A Uniform Management Approach to Optimize Outcome in Fetal Growth Restriction

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KEYWORDS

• Fetal growth restriction • Fetal acidemia • Fetal Doppler • Umbilical artery
• Middle cerebral artery • Biophysical profile score • Neonatal outcome • Fetal testing

KEY POINTS

- A uniform approach to diagnosis and management of fetal growth restriction (FGR) produces better outcomes, prevents unanticipated stillbirth, and allows appropriate timing of delivery.
- An estimated fetal weight less than the tenth percentile in association with either an elevated umbilical artery Doppler index, a decreased middle cerebral artery Doppler index, or a decreased cerebroplacental ratio should be considered evidence of FGR. Early-onset and late-onset FGR represent two distinct clinical phenotypes of placental dysfunction.
- Integration of different testing modalities allows adjustment of monitoring intervals based on Doppler parameters and a more precise prediction of acid-base status based on biophysical variables.
- Antenatal surveillance of the growth-restricted fetus requires adjustment of monitoring intervals based on signs of disease acceleration, when delivery is not yet indicated.
- Thresholds for interventions are defined by the balance of fetal risks of continuation of pregnancy versus the neonatal risks that follow delivery and depend on gestational age.

INTRODUCTION

The main challenges in the management of pregnancies complicated by fetal growth restriction (FGR) are accurate identification of the small fetus at risk for adverse outcome, prevention of unanticipated stillbirth, and appropriate timing of delivery. A

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uniform management approach to diagnosis and management of FGR consistently produces better outcome than is reported in observational studies that rely on a range of diagnostic, surveillance, and delivery criteria.[1–5] Once the diagnosis of FGR has been made, surveillance tests need to be applied at appropriate intervals until the relative risks of delivery outweigh the benefits of ongoing monitoring. These factors are determined by the clinical phenotype of FGR across gestational ages.

CLINICAL PHENOTYPE OF FETAL GROWTH RESTRICTION IN RELATION TO GESTATIONAL AGE

FGR evolves from a preclinical phase to clinically apparent growth delay and may eventually lead to fetal deterioration before the spontaneous onset of labor. Growth delay due to decreased nutrient delivery affects liver size and therefore the abdominal circumference (AC) first, and then growth of the head and entire body.[6] Abnormal placental perfusion in the maternal compartment results in increased blood flow resistance in the uterine artery flow-velocity waveform.[7] Abnormal perfusion of the fetal villous vascular tree is associated with decreased umbilical artery (UA) end-diastolic velocity proportional to the degree of flow impairment.[8] Abnormal oxygen diffusion across the villous membrane leading to lower fetal arterial PaO_2 is associated with a decrease in middle cerebral artery (MCA) blood flow resistance,[9] whereas decreased CO_2 clearance additionally increases the MCA peak systolic velocity (**Fig. 1**).[10] The relative predominance of these mechanisms determines the clinical picture of FGR.[11–16]

FGR that is established by the second trimester is associated with a greater degree of vascular abnormality in the maternal and fetal compartments of the placenta. In the mother, high-resistance uterine artery flow velocity waveforms and a 40% to 70% rate of associated pre-eclampsia are characteristic. In the fetal compartment, an elevation

