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# Fetal Growth Restriction

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**Normal fetal growth is determined by the genetically predetermined growth potential and further modulated by maternal, fetal, placental, and external factors. Fetal growth restriction (FGR) is a failure to reach this potential and is clinically suspected if sonographic estimates of fetal weight, size, or symmetry are abnormal. Integration of fetal anatomy assessment, amniotic fluid dynamics, uterine, umbilical, and fetal middle cerebral artery Doppler is the most effective approach to differentiate potentially manageable placenta-based FGR from aneuploidy, nonaneuploid syndromes, and viral infection. Although placental dysfunction results in a multisystem fetal syndrome with impacts on short- and long-term outcome, only cardiovascular and behavioral responses are helpful to guide surveillance and intervention. Early-onset FGR before 34 weeks gestation is readily recognized but challenging to manage as questions about optimal delivery timing remain unanswered. In contrast, near-term FGR provides less of a management challenge but is often missed as clinical findings are more subtle. Once placenta-based FGR is diagnosed, integrating multivessel Doppler and biophysical profile score provides information on longitudinal progression of placental dysfunction and degree of fetal acidemia, respectively. Choosing appropriate monitoring intervals based on anticipated disease acceleration and intervention when fetal risks exceed neonatal risks are the prevailing current management approaches.**



**KEYWORDS** fetal growth restriction, placental dysfunction, antenatal surveillance, biophysical profile scoring, Doppler ultrasound

Normal fetal growth depends on maternal, fetal, placental, and external factors combined with the genetically predetermined growth potential.[1] The multisystem impacts of placental dysfunction produce an increase in the already elevated background mortality and morbidity.[2,3] In preterm fetal growth restriction (FGR) uncertainty about delivery timing increases perinatal mortality and morbidity due to iatrogenic prematurity.[4,5] Near-term questions about delivery timing are less critical. However, difficulty in identifying term FGR contributes to over 50% of unexplained stillbirths.[6,7] Accurate diagnosis, appropriate surveillance, and certainty about timing interventions are considered important prerequisites to improve these statistics. A systematic approach to the diagnosis and management of placenta-based FGR requires recognition of the clinical spectrum of this condition.

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## Pathophysiology of Placental Dysfunction

Effective first-trimester trophoblastic adherence initiates placental development, ultimately resulting in the formation of a low impedance and high capacitance circulatory interface between the fetal and maternal circulations as well as a carrier system for principal nutrients.[8] Despite this efficiency of the placental unit in normal pregnancies, the fetus is vulnerable to nutrient deprivation when placental dysfunction supervenes. As the placenta extracts a fixed proportion of the nutrient stream (70% of glucose and 40% of oxygen supplied to the uterus), fetal nutrition is restricted to the surplus that remains after placental demands have been met.[8] Even mild placental dysfunction may restrict nutrient transfer and blood flow to the fetus while placental nutrition is maintained.[9] When growth delay becomes clinically apparent, a number of fetal responses including adjustments in metabolism, endocrine axes, and hematologic parameters as well as cardiovascular and behavioral responses may already have taken place. Of these, cardiovascular and behavioral manifestations can be used in FGR management. While not amenable to management, adjustments in other organ systems still have

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a profound impact on short- and long-term outcome and ultimately define the consequences of placental dysfunction.

## Maturational Impacts of Placental Dysfunction

A reduction of uterine perfusion below 0.6 mL/Kg/min measurably decreases fetal glucose and amino acid delivery. This reduction in substrate availability leads to downregulation of both the insulin and the insulin-like growth factor-1 endocrine axis and hepatic glucose metabolism.[10] The result is glycogenolysis with a decrease in liver size, redirection of gluconeogenic amino acids from endogenous protein breakdown, and eventually, delayed longitudinal growth.[8] A reduction in fatty acid transfer decreases the availability of precursor molecules for a wide range of bioactive substances. These changes are important antecedents for the manifestation of FGR.[8] With increased accumulation of lactate and ketone bodies the fetal brain, heart, and erythrocytes become scavengers for these metabolites, thereby maintaining acid–base balance. Endocrine responses correlate with the degree and level of hypoxemia and include central and peripheral hypothyroidism, upregulation of the adrenocortical axis, and bone demineralization.[8]

