GUIDELINES

Management of fetal growth restriction

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Fetal growth restriction (FGR) is challenging because of the difficulties in reaching a definitive diagnosis of the cause and planning management. FGR is associated not only with a marked increased risk in perinatal mortality and morbidity but also with long-term outcome risks. Combinations of fetal biometry, amniotic fluid volume, heart rate patterns, arterial and venous Doppler, and biophysical variables allow a comprehensive fetal evaluation of FGR. However, no evidence supports that the use of cardiotocography or the biophysical profile improves perinatal outcome. Therefore, obstetricians aim to identify fetuses with early FGR so delivery can be planned according to gestational age and severity of the condition. The balance of risks and the need for the availability of services mean that the involvement of neonatologists in FGR management is vital. In this review, the focus is on the pathophysiology and management of FGR caused by placental diseases.

coronary heart disease, hypertension and type 2 diabetes—are associated with FGR. Small or disproportionate newborns have increased rates of coronary heart disease, high blood pressure, high cholesterol levels and abnormal glucose–insulin metabolism. These relationships were not associated with the length of gestation, suggesting that they are linked to FGR rather than to premature birth.⁶

FGR and small for gestational age (SGA) are not synonyms. Therefore, the distinction between infants who are growth restricted from those who are constitutionally normal SGA is important.¹ The term SGA is descriptive and means that the fetal size and hence weight at birth are less than expected (3–10% using standard curves for gestational age) regardless of the cause. In other words, it refers to the size, irrespective of the growth velocity in the uterus. It was estimated that about 50–70% of fetuses born weighing less than the 10th centile for gestational age are constitutionally small, with fetal growth appropriate for parental size and ethnicity; these are usually associated with normal placental function and have a normal outcome.⁷ Those SGA fetuses with birth weight <2nd centile for gestational age have a higher likelihood of being growth restricted.⁸

Traditionally, causes of abnormal SGA have been subdivided into fetal, placental and maternal.⁹ However, accurate prenatal assessment of fetal growth is not without difficulties. Although size is a physical parameter that can be measured at any gestational age, growth is a dynamic process that can be assessed only by repeated measurements. Hence, accurate prenatal differentiation between FGR and SGA is challenging.¹⁰

A classification of the severity of FGR in human pregnancies has been proposed on the basis of cardiotocography (CTG) and Doppler velocimetry of the umbilical artery (pulsatility index).¹¹ This classification reflects different degrees of placental insufficiency and is associated with marked differences in placental nutrient exchange.¹⁰

ASSESSMENT OF GROWTH

Precise initial dating by early ultrasonography is vital to ensure accurate pregnancy dating. Sequential assessments are necessary to determine whether there is a decrease in the fetal growth rate.¹² Several methods have been used in the detection of SGA fetuses, including abdominal palpation, measurement of symphyseal fundal height, ultrasound biometry with estimated fetal

Fetal growth restriction (FGR) describes a decrease in the fetal growth rate that prevents an infant from obtaining the complete genetic growth potential.¹ It is surprisingly common, with placental dysfunction occurring in about 3% of pregnancies, and despite advances in obstetric care, FGR remains a major problem in developed countries.² In human pregnancies, placental insufficiency is the leading cause of FGR and is usually due to poor uteroplacental blood flow and placental infarcts. The reduction of placental supply of nutrients to the fetus³ has been associated with several adaptive changes taking place in both the placenta and fetus. Adaptive changes can be followed by pathology leading to fetal death, and therefore staging of the disease is fundamental to timing delivery. Furthermore, marked differences are observed in the transplacental glucose gradient in the most severe cases, and the placental transport of essential amino acids is markedly reduced both in vivo and in vitro. These findings suggest that both placental metabolism and transport are altered in FGR.⁴

Maternal complications such as pre-eclampsia (PET) will affect the prognosis of FGR cases, perhaps as an indicator of the severity of placental failure and subsequent rapid fetal deterioration as well as the risks to the maternal condition. Hence, the association of PET and FGR does have a major effect on antenatal care, timing of delivery, perinatal mortality and morbidity.⁵

Evidence from previous research indicates that several major diseases in adulthood—for example,

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Figure 1 Growth patterns in (A) growth restricted and (B) small for gestational age fetuses.

weight and ultrasound Doppler studies. The biometric parameters most often used to evaluate fetal size are biparietal diameter, head circumference, abdominal circumference (fig 1) and femur length. By using commercially available ultrasound-integrated software, it is possible to estimate fetal weight by combining these parameters in a formula. It is not clear that calculating the estimate fetal weight is better than careful assessment of the raw data. The two most commonly used formulas are the ones by Shepard *et al*¹³ and Hadlock *et al*.¹⁴

