

The role of ultrasound in the diagnosis and management of the growth restricted fetus

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Table 1: non placental causes for small for gestational age fetuses.

Genetic	Aneuploidy (T21, T18, T13)
	Uniparental disomy (particularly 6,14,16)
	Single gene disorders / genetic syndromes affecting growth
	Skeletal dysplasias
Infective	Toxoplasmosis
	Cytomegalovirus
	Herpes Simplex (primary)
	Rubella
	Syphilis
	Parvovirus
Structural Malformation	Cardiac defects
	Anterior abdominal wall defects, particularly gastroschisis
	Neurological abnormalities
Placental / cord abnormalities	Confined placental mosaicism
	Single umbilical artery
	Velamentous cord insertion
	Placental chorioangioma

Table 2: Maternal conditions associated with IUGR.

Hypertension
Pre existing diabetes
Connective tissue disease (such as SLE)
Significant cardiac or respiratory disease, anemia
Inflammatory bowel disease
Thrombophilia (particularly antiphospholipid syndrome)
Malnutrition
Smoking, alcohol, drug use
High altitude

are *small but not growth restricted*. In accurately dated pregnancies, fetuses identified as being SGA may be, a) constitutionally small but healthy, b) truly growth restricted due to uteroplacental insufficiency, or c) affected by chromosomal/structural anomalies or chronic intrauterine infection (Table 1). Equally importantly, some fetuses are *growth restricted but not small*. This subset of IUGR can go undetected with the use of standardised population charts. If the reference ranges for fetal biometric data and birth weight account for maternal height, weight, ethnicity, parity and fetal gender (thus better identifying fetal growth potential), the detection of IUGR is enhanced⁶. Growth potential percentiles have been shown to be superior to conventional reference ranges for the prediction of adverse perinatal outcome^{7,8}. The GROW (gestation related optimal weight) software has customised data for different countries (including Australia), and is able to be downloaded from www.gestation.net.

While acknowledging the importance of other causes for SGA, the remainder of this review will focus on disordered fetal growth associated with uteroplacental insufficiency. A variety of maternal conditions may be associated with placental insufficiency (Table 2), but will not be reviewed further here.

Pathophysiology of IUGR due to uteroplacental insufficiency

In normal pregnancy, the trophoblast invades into the myometrium, remodelling the end arteries (spiral arterioles) and replacing their muscular coat in order to create a “high flow, low resistance” circuit to facilitate exchange of nutrients and oxygen from the maternal to fetal compartment across the placental bed. This is manifest with a fall in uterine artery resistance with advancing gestation through the mid-trimester. In pregnancies affected by IUGR, this normal transformation doesn’t occur and the “high resistance, low flow” circuit persists. Placental floor infarcts and fetal villous

Introduction

It is said that “if you are born small, you keep dying for the rest of your life”. Small babies are more likely to suffer antenatal and intrapartum stillbirth¹. Of pregnancy survivors, early neonatal adaptation is impaired and complications such as necrotising enterocolitis, respiratory distress, neurodevelopmental handicap and neonatal death are more common among small for gestational age (SGA) infants². Many of these problems leave a legacy in childhood, and the fetal origins of *adult* disease are now well described by the Barker hypothesis. Coronary artery disease, obesity, hypertension, type 2 diabetes, the metabolic syndrome and premature death are more likely to occur in adults who were born small for gestational age^{3,4}. This is the long-term legacy of the adaptive behaviours of growth restricted infants in utero to ensure survival.

In contrast to SGA (birthweight less than the 10th centile) the American College of Obstetricians and Gynecologists (ACOG) describes intra-uterine growth restriction (IUGR) as “a fetus that fails to reach its potential growth”⁵. This highlights the importance of recognising that some fetuses

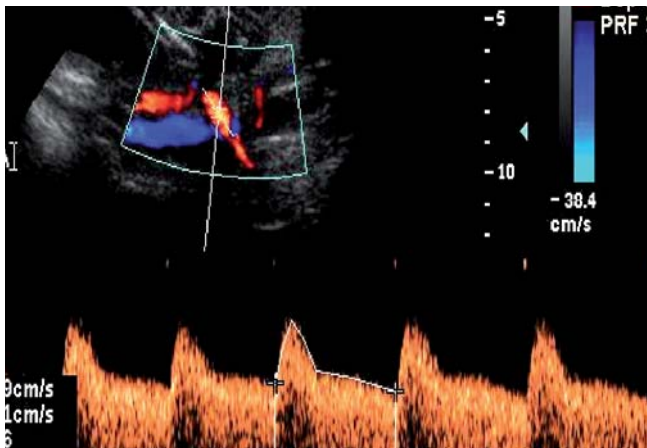


Fig. 1a: Normal “low resistance” uterine artery waveform in the midtrimester.