Hematologic responses of the fetus initially consist of a compensatory increase in red cell mass but eventually may exacerbate placental vascular dysfunction. Hypoxemia-stimulated extramedullary hematopoiesis may no longer be observed as placental dysfunction escalates.[8] Under these circumstances the risk for thrombocytopenia may increase 10-fold[11] and increased blood viscosity, decreased erythrocyte pliability, as well as platelet aggregation worsen intraplacental blood flow dynamics further.[12] Cellular and humoral immune dysfunction also correlates to the degree of fetal acidemia and explains the higher susceptibility to postpartum infection.[8] While these consequences of placental dysfunction have no immediate value in the diagnosis and surveillance in FGR, they illustrate the multisystem effects of placental dysfunction. Accordingly, compromise at many levels is undetectable by antenatal surveillance and not amenable to therapy. When FGR manifests early in pregnancy, marked abnormalities of placental function are typically evident. In near-term FGR these abnormalities are far more subtle and may escape clinical evaluation.

## Doppler Evidence of Placental Dysfunction

An elevated uterine artery Doppler index and/or persistent waveform notching beyond 24 weeks indicate increased spiral artery blood flow resistance in the maternal compartment of the placenta. In the fetal compartment the earliest sign of abnormal villous perfusion is a decrease in umbilical venous flow.[9] Umbilical artery end-diastolic velocity (UA EDV) decreases and resistance indices become elevated when 30% of villous vasculature is abnormal.[13] Progression to absent- or even reversed end-diastolic velocity occurs when 60 to 70% of the villous vascular tree has been damaged.[14] However, placental vascular dysfunction with fetal hypoxemia may exist in the absence of any of these Doppler findings.[15,16] The detection of such subtle placental dysfunction requires the examination of fetal responses (Figs. 1-3).

## Circulatory and Behavioral Responses to Placental Dysfunction

Fetal circulatory responses to placental insufficiency may be passively mediated by high placental blood flow resistance or by active organ autoregulation. Redistribution of cardiac output toward the left ventricle occurs with relative increases in right ventricular afterload as documented by a decrease in the ratio of Doppler indices in cerebral and umbilical arteries

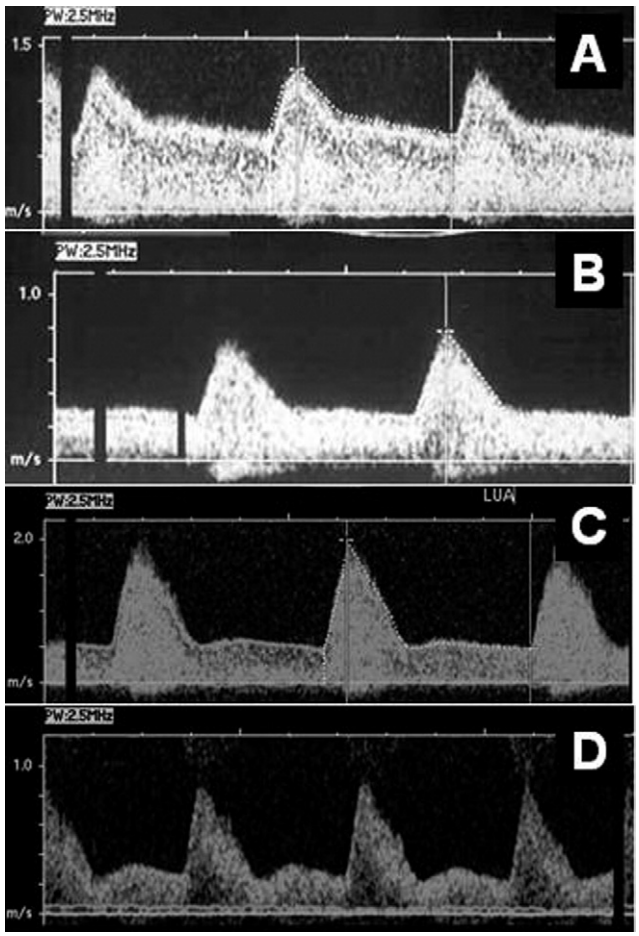


**Figure 1** Flow velocity waveforms obtained from the uterine artery beyond 24 weeks gestation. In the first patient (A) high-volume diastolic flow is established, indicating successful trophoblast invasion. Elevated placental vascular resistance is associated with a decline in diastolic velocities and a subsequent rise in the Doppler index (B). Persistence of an early diastolic notch in the uterine artery flow velocity waveform is evidence of increased spiral artery blood flow resistance. Frequently "notching" is more subtle beyond 32 weeks (C) than in the late second or early third trimesters (D). (Reprinted with permission.[36])