SGA refers to a fetus which has failed to achieve a specific biometric or estimate fetal weight threshold by a specific gestational age. The 10th centile for abdominal circumference and estimated birth weight is the commonly used cut-off value. However, customised birthweight charts have higher sensitivities as well as lower false-positive rates in the detection of SGA fetuses.⁸ Although the diagnosis of SGA relies on biometric tests, abnormal Doppler tests are diagnostic for FGR. It is also important to realise that the assessment of growth requires at least two measurements at least 2 weeks apart,¹⁵ which will in turn differentiate normally growing fetuses from those with restricted growth. However, the biometric parameters are less useful for the management of FGR than for the detection of such cases, and have to be used in association with other techniques of antenatal surveillance to make decisions about the timing of delivery.¹⁶

ANTENATAL SURVEILLANCE

Antenatal surveillance should provide longitudinal assessment that is designed according to the severity of the fetal condition, and directs appropriate intervention to improve outcomes. Although assessment should be detailed, antenatal tests also need to be practicable to facilitate application on a large scale as is necessary for a global problem such as FGR. Doppler ultrasound, CTG analysis (non-stress test in the US), both traditional and computerised, measurement of amniotic fluid volume, and assessment of fetal breathing, movement and tone are primary fetal assessment tools.¹⁷

Cardiotocography

Traditional CTG analysis has the advantage of being familiar but carries the disadvantage of poor interobserver and intraobserver agreement even in the interpretation of key factors such as accelerations, reactivity and decelerations.¹⁸ Although a CTG is assessed as reactive using criteria graded for gestational age, this is very reassuring. However, a non-reactive CTG has a poor correlation with fetal status unless overtly abnormal patterns are observed. Computerised CTG analysis gives an objective assessment, which agrees closely with experienced visual assessment. Also, by being numerical

this can be used in the assessment of fetal heart rate analysis in research.¹⁹ There is a correlation between short-term variation in the fetal heart rate and fetal acidaemia and hypercarbia.^{20 21} However, there is not enough evidence to recommend the use of antenatal CTG for fetal assessment in intrauterine growth restriction, as CTG changes are manifested relatively late in the disease process and are usually preceded by abnormal Doppler velocity patterns.²² Despite the lack of evidence, this technique is widely used and, provided its limitations are well recognised and traces are interpreted with caution and in combination with other evidence, it may be reasonable.²³

Biophysical profile

The biophysical profile (BPP) uses a five-component score assessing fetal responses and behaviour.²⁴ However, as a single assessment tool in FGR, it has several disadvantages. Fetal heart rate scoring is based on visual assessment of reactivity and therefore has the same drawbacks as traditional CTG. Furthermore, in the absence of oligohydramnios, a BPP score provides insufficient information on the severity of the fetal cardiovascular compromise, and abnormalities may only appear in the preterminal stages—for example, a borderline BPP score of 6 is already associated with a 20-fold increase in mortality.^{25 26} There is not enough evidence from randomised trials to evaluate the use of BPP as a test of fetal well-being in high-risk pregnancies and is not used in the UK.^{27 28}

Doppler ultrasound

The antenatal recognition of true FGR helps in preventing or minimising mortality and morbidity. Doppler velocimetry greatly contributes to the differentiation between the fetus that is SGA but healthy and the fetus with true FGR.^{29 30} Although multiple vessels have been investigated in FGR, a combination of arterial and venous vessels is the most practicable to demonstrate the degree of placental disease, level of redistribution and degree of cardiac compromise. The umbilical artery, middle cerebral artery, ductus venosus and inferior vena cava provide a comprehensive evaluation of these aspects. As the longitudinal progression of Doppler abnormalities advances from the arterial to the venous side in most cases, multivessel Doppler may be useful in planning the frequency of fetal testing.^{28 31}

ARTERIAL DOPPLER EXAMINATION

Uterine artery

At 23 weeks' gestation, uterine artery Doppler examination can detect a fetus at higher risk of growth restriction and subsequently adverse perinatal outcome in pregnancy.²⁷ The sensitivities and positive predictive values attributed to the

uterine Doppler ultrasound in a low-risk population are variable in the literature, ranging between 7 and 32% and 10 and 50%, respectively, for FGR.³² However, this screening test for risk is not an assessment of fetal well-being and has no established place in the management of infants diagnosed with FGR.