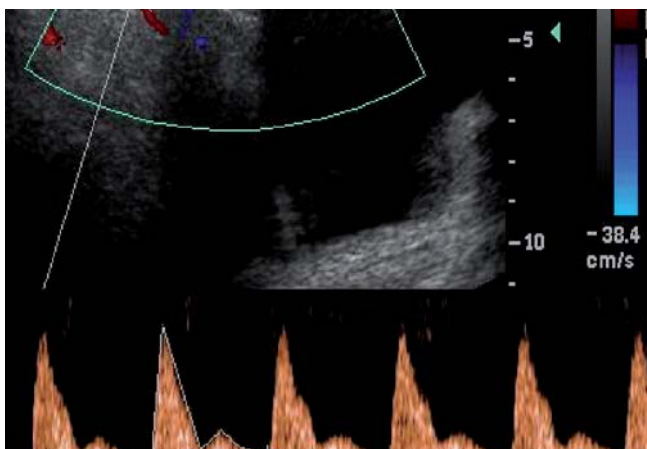


Fig. 1b: Abnormal uterine artery vascular resistance, showing increased pulsatility and the presence of an early diastolic notch.

obliteration further increase placental blood flow resistance, and nutrient exchange decreases or is outgrown. Uterine artery Doppler examinations at 22–24 weeks demonstrating increasing resistance to flow are associated with disorders of abnormal placentation, such as pre-eclampsia, IUGR, placental abruption, preterm birth and perinatal death (Fig. 1).

From the fetal side, umbilical artery waveforms correlate with both the tertiary villous architecture and blood flow resistance. When more than 30% of the fetal villous vasculature is abnormal, umbilical artery end-diastolic velocities are reduced and Doppler resistance indices (SD ratio and PI) are elevated (Fig. 2a). When absent or reversed umbilical artery end-diastolic velocity is observed (Figs. 2b, 2c), this suggests that 60–70% of the villous vascular tree is damaged⁹. In the face of increasing oxygen demand and decreasing supply, highly oxygenated blood is shunted preferentially through the ductus venosus, and streamed towards the left ventricle, favouring the cerebral and coronary circulations. In the face of hypoxia and hypercapnia, cerebral autoregulation results in a fall in cerebral vascular resistance to maximise oxygen delivery to the brain (the so-called “brain sparing” effect) (Fig. 3). The torso is relatively vasoconstricted, resulting in growth asymmetry and echogenic bowel. Redistribution away from the kidneys results in reduced urine output and amniotic fluid volume. All these features are suggestive of “fetal compensation” in the face of hypoxia.

With increasing hypoxia, acidosis and, finally, asphyxia

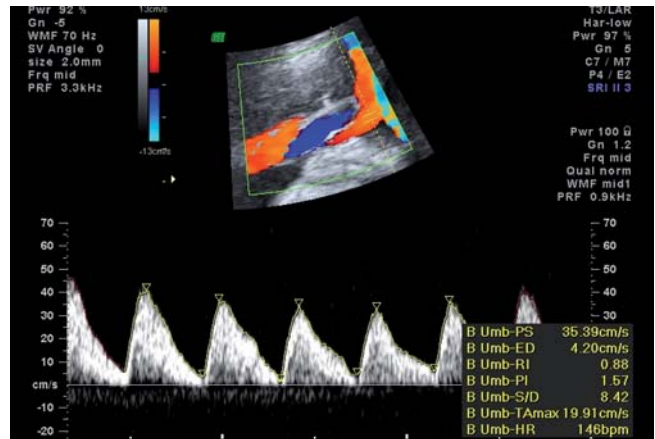


Fig. 2a: Increased SDR in the umbilical artery.