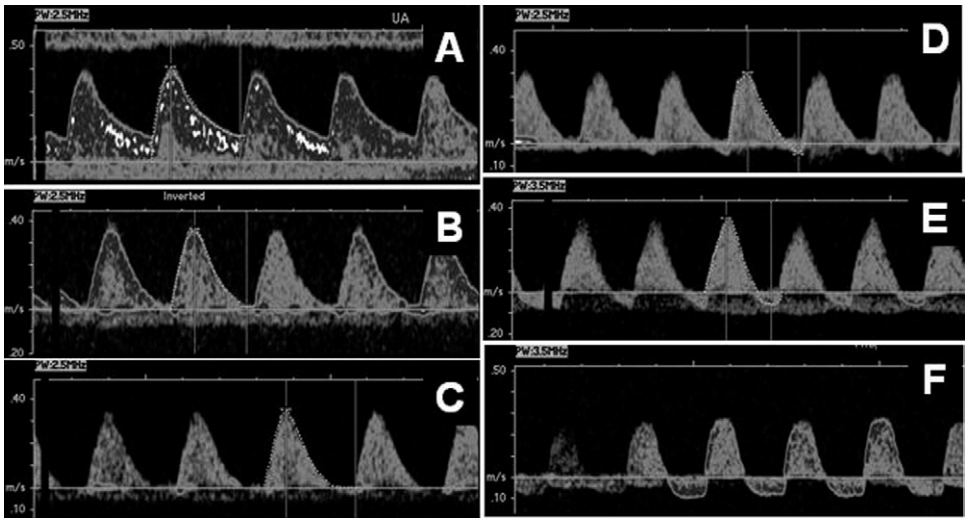


**Figure 2** The normal umbilical artery flow velocity waveform has marked positive end-diastolic velocity that increases in proportion to systole toward term (A). Moderate abnormalities in the villous vascular structure raise the blood flow resistance and are associated with a decline in end-diastolic velocities (B). When a significant proportion of the villous vascular tree is abnormal (50-70%), end-diastolic velocities may be absent (C) or even reversed (D). Depending on the magnitude of placental blood flow resistance and the fetal cardiac function, reversal of end-diastolic velocities may be minimal (D), moderate (E), or severe (F). In the latter case precordial venous flows were universally abnormal. (Reprinted with permission.[36])

(cerebroplacental Doppler ratio = CPR).[16] This is virtually always present in fetuses with absent end diastolic velocity (AEDV). Diversion of umbilical venous blood from the liver to the heart and decrease in cerebral blood flow impedance are active vascular phenomena. Together these compensatory responses result in preferential channeling of oxygen and nutrient-rich umbilical venous blood to the myocardium and brain (venous redistribution and brain sparing).[17]

Reversal of umbilical artery end-diastolic velocity and evidence of abnormal forward cardiac function indicate the progression to late cardiovascular manifestations. Increasing Doppler indices in the precordial veins are the hallmark of circulatory deterioration. This is most apparent through a decrease in atrial systolic forward velocities in the triphasic venous flow velocity waveform. In extreme cases, increased atrial pressure waves are transmitted all the way back into the free umbilical vein, resulting in pulsatile flow (Figs. 4 and 5).

Fetal behavioral responses to placental insufficiency can also be subdivided into early and late. Unlike in the cardiovascular system, early behavioral abnormalities are not clinically apparent as they predominantly consist of maturational delay. Clinically most relevant is delayed establishment of fetal heart rate reactivity, which may be absent in up to 60% of FGR pregnancies before 32 weeks. Individual fetal behaviors are lost in a relatively preserved sequence that is related to gestational age and the degree of hypoxemia. If fetal heart rate reactivity was present, it is lost first. Fetal breathing disappears next followed by decreased gross body movements and tone. This sequence is often accompanied by a gradual decline in amniotic fluid volume. Spontaneous late decelerations may also be observed as a late finding.

