterial or venous Doppler parameters is typically associated with a normal pH. However, elevation of venous Doppler indices, either alone or in combination with umbilical artery pulsations, predicts fetal acidemia with 70% to 90% sensitivity and specificity. Similarly, absence or reversal of the ductus venosus a wave and multiphasic umbilical venous pulsation predict subsequent stillbirth with 65% sensitivity and 95% specificity.
An Integrated Approach to the Diagnosis of FGR

FGR may be a manifestation of placental insufficiency, aneuploidy, genetic syndromes, or viral infection. With this differential diagnosis in mind, a detailed anatomic survey, fetal biometry, assessment of amniotic fluid volume, and placental Doppler studies are necessary in any patient with suspected FGR. The formula for the sonographically estimated fetal weight (SEFW) typically incorporates measurements of the fetal head, abdomen, and femur length. As growth restriction affects the abdominal circumference (AC) first, this measurement is frequently abnormal, whereas the SEFW may still be in the normal range. The abdominal circumference, head to abdomen symmetry, and long bone length should therefore be reviewed individually as they may give additional pointers toward aneuploidy or skeletal dysplasia. The finding of oligohydramnios is another important marker of FGR and may be the first ultrasound sign. Although, oligohydramnios is a poor primary screening tool for FGR or fetal acidemia, its value in clinical practice is as an additional diagnostic sign of placental dysfunction. In contrast, an increased amniotic fluid volume in the setting of small fetal size may suggest aneuploidy or fetal infection.

The diagnostic criteria that best identifies the growth-restricted fetus with placental disease at risk for adverse outcome include a combination of biometry and Doppler parameters. An AC below the 5th percentile predicts FGR with a sensitivity of 98% but only has a positive predictive value of 37%, whereas a SEFW below the 10th percentile has a sensitivity of 86% but a positive predictive value of 51%. But when these biometric parameters are combined with an abnormal umbilical artery Doppler index, sensitivity ranges from 63% to 100%, and positive predictive values between 60% and 80% can be achieved. One notable exception is the near-term fetus, where umbilical artery Doppler studies may be normal but brain sparing is the only evidence of placental dysfunction. An integrated diagnostic approach to FGR that incorporates these concepts is described in Figure 3.
Choosing Monitoring Intervals

The choice of monitoring intervals depends on the anticipated speed of clinical deterioration and risk for impending acidemia and/or stillbirth. With the exception of trend-analysis of the cCTG short-term variation, amniotic fluid volume and short-term biophysical parameters provide limited information on the rate of fetal deterioration since they are dependent on the metabolic state at the time of testing. The need to consider Doppler parameters was recognized almost two decades ago when Divon and coworkers published their outcome of FGR pregnancies with absent umbilical artery end-diastolic velocity that underwent daily biophysical profile scoring with strict criteria for delivery. Their management approach resulted in excellent outcome without any stillbirths or acidemia.23

Today, with a better understanding of the sequence of deterioration in FGR, the value of integrating biophysical and Doppler parameters for FGR monitoring is even more apparent. For the fetus with mildly abnormal umbilical artery Doppler studies, new onset of brain sparing or evidence of pulmonary sparing thereafter.26 There are important differences in the cardiovascular manifestations in FGR that are determined by the severity of placental disease and gestational age. In mild, nonprogressive placental dysfunction, the umbilical artery Doppler index does not increase above 3 standard deviations and vascular deterioration beyond brain sparing is not observed. In progressive placental dysfunction, disease onset is earlier in gestation and umbilical artery Doppler indices progressively rise. The most severe early-onset disease is associated with severe umbilical artery Doppler abnormalities. It is only in these two more severe patterns where progression to venous Doppler abnormalities is observed. Accordingly, once FGR has been diagnosed, weekly umbilical artery Doppler is suggested to determine the pattern of progression. After the initial 14 days, rapidly progressive severe disease will be revealed by definitive deterioration of umbilical artery Doppler and emergence of additional vessel abnormalities. For the remainder, a less fulminant course is expected. If there is still no change over the next 2 weeks, then venous Doppler monitoring is unlikely to yield abnormal results.27

**Intervention Triggers**

There is only limited intrauterine therapy available once FGR is established, and delivery is frequently the only option. The decision on delivery timing is in principle determined by the balance of fetal and postdelivery risks. These have mostly been studied for the preterm growth-restricted fetus as fetal and neonatal risks are prominent in this subset of FGR.2,28 There are no randomized controlled studies that clarify when the preterm growth-restricted fetus should ideally be delivered. Growth-restricted fetuses have a less than 50% chance of survival before 26 weeks and below a birth weight of 600 g. Until 28 weeks gestation, a growth-restricted fetus may gain 2% increase in survival for each day he remains in utero.28 The growth restriction intervention trial suggests that early delivery carries the risk of higher neonatal mortality and adverse neurodevelopment at age 2, which is predominantly related to prematurity-related complications.2,29 Based on these observations, the prevailing opinion is that safe prolongation of pregnancy in FGR presenting before 34 weeks is desirable.28 However, delivery triggers have not been identified and are based on expert opinion.

Several observations in preterm FGR strongly support the integration of biophysical and Doppler parameters. The sequence of arterial and venous Doppler abnormalities that presage the deterioration of biophysical parameters has been reasonably well established.1,13,18,19,24,25,27,30 Biophysical variables including the cCTG and arterial and venous Doppler parameters appear to synergistically predict fetal risks.31-34 At early gestational ages where safe prolongation of pregnancy is important, close surveillance of biophysical and multivessel Doppler parameters may gain up to 1 week in utero.24,23,30 As gestational age remains the main determinant of neonatal outcomes, late Doppler findings such as an abnormal BPP and/or ductus venosus a-wave reversal may need to be present before delivery is considered. The integrated man-
The management protocol that is practiced at our institution is displayed in Figure 4.

In pregnancies presenting after 34 weeks gestation, the neonatal risks are low. When these are related to the stillbirth risk for undelivered fetuses (prospective stillbirth risk), the balance is in favor of delivery from 38 weeks onwards. Although this has not been studied in a randomized fashion, these data support a low delivery threshold in growth-restricted fetuses identified near term.3,35

**Conclusion**

As our understanding of the multi-system impacts of placental dysfunction is evolving, there is little advance in the management approach to these pregnancies. Randomized evaluation of preventive strategies, delivery triggers, and neonatal management are of high priority. In this context, an integrated approach to diagnosis and monitoring provides the most comprehensive framework to evaluate FGR.

**References**


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**Figure 4** The management algorithm for pregnancies complicated by FGR is based on the ability to perform arterial and venous Doppler as well as a full five-component biophysical profile score. This is the typical management approach we practice at the University of Maryland, Baltimore for preterm growth restricted fetuses (unless otherwise indicated). Max, maximum; A/REDV, absent/reversed end-diastolic velocity; BPS, biophysical profile score; DV, ductus venosus; MCA, middle cerebral artery; NICU, neonatal intensive care unit; UA, umbilical artery.