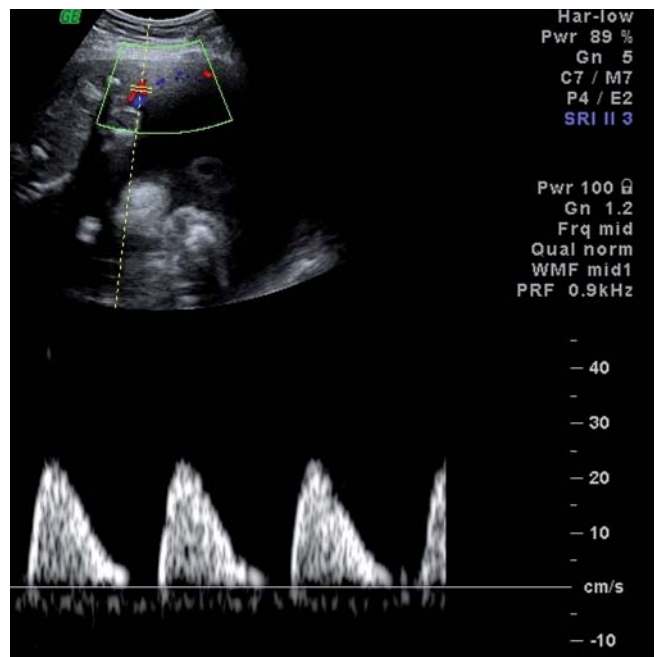


Fig. 2b: Absent end-diastolic flow in the umbilical artery.

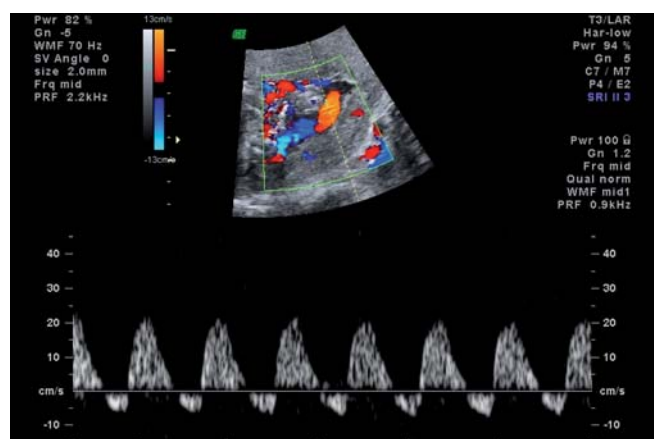


Fig. 2c: Reversed end diastolic flow in the umbilical artery.

may result. Features of decompensation include worsening of fetal cardiac performance. Abnormal blood flow in the precordial veins is observed. In the ductus venosus (DV), increased pulsatility in the a wave (Fig. 4a) is followed by absence or reversal of the a wave, signifying impaired cardiac emptying during atrial systole (Figs. 4b, c). Neurologically, decompensation is evidenced by an impaired biophysical profile with deterioration in fetal breathing, body

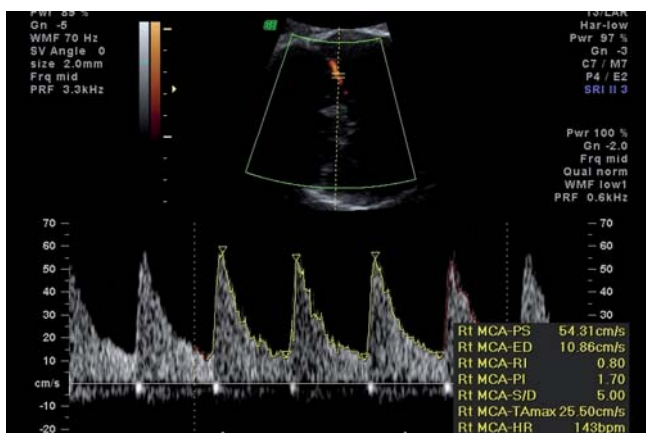


Fig. 3a: Middle cerebral artery normal waveform.

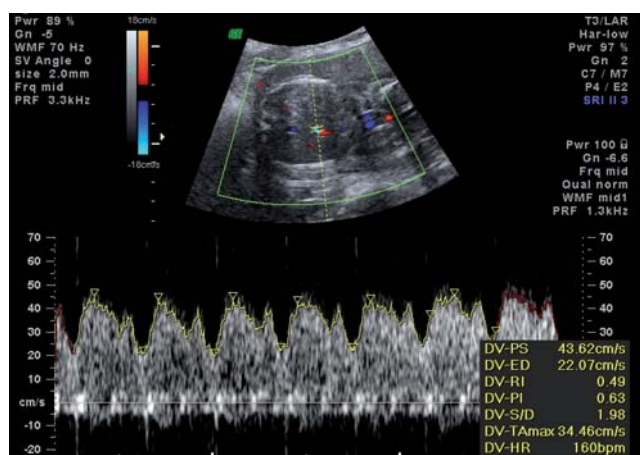


Fig. 4a: Normal ductus venosus waveform.