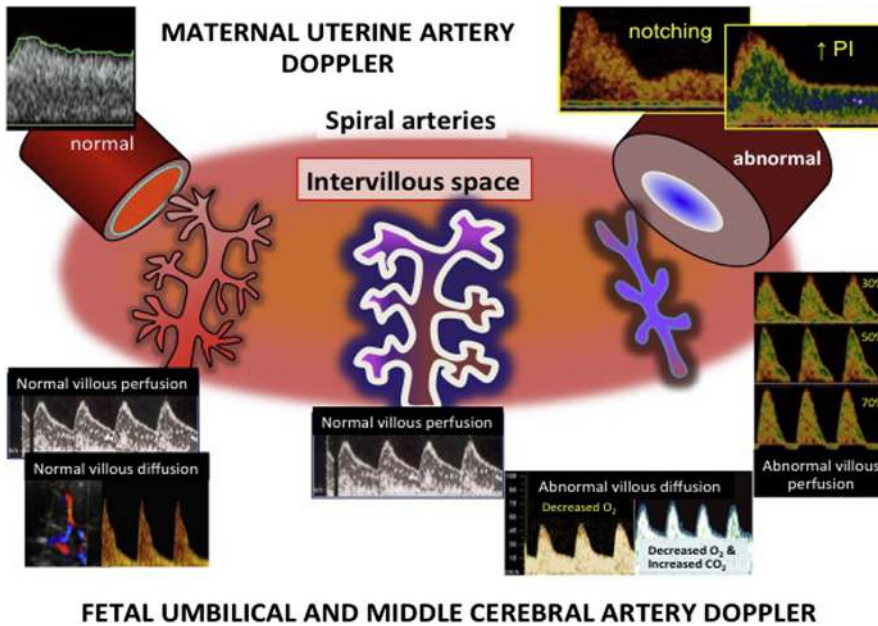

Fig. 1. Clinical correlates of maternal and fetal aspects of placental function.

of the UA pulsatility index (PI) is typical.[11,12] In FGR that is not established until 31 to 34 weeks (late-onset FGR), villous diffusion and perfusion defects coexist in various proportions,[17–21] leading to cerebral or UA Doppler abnormalities that may be present independent of each other (**Fig. 2**).[22–24] Because of this variable association between small fetal size and abnormal Doppler velocimetry, distinction between growth restriction and constitutional smallness can be challenging. Accordingly, management challenges in early-onset FGR revolve around prematurity and coexisting maternal hypertensive disease, whereas in late-onset disease, failure of diagnosis or surveillance leading to unanticipated stillbirth is the primary issue.[25,26]

DIAGNOSIS OF FETAL GROWTH RESTRICTION

The diagnosis of fetal growth delay can be based on fetal biometry alone or by also taking umbilical or cerebral artery Doppler indices into consideration. An AC less than the tenth percentile has the highest sensitivity for the diagnosis of FGR, whereas a sonographically estimated fetal weight (SEFW) less than the tenth percentile has greater specificity.[11] Most national societies agree on the tenth percentile for the SEFW as a diagnostic cutoff for small for gestational age (SGA). The disadvantage of this cutoff is the inclusion of a variable number of normal constitutionally small fetuses that do not require surveillance. Using an SEFW less than the third percentile or a decreased AC growth rate is more likely to identify "true FGR,"[27] but has the disadvantage that less severe forms of FGR at risk for deterioration are missed and therefore their risk for stillbirth remains. Combining an SEFW less than the tenth percentile with either an abnormal UA, MCA, or cerebroplacental ratio (CPR, defined as UA/MCA index), increases the identification of the small fetus at risk for adverse outcome. Although UA Doppler velocimetry is sufficient for the diagnosis of FGR before 32 weeks gestation, thereafter MCA Doppler is also required to represent the whole clinical spectrum found in early-onset and late-onset placental disease.[12,14,16,24] Because the CPR mathematically amplifies mild abnormalities in the umbilical and middle cerebral arteries, it is