Umbilical artery

In contrast, umbilical artery Doppler measurement offers a completely different contribution to the management of FGR because it does not identify a high-risk group for the future but indicates whether an identified SGA fetus is affected by placental dysfunction or not. In the presence of placental insufficiency with progressive severity, there is a higher placental resistance, indicated by a high pulsatility index, absent or reversed end-diastolic component of the umbilical artery waveform.³³ Absent or reversed end-diastolic flow velocities in the umbilical arteries are associated with worse perinatal outcome and high perinatal mortality, depending on gestational age.³⁴

Middle cerebral artery

Under conditions of limited oxygen and nutrient supply, fetal vascular redistribution in favour of vital organs can be detected by Doppler studies of the selected fetal organs. Doppler indices of resistance decrease in the middle cerebral artery, as a reflection of the brain-sparing effect of the fetus.³⁵

VENOUS DOPPLER EXAMINATION

The deterioration of fetal condition due to severe FGR is usually accompanied by signs of cardiovascular changes that can be shown by venous Doppler studies (fig 2). The normal forward venous blood flow is dependent on cardiac contractility, compliance and after load. Evidence of impaired cardiac function has been documented using Doppler flow studies of the precordial veins (ductus venosus, inferior vena cava and superior vena cava), hepatic veins (right, middle and left

hepatic), and head and neck veins (jugular veins and cerebral transverse sinus).³⁶ Abnormal venous Doppler flow indices of these veins suggest impaired preload handling.

A decline in the "a" wave in ductus venosus Doppler velocimetry reflects a decrease in forward flow during atrial systole (fig 3). Moreover, increased umbilical venous pulsations may reflect increased central venous pressure and also tricuspid insufficiency resulting from severe cardiac dilatation.

FETAL BLOOD SAMPLING

The acid-base balance before labour can be determined by the analysis of fetal blood obtained by cordocentesis. The importance of long-standing acidosis has been shown by its association with reduced long-term neurodevelopment.³⁷ However, fetal blood sampling is now only used occasionally in the management of intrauterine growth restriction because research using the technique has established that non-invasive tests, and especially Doppler, are effective. Also, it carries a procedure-related risk of about 1%. Possible interventions, such as preterm delivery based on the assessment of fetal acid-base status, have not been tested by any clinical trial; and fetal acidemia may now be effectively ruled out with non-invasive studies.^{38–40}

OTHER MATERNAL ASSESSMENTS

Over the past few years, measurements of several markers in maternal blood have shown the relationship between FGR and placental dysfunction. Maternal serum activin A and inhibin A were raised in fetal-growth-restricted pregnancies but not in normal SGA pregnancies as classified by umbilical artery Doppler indices.⁴¹ Moreover, low maternal serum level of insulin-like growth factor I was shown to relate to poor placental transfer.⁴² Recently, increased circulating levels of fetal DNA were documented as a marker for placental abnormalities secondary to trophoblast apoptosis. A high rate of apoptosis is found in trophoblast cells in pregnancies

Figure 2 A progressive deterioration in fetal cardiovascular and variables that are observed with decline of metabolic status (reproduced with permission from Baschat and Hecher³⁶). AV, aortic valve; BPS, bronchopulmonary sequestration; EDV, end-diastolic velocity; FH, fetal height; UA, umbilical artery; UV, umbilical venous.

Figure 3 Progressive changes in the ductus venosus pulsatility ('a' wave) associated with increased severity of FGR (fetal growth restriction). Fetus: normal pulsatility at the inlet (A) and the outlet, (B) decreased, (C) absent, (D) reversed, (E) severe and abnormal waveform at 28 weeks, (F). Doppler changes 'a' wave at, (C–F) (Reproduced with permission from Baschat and Hecher³⁶).

complicated by FGR and PET.⁴³ Free fetal DNA, therefore, has the potential to be a marker in the diagnosis of FGR and might serve as an indicator of severity; yet all the previously mentioned markers are still under investigation and have not been used clinically.

INTERVENTION

Despite numerous approaches to managing FGR, there are no effective treatments to improve the growth pattern of a fetus. Modalities tested include maternal nutritional supplementation, plasma volume expansion, administration of amino acids and medications for the mother, such as low-dose aspirin.^{44–45} Moreover, maternal hyperoxygenation resulted in fetal pO₂ reaching or nearing the normal range.⁴⁶ Even fetal glucose supplementation has been tried and proved not to be of benefit, and may exacerbate underlying acidosis.⁴⁷ However, the universally available therapeutic option that shows improvement in outcome includes the antenatal administration of steroids in preterm pregnancies and delivery at an institution with a neonatal care unit that is able to deal with the management complexities of the growth-restricted neonate. Antenatal steroids should be given to any growth-restricted fetus whose delivery is expected before 34 weeks' gestation.⁴⁸ Although there is a trend towards the benefit of steroids given after 34 weeks (especially for elective caesarean section), this respiratory distress syndrome reduction in babies born after 34 weeks did not reach statistical significance.⁴⁹