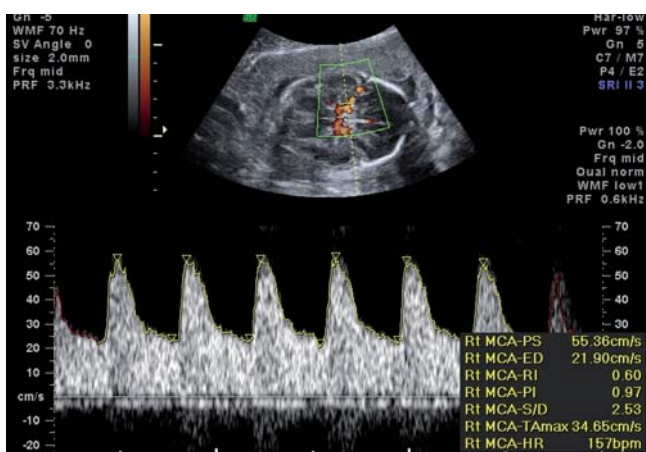


Fig. 3b: Middle cerebral artery waveform showing reduced resistance (lowered PI), known as "brain sparing".

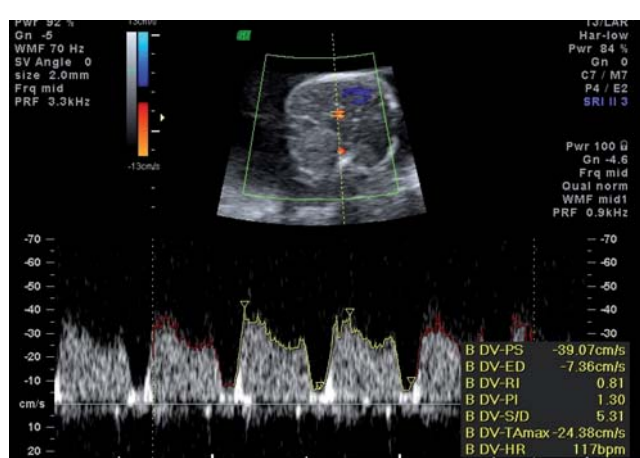


Fig. 4b: Ductus venosus showing increased pulsatility.

movements and tone. Reduced or absent fetal heart rate variability and late decelerations on computerised cardiograph are among the last signs to develop and are commonly associated with severe fetal acidemia. Final cardiac decompensation is seen with a pulsatile umbilical vein (Fig. 5). These "late" signs are associated with increasing acidemia, asphyxia and risk of perinatal death.

While most fetuses display this sequential series of events, a recent study has highlighted that where the pregnancy is complicated by maternal pre-eclampsia, the growth restricted fetus follows a much less predictable course, with the sequential changes described above sometimes occurring rapidly and in a disorganised sequence¹⁰.

The role of ultrasound in screening for IUGR

Simple history taking can detect women at increased risk of fetal IUGR. Women with past obstetric history of an infant with SGA in their first pregnancy are at significantly increased risk of stillbirth¹¹. Maternal medical conditions are significant risk factors for IUGR (Table 2). Clinically, the measurement of the symphyseal fundal height (SFH) has a reported sensitivity that ranges from 56% and 86%^{12,13}. Nevertheless, the predictive ability of these clinical tools is limited.

Deficient placentation as indicated by enhanced vascular resistance in uterine artery Doppler studies in the second trimester is associated with an increased risk of pre-eclampsia, IUGR and perinatal death. An increase in uterine artery resistance may be evidenced by an increase in resistance index (RI), pulsatility index (PI) or early diastolic notching. Uterine artery Doppler abnormalities are better for identify-