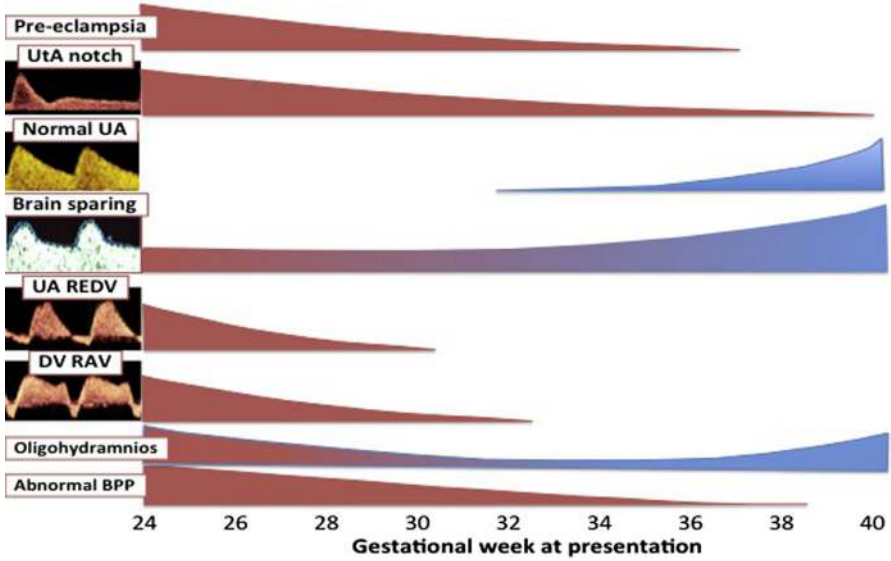

Fig. 2. Clinical signs of placental dysfunction and gestational age at presentation. BPP, biophysical profile; RAV, reversed a-wave velocity; UtA, uterine artery.

the most sensitive Doppler parameter, especially after 28 weeks of gestation, and its decrease should alert the clinician to the possibility of evolving brain sparing. Here, an SEFW less than the tenth percentile in association with either an elevated UA Doppler index, a decreased MCA Doppler index, or a decreased CPR should be considered evidence of FGR (**Table 1**).[11,12,14,16,24] The proportion of growth-restricted fetuses with normal UA blood-flow resistance but isolated MCA brain sparing is higher toward the late third trimester. Accordingly, MCA Doppler better identifies FGR after 34 weeks of gestation, when the predictive accuracy of CPR decreases.[12]

ASSESSMENT OF THE DEGREE OF FETAL DETERIORATION

Fetal surveillance tests are applied to pregnancies with suspected FGR to estimate the risk for hypoxemia, prelabor acidemia or stillbirth, as well as the rate of clinical deterioration. The required accuracy of this assessment is highest at early gestational ages, when prematurity-related risks are high and each additional day gained in utero can significantly increase chance of neonatal survival. An accurate estimation of pH is important to predict fetal compromise that precedes stillbirth and therefore critical to time delivery.

The association between the abnormalities in Doppler parameters and the deterioration of fetal acid-base status has been demonstrated in several studies,[28–31] predominantly in the preterm fetus. Abnormal umbilical flow patterns indicate an increased risk of hypoxemia and acidemia proportional to the severity of Doppler abnormality. Although Doppler findings in each of the examined vascular beds correlate with fetal acid-base status, there is a wide variation in fetal pH with abnormal results. Among Doppler parameters, the elevation of the precordial venous Doppler indices provides the best prediction of acidemia in fetuses with FGR.[31,32] Therefore, fetal Doppler assessment that is based on the UA indices alone is no longer appropriate in early-onset FGR, and the incorporation of venous Doppler is necessary to assess the rate and degree of fetal compromise. In preterm growth-restricted fetuses, MCA Doppler study has limited accuracy to predict acidemia and adverse outcome and should not be used to time delivery. Beyond 34 weeks, the UA waveform may be normal, and therefore, the best predictor of fetal adaptation to hypoxemia is considered the MCA PI. However, studies on fetal brain circulation in late-onset FGR[33,34] primarily evaluated the relationship of MCA Doppler with intrapartum fetal distress or neonatal acidosis rather than prelabor acid-base status. Accordingly, conclusions relating MCA Doppler to fetal pH are generally extrapolated.