As there are no effective treatments to reverse fetal growth restriction, prenatal management is aimed primarily at determining the ideal timing and mode of delivery. This assessment must be individualised, depending on several variables: gestational age of the fetus, maternal health, severity of growth restriction and fetal well-being. Perhaps optimising the delivery time and removing the fetus from a suboptimal environment can prevent the risk of hypoxia and major morbidities.⁵⁰

Timing of delivery

Gestational age of the fetus is a critical component of the delivery decision-making process. Unfortunately, no randomised management trials have conclusively dealt with the issue of delivery timing across the whole clinical spectrum of FGR. In principle, delivery timing is straightforward in the term fetus when fetal lung maturity has been documented, if there is fetal distress or if the maternal condition dictates delivery. Management is more complicated for pregnancies between 25 and 32 weeks' gestation, where each day gained in utero may improve survival by 1–2%.⁴⁰ Early delivery of growth-restricted fetuses with abnormal umbilical artery waveform (after completion of antenatal steroid course) offers the benefit of a higher liveborn rate and disadvantage of a high neonatal mortality.⁵¹ Delaying delivery until fetal distress is evident may be associated with stillbirths rising nearly fivefold and neonatal deaths before discharge falling by more than a third, although the total mortality was unchanged.⁵¹ It seems there was insufficient evidence to convince enthusiasts for either immediate or delayed delivery that they were wrong. When a temporising approach is elected, assessment of fetal status needs to be accurate to avoid preventable adverse outcomes. Therefore, the ultimate effect of antenatal management protocols on outcomes is probably greatest if critical outcomes are accurately predicted prenatally. Such outcomes include the risk of stillbirth and moderate to severe peripartum acidemia, which has been related to poor neurodevelopment.³⁸

Mode of delivery

Roughly one third of pregnancies with SGA fetuses require caesarean delivery.⁵¹ Some studies have shown that elective caesarean section for growth-restricted fetuses results in lower rates of respiratory distress syndrome, neonatal seizures and deaths, but these differences did not reach statistical significance,⁵² and these mothers were more likely to have serious

morbidity. On the other hand, when the cause of FGR is chronic hypoxia, it seems logical to avoid acute hypoxia during labour and delivery.⁵³ It is important that delivery be arranged in a high-risk maternity unit with the appropriate neonatal staff in attendance. The provision of full support for resuscitation and stabilisation of these infants is crucial to the short-term and long-term health of these infants who have had chronic hypoxia and malnutrition in utero.⁵²

CONCLUSION

FGR is associated not only with increased perinatal mortality and morbidity but also with increased risk of long-term complications, such as impaired neurodevelopment, adult type 2 diabetes and hypertension. Obstetricians should identify fetuses at risk of developing growth restriction, design a comprehensive surveillance plan, and carefully choose the time and mode of delivery.

Accurate early pregnancy dating scans and good antenatal care in the form of abdominal palpation and symphyseal fundal height measurement followed by ultrasound biometry are pivotal steps in identifying SGA fetuses. FGR due to placental insufficiency is diagnosed when decreased amniotic fluid volume, abnormal umbilical artery Doppler and failure of growth are evident using serial growth scans, provided that chromosomal abnormalities, malformations and infections are excluded. Antenatal surveillance should be instituted on the basis of the severity of the maternal or fetal condition, with an emphasis on Doppler analysis as the most important tool to grade the severity of the fetal disease. Once delivery is planned, the presence of a qualified neonatology team and a tertiary-level neonatal intensive care unit is an important initial step in managing growth-restricted neonates.

Key points

- The term fetal growth restriction (FGR) should be used to describe only those fetuses with inadequate growth due to placental dysfunction.
- Other causes of small-for-gestational age (SGA) fetuses, such as chromosomal abnormalities and intrauterine infections, should be considered before the diagnosis of FGR is made.
- Normal SGA is not a milder form of FGR but a different condition with excellent prognosis and outcome.
- Symphyseal fundal height measurement is used to screen for SGA fetuses but must be followed by detailed ultrasound scans to confirm or refute the diagnosis.
- Fetal Doppler studies give the most accurate non-invasive assessment of placental function. A combination of umbilical artery, middle cerebral artery and precordial vein Doppler can show the degree of placental disease, level of redistribution and degree of cardiac compromise, respectively.
- Changes in venous Doppler precede abnormalities on cardiotocography, which occur late during the course of FGR.
- The management of a fetus with growth restriction must include a balance of the risks of intrauterine chronic hypoxia with preterm delivery and its associated risks.
- Research based on cohorts identified by neonatal birth weights or birth centiles should be interpreted with great caution. Unless there is a diagnosis of the prenatal cause, these studies will include a very heterogeneous group.

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