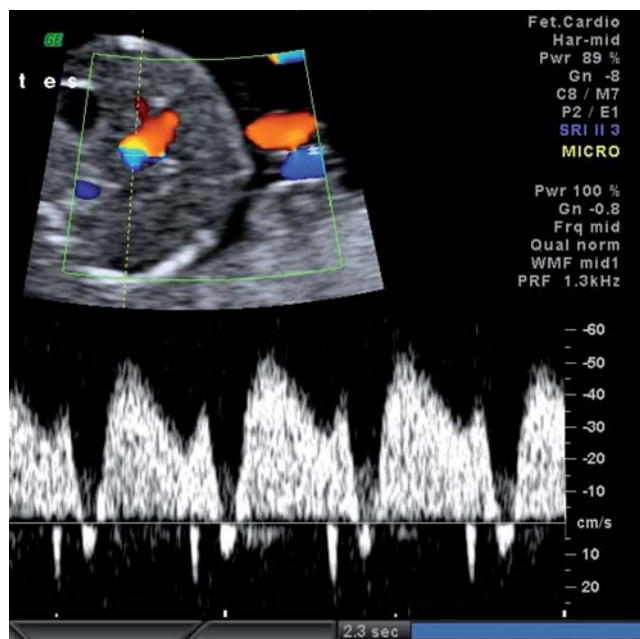


Fig. 4c: Ductus venosus showing reversal of the wave.

ing severe, early onset IUGR or pre-eclampsia than late or mild disease. In a recent meta-analysis, abnormal uterine artery Doppler studies (increased uterine artery PI and/or notching) in the second trimester carried a positive likelihood ratio (LR) of 7.5 for pre-eclampsia, 15.6 for severe pre-eclampsia, 9.1 for IUGR and 14.6 for severe IUGR. In the setting of normal Doppler studies, the corresponding negative likelihood ratios were 0.6, 0.2, 0.9 and 0.8,

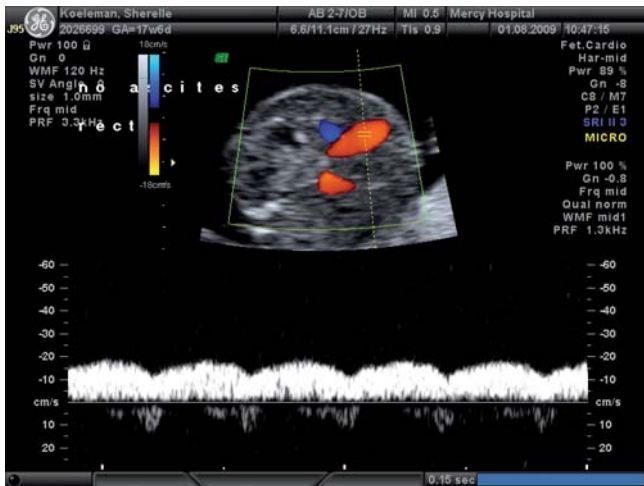


Fig. 5: Pulsatile umbilical vein.

respectively¹⁴. The sensitivity of abnormal uterine artery Doppler examinations in predicting pre-eclampsia (47% and 74% for overall and severe pre-eclampsia, respectively) is better than it is for IUGR (12% and 23% for overall and severe IUGR)¹⁴. Among women with abnormal uterine artery Doppler examinations in the second trimester, several randomised controlled trials have been performed to see if secondary prevention of IUGR or pre-eclampsia with aspirin or Vitamin C and E is possible. Unfortunately, none of these treatments have been shown to be effective¹⁵. Second trimester uterine artery Doppler examination may be beneficial in stratifying risk for subsequent antenatal care, and may be of further value in reassuring high risk women in the setting of normal findings. Nevertheless, the clinical predictive value in low risk women is poor, and abnormalities in the second trimester appear to be too late for useful intervention. This has prompted investigators to consider the role of first trimester uterine artery evaluation.

Doppler velocimetry of uterine artery blood flow is technically feasible between 10 and 14 weeks of gestation, and the resistance index (RI) appears to be the most repeatable and reproducible measurement at this gestational age¹⁶. Although increased uterine artery resistance has been shown to be useful in detecting preterm pre-eclampsia and IUGR, with sensitivities of 60–70%, the corresponding positive predictive values are low^{14,17}. Pilalis, *et al.* have reported that the predictive value of first trimester uterine artery Doppler results can be improved with the addition of maternal serum PAPP-A, suggesting that both markers in combination may be better than either alone¹⁸. If the predictive value of single or combination markers in the first trimester can be improved, then therapeutic initiatives are more likely to be successful. A recent systematic review and meta-analysis has confirmed that ASA treatment started before 16 weeks gestation was linked with a significant reduction in IUGR of 49%¹⁹.