In preterm FGR before 30 to 32 weeks, late Doppler abnormalities precede the deterioration of the biophysical profile score (BPS). While the progression from brain sparing to spontaneous late decelerations has been reported within 2 weeks, the interval is variable and probably influenced by gestational age, maternal factors, and severity of placental disease.[18-22] For the clinician, escalating ductus venosus Doppler indices indicate accelerating fetal disease, while the BPS may still be normal. In term FGR where Doppler abnormalities are subtle, isolated brain sparing may provide such evidence. However, deterioration of the BPS is more likely associated with oligohydramnios or may have no antecedents.[23]

## Relationship Between Fetal Testing Parameters and Acid–Base Balance

Both Doppler and biophysical parameters predict acid–base balance in FGR. A decreased CPR, brain sparing, and UA AEDV indicate an increased risk for hypoxemia with a normal pH as long as venous Doppler parameters are normal. Elevation of venous Doppler indices, either alone or in combination with umbilical venous pulsations, increase the risk for acidemia. Dependent on the cutoff (2 versus 3 SD) and the combinations of veins examined, sensitivity for prediction of acidemia in preterm FGR ranges from 70 to 90% and specificity from 70 to 80%.[24,25] The five-component BPS shows a reliable and reproducible relationship with the fetal pH irrespective of the underlying pathology and gestational age.[26] 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 academia.[27] In contrast to Doppler parameters which are under the influence of several factors,

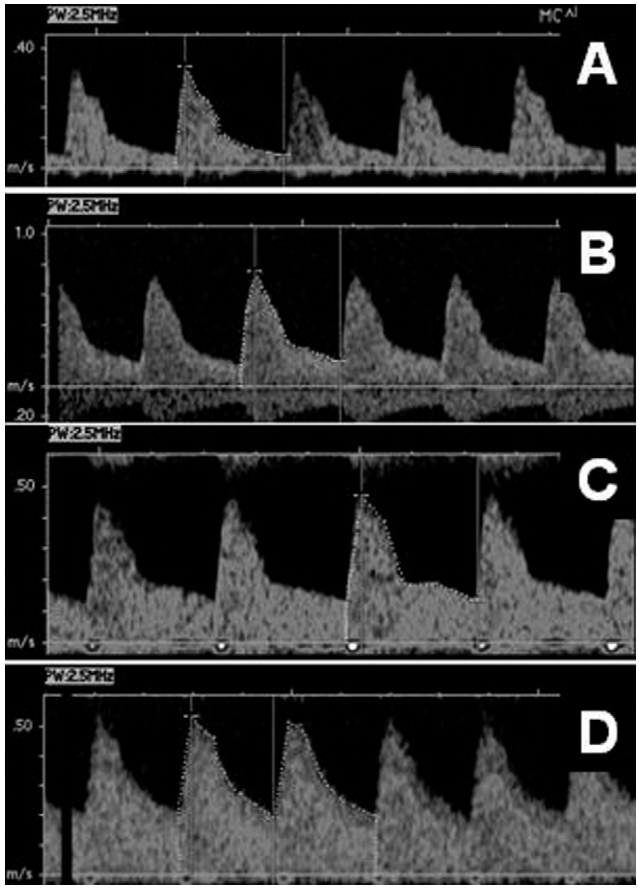


**Figure 3** The normal middle cerebral artery flow pattern has relatively little diastolic flow (A). With elevation of placental blood flow resistance the changes in the middle cerebral artery waveform may be subtle, although the cerebroplacental ratio may become abnormal as in fetus B. With progressive placental dysfunction there may be an increase in the diastolic velocity, resulting in a decrease in the Doppler index (Brain sparing, C). With marked brain sparing, the systolic down slope of the waveform becomes smoother so that the waveform almost resembles that of the umbilical artery (D). The associated rise in the mean velocity results in a marked decline in the Doppler index. (Reprinted with permission.[36])

regulation of fetal behaviors is more closely linked to oxygenation of their regulatory centers. Therefore, a closer correlation between behaviors and acid–base status has been observed at steady state.

## Diagnosis of Growth Restriction due to Placental Disease

The diagnosis of FGR due to placental disease is essential to identify the fetus in need of management. This excludes constitutionally small fetuses and those with other underlying etiologies where outcomes are unlikely improved by intervention. The physical manifestations of FGR and the cardiovascular signs of placental disease are listed in Table 1. Any combination of these abnormalities should raise the suspicion of placenta-based FGR. In preterm FGR diagnostic Doppler abnormalities of the umbilical arteries are common. In term FGR attention should focus on the middle cerebral artery Doppler and amniotic fluid volume. The differential diagnosis always needs to consider aneuploidy, nonaneuploid syndromes, viral infection, other toxins (smoking, cocaine), and the constitutionally small fetus. A clinical history, review of dates, sonographic exclusion of anomalies, consideration of invasive tests, and serial observations are often necessary to confirm the diagnosis. Once the diagnosis of placenta-based FGR has been made, perinatal management is warranted. This requires the consideration of fetal status and gestational age. A reduction of potentially preventable perinatal damage therefore relies on an accurate assessment of these variables.