Table 1
Implications of diagnostic cutoffs for management of fetal growth restriction

Diagnostic Cutoff	Advantage	Disadvantage
AC <10th percentile	Highest sensitivity for FGR	Lowest specificity for FGR
SEFW <10th percentile	Acceptable sensitivity for FGR	Unnecessary monitoring of normal fetuses
SEFW <3rd percentile	Greater specificity for FGR	Less severe FGR is missed
SEFW <10th percentile & abnormal UA Doppler	Greatest specificity for FGR at risk for adverse outcome	Misses term FGR with normal UA Doppler
SEFW <10th percentile with abnormal UA or MCA	Greatest specificity for FGR at risk for adverse outcome across all gestational ages	Requires interpretation of umbilical and cerebral Doppler studies

The 5-component biophysical profile scoring (BPS) shows a reliable and reproducible relationship with the fetal pH, irrespective of gestational age.[35,36] An abnormal BPS of 4 or less is associated with a mean pH of less than 7.20 and a score of less than 2 has a sensitivity of 100% for acidemia.[36] When the relationship between the various testing modalities and fetal acid-base status is compared, biophysical parameters show a closer relationship with the pH, whereas there is a wide variation in fetal pH with abnormal Doppler results. On the other hand, the BPS alone has limited utility in the prediction of longitudinal deterioration,[37,38] which is better assessed with multi-vessel Doppler studies.

Fetal heart rate is one of the 5 components of the BPS. A nonreactive cardiotocogram (CTG) has been correlated with fetal hypoxemia and acidemia,[39,40] but it is associated with a wide range of pH values,[39] and as for the other components of the BPS, it does not anticipate the rate of deterioration. Computerized heart rate monitoring (cCTG) has been introduced to improve the interpretation of fetal heart rate traces, by determining quantitative parameters, such as the short-term variation, that cannot be visually assessed. In fetuses with intrauterine growth restriction, a short-term variation less than 3.5 ms appears the best predictor of an UA pH of less than 7.20.[41] However, cCTG as a stand-alone test in FGR offers limited accuracy, and it performs best when combined with venous Doppler or as a substitute for the traditional NST in the BPS.[42]

SELECTION OF MONITORING INTERVALS

The goal of fetal surveillance is to prevent stillbirth and irreversible fetal deterioration; this requires adjustment of monitoring intervals based on signs of disease acceleration, when delivery is not yet indicated.

With standardization of antenatal surveillance, a reduction in antenatal mortality might be achieved without worsening neonatal outcome.[3] The optimal surveillance pattern and timing of delivery remain the objects of much debate and research. There is no general consensus between national guidelines on the appropriate frequency of testing, and they are based on expert opinion of key authors because there is no high-quality evidence to guide practice.

In the authors' opinion, the best approach consists of a longitudinal surveillance starting at 24 to 26 weeks with integrated fetal testing, including multivessel Doppler examination, fetal heart rate analysis, and assessment of fetal activity through BPS, because the combination of tests improves the prediction of acidemia and stillbirth compared with single tests.[37,42–44]

Monitoring interval choice depends on gestational age at onset and signs of deterioration at Doppler study. When new features indicating disease acceleration or fetal deterioration develop, monitoring frequency needs to be increased until the delivery threshold is reached. Because early-onset and late-onset FGR represent 2 distinct clinical phenotypes of placental dysfunction, they show different signs of disease progression. In early-onset FGR, fetal deterioration typically evolves from abnormal UA Doppler studies, to brain-sparing, abnormal venous Doppler parameters, abnormal computerized CTG, and finally, an abnormal 5-component BPS.[38,45–52] The rate of progression is determined by the interval between diagnosis to loss of UA end-diastolic velocity[49–51,53] and typically takes 4 to 6 weeks.[51] Once forward velocities in the ductus venosus (DV) become absent or reversed, fetal survival of longer than 1 week is unlikely.[54] Late-onset FGRs are characterized by a slower progression (up to 9 weeks), with predominant cerebral or UA Doppler abnormalities. There are no evident Doppler changes in the precordial veins and brain sparing may be the

only observed Doppler sign of hypoxemia (see Fig. 2).[16,55] Importantly, however, terminal deterioration resulting in stillbirth occurs more rapidly and unanticipated in term FGR.[56] Therefore, a closer surveillance is required after 34 weeks, and new onset of Doppler abnormalities at this age should raise consideration for delivery.

The observed progression of Doppler abnormalities should determine the interval of monitoring as follows, until the threshold for delivery is reached.