Ultrasound diagnosis of IUGR

The detection of IUGR is maximised when gestational age is well established, preferably with first trimester ultrasound. When gestational age is uncertain, the transcerebellar diameter is useful because it is one of the few soft tissue measurements that correlates well with gestational age even in the face of IUGR²⁰. Having established gestational age, a multiparameter regression equation is used to calculate an estimated fetal weight, and a centile can be calculated

using population based or – ideally – customised charts. As a single parameter, the abdominal circumference (AC) has good sensitivity and the highest positive predictive value for IUGR because it reflects both decreased subcutaneous fat and depleted liver glycogen stores²¹. The abdominal circumference percentile has the highest sensitivity and negative predictive value for the sonographic diagnosis of IUGR, defined postnatally by birth weight percentile²². Having identified the small fetus, it is important to do a targeted ultrasound examination for non-placental causes (Table 1).

When the estimated fetal weight falls below the 10th percentile, umbilical artery Doppler examination is the most useful test for confirming the diagnosis of uteroplacental insufficiency²³. Oligohydramnios further supports this diagnosis. It should be noted that the near term growth restricted fetus is much less likely to have an abnormal umbilical artery Doppler. In these fetuses, Doppler changes are likely to be more subtle, such as MCA evidence of redistribution²⁴, and/or abnormal uterine artery waveforms²⁵. Ghosh, *et al.* have recently reported that among women with a growth restricted fetus but normal umbilical artery Doppler examination, an abnormal uterine artery Doppler was similarly predictive for adverse perinatal outcome²⁶.

Ultrasound surveillance of the growth restricted fetus

In the absence of any clearly effective therapy, the mainstay of management of IUGR is appropriate surveillance and timely delivery. In term IUGR, the prospective risk of stillbirth undoubtedly favours delivery. Preterm IUGR – particularly extreme preterm IUGR (< 32 weeks) – involves balancing the risks of awaiting organ maturation, (accepting an increasing risk of acidemia, asphyxia and stillbirth) and delivery, (accepting the risk of permanent injury from prematurity). The Growth Restriction Intervention Trial found that – among fetuses affected with severe early onset IUGR – long term neurological morbidity was improved among pregnancies where delivery was deferred as long as possible, even though perinatal mortality was unaltered²⁷. Despite the limitations of this data, it suggests that delayed delivery is preferable, particularly at extremely early gestation (24–28 weeks) where survival may improve by up to 2% for every day that the fetus remains undelivered. Antenatal surveillance modalities include cardiotocography, biophysical profile score (tone, movement, breathing and amniotic fluid index) and arterial and venous fetal Doppler studies. These modalities used in combination, known as integrated fetal testing, allow the most precise assessment of fetal wellbeing²⁸. During this time of surveillance, maternal contributors should be minimised and medical condition optimised. When delivery is anticipated before 34 weeks gestation, antenatal corticosteroids should be administered, and if delivery is to occur at less than 30 weeks gestation, magnesium sulphate should be administered for protection against cerebral palsy²⁹.

The biophysical profile

A reactive cardiotocograph virtually excludes hypoxaemia, but a non-reactive cardiotocograph is associated with a wide range of pH values. The biophysical profile score (BPS) applies categorical cutoffs for fetal tone, breathing, gross motor movement, and amniotic fluid index. It infers that if the peripheral biophysical variable is normal, then its

corresponding central neuroregulatory centre is functional and not affected by hypoxia or acidosis. Consistent with this, a normal biophysical profile is associated with reduced rates of fetal death within the week³⁰. In compromised fetuses, loss of fetal breathing movements occurs first, but this may be seen over a wide range of fetal arterial pH. Loss of fetal tone and movements are more reliably associated with pre-labour acidemia (median pH of 7.1)³¹. The difficulty with using these biophysical variables alone is their limited ability to detect longitudinal deterioration. In addition, a recent study has demonstrated that the BPP performs poorly as a predictor of acidemia and fetal death in infants < 1000 g³². This study involved preterm growth restricted infants with abnormal umbilical artery Doppler examinations, who were subsequently delivered at a median gestational age of 27.6 weeks gestation and birth weight of 632 g. Among 27 fetuses with a BPP of 8/10 within 24 hours of delivery, there were three intrauterine fetal deaths, and 12 fetuses were born acidemic. Among 13 fetuses with a BPP of 6/10, there were three deaths, and seven were born acidemic. This suggests a more rapid and unpredictable deterioration in these fetuses than previously thought, and that increased frequency of multi-parameter surveillance is necessary in pregnancies complicated by severe preterm growth restriction.