## Surveillance of the Growth-Restricted Fetus

As there is no intrauterine therapy for FGR, accurate determination of fetal status by antenatal surveillance is a key component to direct intervention and monitoring intervals. Both of these requirements must be met to decrease perinatal damage. In this context performance of fetal surveillance tests is greatly influenced by the manifestation of fetal compromise across gestational age. Biophysical parameters are closely related to acid–base balance and therefore reflect current fetal status. Doppler parameters and amniotic fluid volume reflect disease progression and therefore guide in the choice of monitoring intervals.

The American College of Obstetricians and Gynecologists recommends twice weekly modified BPS (nonstress test and amniotic fluid index) and umbilical artery Doppler velocimetry for the surveillance of FGR.[28] Application of this recommendation requires some modification based on the clinical presentation. If fetal heart rate reactivity is not established, as can be expected in early-onset FGR, a full five-component BPS is required. If there are signs of advancing disease as indicated by loss of umbilical artery end-diastolic velocity or oligohydramnios, frequency of testing may be increased up to daily testing to avoid unexpected stillbirth.[29] In FGR presenting before 32 weeks where safe prolongation of pregnancy may be a key component of improving outcome, a more complex integrated approach has been proposed. Integrated fetal testing requires the concurrent evaluation of arterial and venous Doppler with the BPS. In addition to UA AEDV and oligohydramnios, onset of brain sparing or elevated venous Doppler indices are also considered as markers of accelerating disease requiring appropriate adjustment of monitoring intervals (Tables 2 and 3).[8]

## Management of Placenta-Based Growth Restriction

In the perinatal management of FGR the timing of interventions depends on the balance of fetal and neonatal risks. In term FGR where the primary problem lies in identifying the

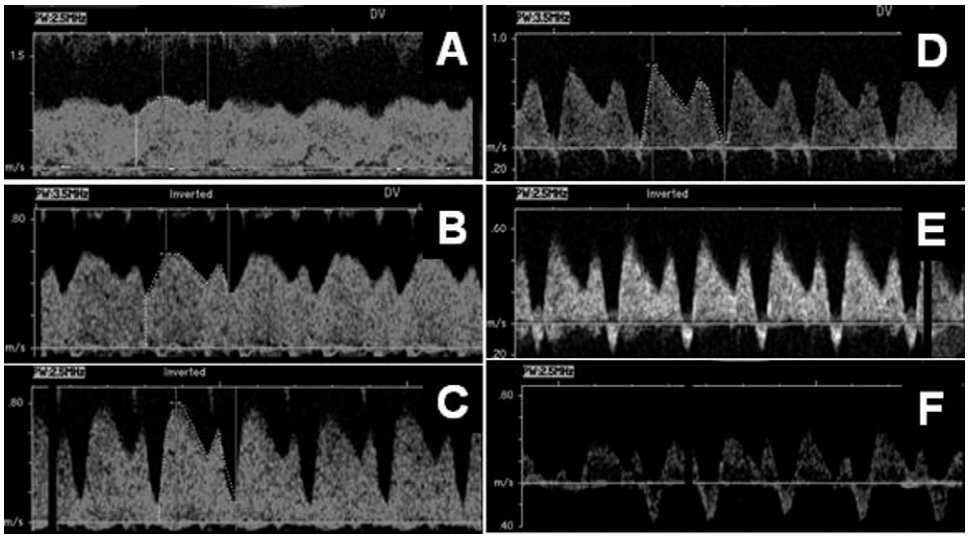


**Figure 4** In the ductus venosus blood flow is always antegrade throughout the cardiac cycle under normal circumstances. Pulsatility is less pronounced in waveform patterns obtained at the inlet (A) versus the outlet (B). With impaired cardiac forward function there is a decline in forward flow during atrial systole (C). If progressive atrial forward flow may be lost (D) or reversed (E, F). (Reprinted with permission.[36])