Early-onset fetal growth restriction
- Elevated UA Doppler PI (≥2 SDs above the mean for gestational age), no other abnormality: every 2 weeks Doppler, weekly BPS
- Low MCA PI or CPR: weekly Doppler + BPS
- UA absent end-diastolic velocity (AEDV): consider admission, 2 times per week Doppler + BPS
- UA reversed end-diastolic velocity (REDV), increased DV Doppler indices, and/or oligohydramnios (maximum vertical pocket of fluid <2 cm): admission, 3 times per week Doppler + BPS, daily CTG
- Absent/reversed DV a-wave: admission, daily Doppler + BPS, prepare for delivery

Late-onset fetal growth restriction (>34 weeks)
- Elevated UA Doppler PI (≥2 SDs above the mean for gestational age), no other abnormality: weekly Doppler + BPP
- Low MCA PI or CPR: 2 to 3 times per week Doppler + BPS

PLANNING DELIVERY: GESTATIONAL AGE AS A DETERMINANT OF INTERVENTION THRESHOLDS

In pregnancies complicated by FGR, the thresholds for interventions are defined by the balance of fetal risks of continuation of pregnancy versus the neonatal risks that follow delivery. The principle neonatal risks are neonatal mortality, major neonatal morbidity, which is associated with long-term impacts on health, and adverse neonatal development. These risks change in specific gestation age epoch (Fig. 3, Table 2), and the outcome is comparable to that of appropriate for gestational age infants born at a 2-week shorter gestational age.[57] Accordingly, the threshold for delivery needs to be higher at earlier gestational age.

The neurodevelopmental outcome of growth-restricted babies has received growing attention in recent years, given the impact on quality of life.[4,58,59] In early-onset FGR, gestational age has been found to be one of the major determinants of neurodevelopment. However, it remains to be determined if interventions other than modulating disease course might improve neurodevelopment.

Taking in account the data on neonatal survival derived from 2 large observational studies (see Fig. 3),[3,5] the following delivery indications per gestational epoch are suggested.

24 to 26 Weeks Gestation

The survival rate of FGR neonates averages less than 50%.[5] In surviving babies, the risks for major neonatal complications are as high as 80%. With these neonatal morbidities, especially higher grades of intraventricular hemorrhage, the motor neurodevelopmental adverse outcomes are equally high. These risks gradually decrease and there is an improvement in survival by an average of 2% per gestational day that is gained in utero. The survival rates exceed 50% once the estimate of fetal weight exceeds 500 g or 26 weeks are reached. Because of these significant neonatal morbidities, delivery for fetal deterioration may not be considered in certain health care