Fetal Doppler examination

Brain-sparing, as evidenced by a decrease in the pulsatility index of the middle cerebral artery (MCA), reflects fetal cerebral autoregulation in the face of presumed hypoxia. The MCA PSV (peak systolic velocity) has been reported to provide additional information in fetuses with an abnormal MCA PI³³. This study reported a better perinatal outcome in fetuses with an abnormal PI but normal PSV, compared to those with an abnormal PI accompanied by an elevated PSV. In addition, this study reported that the PSV remains elevated until death or delivery, where the MCA PI may rise in a preterminal phase of failed cerebral autoregulation³³.

In the fetus with impaired growth and mildly abnormal umbilical artery Doppler studies, the appearance of brain sparing and oligohydramnios indicates an acceleration of the disease, with features now of fetal compensation. The frequency of surveillance needs to be increased, and in the moderately preterm fetus (e.g. 32–34 weeks gestation), consideration may be given to delivery. With progressive placental dysfunction, the fetus is at risk of decompensation and deterioration of venous indices. This reflects the cardiac dysfunction associated with increasing hypoxia and acidemia, with the right heart affected more than the left, and diastolic function worse than systolic function³⁴. While elevated umbilical artery and brain sparing with normal venous studies is generally associated with a normal pH, elevated venous indices predicts fetal acidemia with 70–90% sensitivity and specificity. In view of the real risk of fetal acidosis and asphyxia, full multiparameter testing may be necessary up to several times per day if delivery is not planned. Absence or reversal of the DV a wave, or umbilical vein pulsations predict stillbirth with 65% sensitivity and 95% specificity²⁸, and delivery – if at a viable gestation and weight – should be expedited. Interestingly, while absent / reversed a wave is a good predictor of fetal death, it does not seem to confer a worse long term neurological prognosis

among survivors³⁵, and others have challenged the notion that the DV is reliably associated with fetal acidosis³⁶. The final trigger for delivery remains to be determined in the extremely preterm growth restricted fetus. A multicentre, randomised controlled trial (TRUFFLE Study) is currently investigating whether measurement of the fetal ductus venosus is the best parameter to guide timing of delivery of early preterm IUGR fetuses by comparing severe and mild DV abnormalities with traditional monitoring based on cardiotocography, and these data are eagerly awaited.

Future advances

Given the increased risks of late changes in the fetus with IUGR, it would be helpful to have a longitudinal parameter to follow during the phase between the early changes of compensation and the late changes of decompensation. It has been proposed that Doppler studies of blood flow in the aortic isthmus may be such a parameter. The aortic isthmus (AI) represents the only arterial connection between the right ventricle, (supplying the systemic and placental circulations), and the left ventricle, which preferentially supplies the cerebral circulation. The blood flow pattern of the aortic isthmus thus reflects the differences in vascular resistance between these systems. A recent study has found that AI-PI consistently became abnormal (PI > 95th centile or retrograde flow) 1–2 weeks after abnormal UA and MCA flows were observed, and one week earlier than abnormal DV flow (> 95th percentile)³⁷. AI Doppler studies could potentially be used to improve current algorithms for the prediction of poor perinatal outcome in preterm IUGR fetuses, and provide further guidance on optimising the time of delivery.

Conclusion

Fetal growth restriction is a complex multi-system syndrome. It imposes a significant short and long-term health burden on the affected fetus. Screening for growth restriction is important because it identifies the at-risk population, and perinatal outcomes are improved in pregnancies with recognised, rather than unrecognised, growth restriction³⁸. Accurate diagnosis of IUGR is enhanced by the use of customised growth charts and fetal biometry that places more emphasis on abdominal circumference than other biometric parameters. Once a fetus is found to be SGA, the diagnosis of uteroplacental IUGR can be achieved by excluding causes such as aneuploidy and infection, and the observation of umbilical and fetal Doppler abnormalities. Although there are continuing efforts to find effective therapies for established IUGR, the mainstay of management is appropriate multiparameter fetal surveillance, (including cardiotocography, biophysical variables and Doppler studies of the umbilical artery, middle cerebral artery, ductus venosus and umbilical vein) and optimal timing of delivery in order to maximise gestation in the severely preterm growth restricted infant.

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