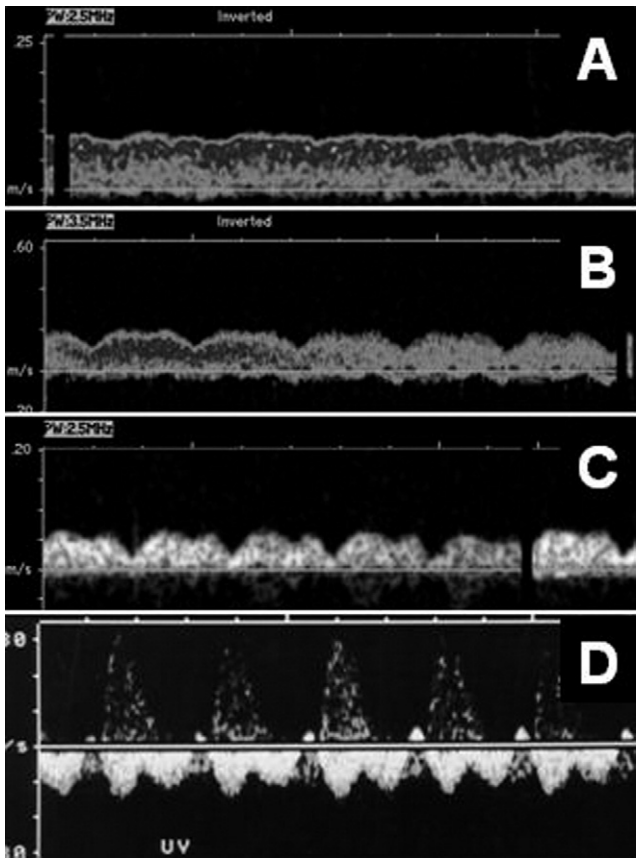


**Figure 5** In the umbilical vein the normally constant waveform pattern may show subtle pulsations with elevated placental blood flow resistance (A). With progressive increase in precordial venous indices monophasic, biphasic, and even triphasic pulsations may be observed (B, C, D). (Reprinted with permission.[36])

fetus at risk the neonatal risks are low. There are no randomized trials of elective delivery once the diagnosis of FGR has been made near term. However, prospective stillbirth risk data from a large US cohort suggest that in the presence of risk factors such as FGR delivery as early as 37 weeks may be required to decrease stillbirth rate.[30] From this it may be

**Table 1** Manifestations of Diagnostic Value

| |
|---|
| **Physical manifestations of fetal growth delay** |
| • Sonographically estimated fetal weight below the 10th percentile |
| • Abdominal circumference <5th percentile |
| • HC/AC ratio <10th percentile |
| • Individualized growth potential <10th percentile |
| • Femur length/abdominal circumference ratio >23.5 |
| • Abdominal circumference growth velocity <11 mm in 14 days |
| **Cardiovascular manifestations of placental dysfunction** |
| • Increased uterine artery Doppler index and/or notching |
| • Increased umbilical artery Doppler index |
| • Decreased middle cerebral artery Doppler index |
| • Decreased cerebroplacental Doppler ratio |
| • Maximum amniotic fluid pocket <2 cm |
| • Amniotic fluid index <5 cm |

**Table 2** Signs of Accelerating Placental Dysfunction

| |
|---|
| • Umbilical artery absent or reversed end-diastolic velocity |
| • Decreased cerebroplacental ratio |
| • Onset of brain sparing |
| • Elevated venous Doppler indices |
| • Umbilical vein pulsations |
| • Oligohydramnios |
| • Abnormal biophysical profile score |
| • Spontaneous late decelerations |

**Table 3** Integrated Fetal Testing in Fetal Growth Restriction

| Finding | Interpretation | Action |
|---|---|---|
| Abnormal UA and/or CPR; normal MCA and veins | Asphyxia extremely rare | Deliver for obstetric, or maternal factors only, fortnightly Doppler |
| BPS ≥8/10, AFV normal | Increased risk for intrapartum distress | Weekly BPS |
| Blood flow redistribution | | |
| Low MCA, normal veins | Hypoxemia possible, asphyxia rare | Deliver for obstetric, or maternal factors only, weekly Doppler |
| BPS ≥8/10, AFV normal | Increased risk for intrapartum distress | BPS 2 times/wk |
| Significant blood flow redistribution | | |
| UA A/REDV normal veins BPS ≥ 6/10, Oligohydramnios | Hypoxemia common, acidemia or asphyxia possible, onset of fetal compromise | >34 weeks: deliver; <32 weeks: antenatal steroids repeat all testing daily |
| Fetal compromise | | |
| Increased DV pulsatility BPS ≥6/10, Oligohydramnios | Hypoxemia common, acidemia or asphyxia likely | >32 weeks: deliver<br><32 weeks: admit, steroids, individualize testing daily vs. three times per day |
| Fetal decompensation | | |
| Compromise by above criteria, absent or reversed DV a-wave, pulsatile UV BPS <6/10, Oligohydramnios | Cardiovascular instability, metabolic compromise, stillbirth imminent, high perinatal mortality irrespective of intervention | Deliver at tertiary care center with the highest level of NICU care |

concluded that a low threshold for delivery should be used in these fetuses. Delivery criteria may include documented lung maturity, complete arrest of fetal growth, oligohydramnios, abnormal BPS, and UA AEDV.