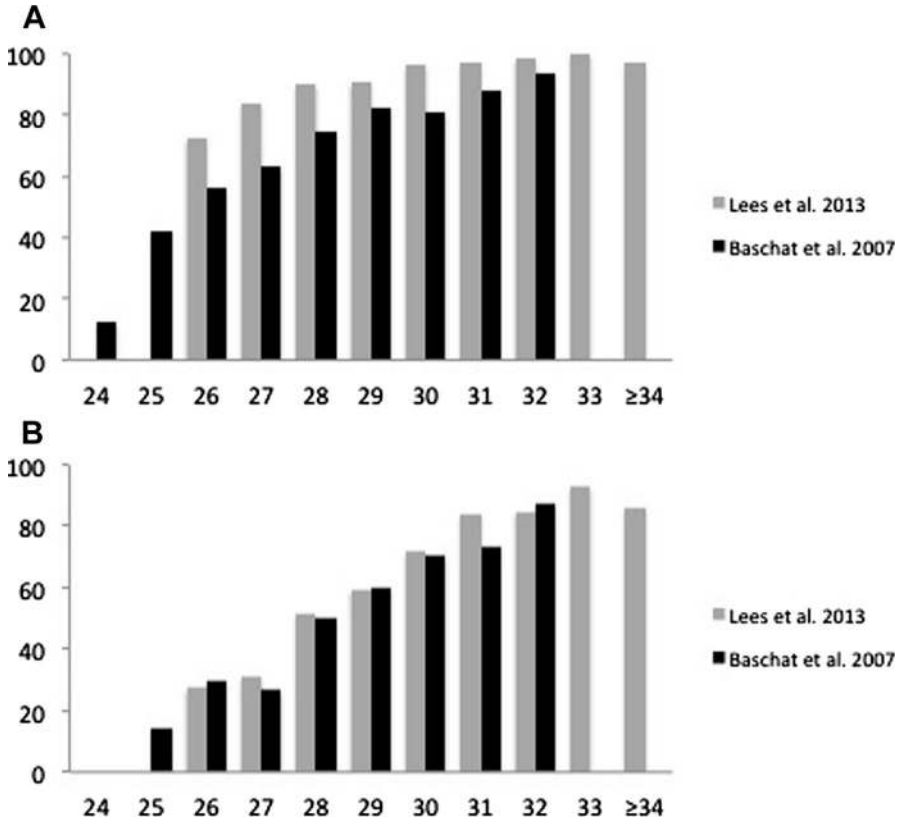

Fig. 3. Data on neonatal survival (*A*) and intact survival (*B*). (*Data from* Lees C, Marlow N, Arabin B, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol 2013;42(4):400–8; and Baschat AA, Cosmi E, Bilardo CM, et al. Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol 2007;109(2 Pt 1):253–61.)

settings. Maternal indications such as severe pre-eclampsia are the primary indications for delivery.

26 to 28 Weeks Gestation

Neonatal survival exceeds 50%. However, intact survival at 26 to 27 weeks remains around 30% (see **Fig. 3**).[3,5] Because neonatal morbidity rates are high, additional fetal deterioration before delivery does not appear to produce a statistical impact on survival. Although maternal disease remains an absolute delivery indication, fetal status may not qualify until acidemia is certain. Although an abnormal 5-component BPS (<6/10) is an indication to delivery from 26 weeks of gestation, because of its strong association with fetal acidemia, the evidence of venous Doppler abnormalities is not considered an indication to intervention until 28 weeks. The observed median time interval between the detection of abnormal venous Doppler indices and the deterioration of the BPS is 1 week,[52] which could potentially increase neonatal survival by 14% (see **Table 2**). Individualization of care in these pregnancies needs to be discussed with the patient, including the option of nonintervention.

Table 2
Management goals at different gestational ages

	24–26 wk	26–28 wk	28–30 wk	30–32 wk	32–34 wk	34–38 wk	>38 wk
Absolute delivery indications	Maternal indications, abnormal BPS						
Goal	Delay to reach viability	Delay to gain neonatal survival	Delay to improve neonatal morbidity		Delay for administration of steroids	Delay to decrease NICU admission rate	Delay not justified
Evidence	Birth-weight <500 g & gestational age <26 wk at delivery associated with >50% mortality	Each day in utero increases neonatal survival by median of 2% Fetal deterioration has no statistical impact on neonatal outcome	Each day in utero increases neonatal survival by median of 1% Reversed DV a-wave before delivery is associated with lower neonatal survival		SGA fetuses receiving prenatal steroids have lower rate of RDS, BPD, IVH, and mortality	SGA neonates delivered before 38 wk have a higher rate of NICU admission	Risks of surveillance failure, risks for progressive decline in growth, low neonatal morbidities favor delivery at 38 wk
Delivery threshold	Maternal conditions	Abnormal BPS (<6)	Reversed DV a-wave		UA REDV	UA AEDV	

Abbreviations: BPD, bronchopulmonary dysplasia; IVH, Intraventricular hemorrhage; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; SGA, small for gestational age.