Matters are more complicated in preterm FGR presenting before 34 weeks where deterioration may occur rapidly and where prematurity-related morbidity is significantly increased compared with appropriately grown counterparts.[31] With early-onset growth restriction viability (50% neonatal survival) is reached at 26 weeks and over half of these neonates do have major morbidity until 29 weeks. The neonatal survival benefit for each additional day in utero is estimated at 2% until 29 weeks gestation.[32] Moreover, long-term follow-up from the Growth Restriction Intervention Trial shows an increased risk of prematurity provoked neurodevelopmental delay if these fetuses are delivered too early.[33] Unfortunately there are no concluded randomized intervention trials that identify optimal intervention in this critical subset of growth-restricted fetuses.

The Growth Restriction Intervention Trial was a prospective randomized multicenter study of over 500 women with pregnancies complicated by FGR. Patients were randomly assigned to immediate versus delayed delivery based on physician discomfort. No difference in short-term outcome was observed but immediate delivery was associated with higher neonatal mortality while delayed delivery carried the price of a higher stillbirth rate. The long-term impacts on neurodevelopment were not anticipated by these short-term outcomes. Based on these studies it has been concluded that safe prolongation of pregnancy offers the best combination of decreased perinatal mortality, morbidity, and improved neurodevelopment.[34] In this context, the trial of umbilical and fetal flow in Europe compares the performance of computerized fetal heart rate analysis with ductus venosus Doppler. In the integrated fetal management approach multivessel Doppler and BPS are combined as indicated in Table 3. This protocol is based on the observation that integration of testing variables provides improved prediction of outcome even when the computerized fetal heart rate analysis is used.[35]

Integrated fetal testing is initiated at 24 weeks. If umbilical artery pulsatility is increased but end-diastolic flow is preserved, weekly BPS and biweekly Dopplers are performed. With the onset of brain-sparing, BPS *and* Doppler are repeated weekly. Testing frequency escalates with the degree of cardiovascular compromise. Delivery is based on a combination of late Doppler and biophysical abnormalities. The variety of management approaches to these highest risk pregnancies is not based on strong evidence and underlines the urgent need for development of randomized management trials.

## References


1. Gardosi J, Chang A, Kalyan B, et al: Customised antenatal growth charts. Lancet 339:283-287, 1992
2. Baschat AA, Gembruch U, Reiss I, et al: Relationship between arterial and venous Doppler and perinatal outcome in fetal growth restriction. Ultrasound Obstet Gynecol 16:407-413, 2000
3. Bernstein IM, Horbar JD, Badger GJ, et al: Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. Am J Obstet Gynecol 182: 198-206, 2000
4. Zeitlin J, Ancel PY, Saurel-Cubizolles MJ, et al: The relationship between intrauterine growth restriction and preterm delivery: an empirical approach using data from a European case-control study. BJOG 107:750-758, 2000
5. GRIT Study Group: A randomized trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. BJOG 110:27-32, 2003
6. Clausson B, Cnattignius S, Axelsson O: Outcomes of post-term births; the role of fetal growth restriction and malsformations. Obstet Gynecol 94:758-762, 1999

7. Froen JF, Gardosi JO, Thurmann A, et al: Restricted fetal growth in sudden intrauterine unexplained death. Acta Obstet Gynecol Scand 83:801-807, 2004
8. Baschat A: fetal responses to placental insufficiency: an update. BJOG 111:1031-1041, 2004
9. Rigano S, Bozzo M, Ferrazzi E, et al: Early and persistent reduction in umbilical vein blood flow in the growth-restricted fetus: a longitudinal study. Am J Obstet Gynecol 185:834-838, 2001
10. Reece EA, Wiznitzer A, Le E, et al: The relation between human fetal growth and fetal blood levels of insulin-like growth factors I and II, their binding proteins, and receptors. Obstet Gynecol 84:88-95, 1994
11. Baschat AA, Gembruch U, Reiss I, et al: Absent umbilical artery end-diastolic velocity in growth-restricted fetuses: a risk factor for neonatal thrombocytopenia. Obstet Gynecol 96:162-166, 2000
12. Trudinger B, Song JZ, Wu ZH, et al: Placental insufficiency is characterized by platelet activation in the fetus. Obstet Gynecol 93:180, 1999
13. Giles WB, Trudinger BJ, Baird PJ: Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. Br J Obstet Gynaecol 92:31-38, 1985
14. Morrow RJ, Adamson SL, Bull SB, et al: Effect of placental embolization on the umbilical arterial velocity waveform in fetal sheep. Am J Obstet Gynecol 161:1055-1060, 1989
15. Hecher K, Spernol R, Stettner H, et al: Potential for diagnosing imminent risk to appropriate- and small-for-gestational-age fetuses by Doppler sonographic examination of umbilical and cerebral arterial blood flow. Ultrasound Obstet Gynecol 2:266-271, 1992
16. Bahado-Singh RO, Kovanci E, Jeffers A, et al: The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. Am J Obstet Gynecol 180:750-756, 1999
17. Baschat A: The fetal circulation and essential organs—a new twist to an old tale. Ultrasound Obstet Gynecol 27:349-354, 2006
18. Hecher K, Bilardo CM, Stigter RH, et al: Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet Gynecol 18:564-570, 2001
19. Ferrazzi E, Bozzo M, Rigano S, et al: Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol 19: 140-146, 2002
20. Baschat AA, Gembruch U, Harman CR: The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol 18:571-577, 2001
21. Cosmi E, Ambrosini G, D'Antona D, et al: Doppler, cardiotocography, and biophysical profile changes in growth-restricted fetuses. Obstet Gynecol 106:1240-1245, 2005
22. Baschat AA, Galan HL, Bhide A, et al: Doppler and biophysical assessment in growth restricted fetuses: distribution of test results. Ultrasound Obstet Gynecol 27:41-47, 2006
23. Manning FA, Hill LM, Platt LD: Qualitative amniotic fluid volume determination by ultrasound: antepartum detection of intrauterine growth retardation. Am J Obstet Gynecol 139:254-258, 1981
24. Rizzo G, Capponi A, Talone PE, et al: Doppler indices from inferior vena cava and ductus venosus in predicting pH and oxygen tension in umbilical blood at cordocentesis in growth-retarded fetuses. Ultrasound Obstet Gynecol 7:401-410, 1996
25. Baschat AA, Güclü S, Kush ML, et al: Venous Doppler in the prediction of acid-base status of growth-restricted fetuses with elevated placental blood flow resistance. Am J Obstet Gynecol 191:277-284, 2004
26. Manning FA, Snijders R, Harman CR, et al: Fetal biophysical profile score. VI. Correlation with antepartum umbilical venous fetal pH. Am J Obstet Gynecol 169:755-763, 1993
27. Vintzileos AM, Fleming AD, Scorza WE, et al: Relationship between fetal biophysical activities and umbilical cord blood gas values. Am J Obstet Gynecol 165:707-713, 1991
28. American College of Obstetricians and Gynecologists (ACOG): Intrauterine Growth Restriction. ACOG Pract Bull 12:1-12, 2000
29. Divon MY, Girz BA, Lieblich R, et al: Clinical management of the fetus with markedly diminished umbilical artery end-diastolic flow. Am J Obstet Gynecol 161:1523-1527, 1989
30. Kahn B, Lumey LH, Zybert PA, et al: Prospective risk of fetal death in singleton, twin, and triplet gestations: implications for practice. Obstet Gynecol 102:685-692, 2003
31. Garite TJ, Clark R, Thorp JA: Intrauterine growth restriction increases morbidity and mortality among premature neonates. Am J Obstet Gynecol 191:481-487, 2004
32. Baschat AA, Cosmi E, Bilardo CM, et al: Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol 109:253-261, 2007
33. Thornton JG, Hornbuckle J, Vail A, et al: GRIT study group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. Lancet 364:513-520, 2004
34. Lees C, Baumgartner H: The TRUFFLE study—a collaborative publicly funded project from concept to reality: how to negotiate an ethical, administrative and funding obstacle course in the European Union. Ultrasound Obstet Gynecol 25:1005-1007, 2005
35. Turan S, Turan OM, Berg C, et al: Computerized fetal heart rate analysis. Doppler ultrasound and biophysical profile score in the prediction of acid-base status of growth-restricted fetuses. Ultrasound Obstet Gynecol 30:750-756, 2007
36. Baschat AA, Hecher K: Fetal growth restriction due to placental disease. Semin Perinatol 28:67-80, 2004