28 to 32 Weeks Gestation

Neonatal survival exceeds 70% at 28 weeks and increases to more than 90% at 32 weeks (see **Fig. 3**). Survival gain per day in utero now averages 1% and neonatal mortality and morbidity progressively decrease. Fetal deterioration of venous Doppler parameters may be tolerated as long as DV a-wave velocities are antegrade. Reversal of the DV a-wave before delivery has an independent additional impact on neonatal morbidities, and persistence of this abnormality beyond 1 week carries significant risk for stillbirth. For this reason, the presence of a DV reversed a-wave is generally considered an indication to intervention from 28 weeks. However, delivery before 30 weeks gestation still carries a significantly higher risk for adverse neurodevelopment at age 2 because of neonatal complications and their impact on motor development.[4]

32 to 34 Weeks Gestation

Thirty-two to 34 weeks gestation is a time in fetal development whereby the cerebral circulation gains an additional structural layer, and, accordingly, there is a significant reduction in the rates of intraventricular hemorrhage. This reduction has measurable impact on motor development at age 3. Now, up until 34 weeks gestational age especially, the administration of antenatal steroids has an added benefit in reducing respiratory neonatal morbidity as well as intraventricular hemorrhage rates, and babies who have received steroids have improved survival. Moreover, recent evidence suggests that neurodevelopment is also improved by the administration of steroids[60]; this is most likely due to the beneficial impact on the respiratory performance and the decrease of ventilation related intraventricular bleeding.

Evidence of reversed UA end-diastolic velocity is generally considered a delivery indication from 32 weeks onward, whereas an AEDV is an indication from 34 weeks onward.

34 to 38 Weeks Gestation

At this gestational age, the gain in survival as well as neonatal morbidity is minimal; however, up to 38 weeks gestation, the rate of neonatal admissions to the intensive care nursery is still significantly greater for FGR infants, and the overall neonatal adverse outcome scores are higher. Accordingly, delivery thresholds should be based on clear maternal or fetal indications. The absence of UA end-diastolic velocity at Doppler study is considered an indication to delivery from 34 weeks onward. In late-onset FGR, the MCA Doppler is considered the best predictor of fetal adaptation to hypoxemia, and some national guidelines recommend the use of this parameter to time delivery in fetuses with normal UA Doppler.[61,62]

After 38 Weeks Gestation

Neonatal adverse events in SGA infants are negligible and, accordingly, ongoing pregnancy must be weighed carefully against the risks of unanticipated stillbirth if the patient remains undelivered. Risks of surveillance failure, risks for progressive decline in head growth, and low neonatal risks favor delivery. The Disproportionate Intrauterine Growth Intervention Study at Term (DIGITAT)[2] showed that among women with suspected intrauterine growth restriction at 36 to 41 weeks, a policy of labor induction affects neither the rate of adverse neonatal outcomes nor the rates of instrumental vaginal delivery or caesarean section, indicating that both approaches are acceptable. The consensus view from the DIGITAT is that the optimum time for induction in SGA with normal Doppler study is at around 38 weeks, because it is associated with the lowest neonatal morbidity[63] and seems to minimize the risk of stillbirth.[64]

Between 24 and 34 weeks, antenatal corticosteroids should be administered over a period of 48 hours for fetal lung maturity if delivery is being considered. At this age, delivery should be planned at a center with a neonatal intensive care unit. The route of delivery depends on the severity of fetal compromise, along with maternal condition and other obstetric factors. If prelabor acidemia is suspected, cesarean section is recommended. In FGR cases with abnormal UA Doppler, induction of labor can be offered, but rates of emergency caesarean section are increased. The use of prostaglandin for cervical preparation is usually discouraged. Because of the increased risk of intrapartum asphyxia in growth-restricted fetuses, continuous fetal heart rate monitoring is recommended from the onset of uterine contractions.

SUMMARY

Detection of FGR must be accompanied by uniform approaches to management to improve perinatal outcomes. The understanding of the clinical phenotype of early-onset and late-onset FGR is actively evolving. A decreased estimated fetal weight coupled with abnormal umbilical, MCA, or CPR studies provides the best identification of fetuses requiring surveillance. Doppler abnormalities precede biophysical deterioration and therefore allow adjustment of monitoring frequency. Concurrent deterioration of Doppler and biophysical variables best predict prelabor acidemia and therefore allow timing of delivery. The threshold for delivery is determined by the neonatal risks at each gestational epoch and decreases with advancing gestational age.

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