Intrauterine growth restriction: diagnosis and management

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The diagnosis of intrauterine growth restruction often results in preterm delivery with its associated morbidity and mortality. This review aims to outline the main diagnostic and management tools available to obstetricians for the management of such pregnancies as well as the aetiological factors that might be associated with this condition.

Intrauterine growth restriction (IUGR) is a major cause of perinatal morbidity and mortality (Ounsted et al, 1981). Fetal development and growth in general is dependent upon a number of endocrine factors, as well as paracrine and autocrine events within the fetoplacental unit. IUGR may cause significant morbidity, with 10% of low birthweight babies having some physical handicap and a further 5% showing neurodevelopmental delay up to 10 years of age (Kok et al, 1998).

As ultrasound improves, the incidence will continue to increase and the potential 'salvaging' of very low birthweight babies means that chronic morbidity will continue to increase. The nomenclature of intrauterine growth restriction implies pathology, with the fetus failing to achieve its optimal 'growth potential'. The similar but not interchangeable term of small for gestational age (SGA) is purely statistical and merely describes the fetus' weight on a percentile chart for an appropriate population. It is important to realize that at least 50% of infants weighing below the 10th percentile will have been normally nourished in utero and many infants with weights above the 10th percentile at birth will not have achieved their optimal growth (Wilcox, 1983). It is acceptable to use the term SGA for a fetus until a diagnosis of IUGR is made.

Fetal growth is the result of the genetic potential of the fetus that is in turn modified by environmental factors. This review aims to highlight how these factors might interact to affect fetal growth and then describes the current strategies employed to diagnose and manage affected pregnancies.

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AETIOLOGY OF IUGR

There are many factors associated with IUGR (*Table 1*). Some of these are discussed below.

Genetic factors

Genetic abnormalities make a significant contribution to IUGR. This was first demonstrated by Walton et al with their work on shirehorse/Shetland pony crosses (Walton and Hammond, 1938). Genetic abberations may be gross, as with chromosome abnormalities contributing up to 6.7% of morphologically normal SGA infants (Eydoux et al, 1989). The commonest of these are triploidy and the trisomies 13, 18 and 21. Confined placental mosaicisms are also associated with IUGR, particularly uniparental disomy of trisomy 16.

Abnormal growth in utero is also seen as part of numerous genetic syndromes or sporadic mutations. Such syndromes may cause a primary disturbance in bone growth (e.g. osteogenesis imperfecta) or be associated with generalized reduction in body growth (e.g. Donohue syndrome, leprechaunism where there is a mutation in the insulin receptor genes, or Russel Silver syndrome). Many of the gene loci and associated mutations have now been identified and as such our understanding of the normal regulation of fetal growth is increasing.

Perinatal viral infections

It is estimated that infectious disease accounts for 5–10% of cases of IUGR (Creasy and Resnik, 1994). There is at present a direct causal relationship to only two viruses, rubella and cytomegalovirus, although the possibility of a relationship with varicella zoster and human immunodeficiency virus exists. Maternal viraemia with transplacental infection can lead to IUGR with or without associated fetal structural abnormalities. The association of maternal viraemia with IUGR often carries a poor prognosis (up to 50% mortality; Lin et al, 1991), with

little evidence at present that therapeutic intervention improves outcomes.

Pharmacological factors

A number of therapeutic and recreational drugs have been associated with IUGR. It should, however, be remembered that pre-existing maternal disease requiring pharmacological treatment is often itself associated with prematurity and low birthweight. As such it can be difficult to determine the relationship between individual agents and IUGR, although for corticosteroids, cyclosporin and beta-adrenoreceptor antagonists (atenolol) the association with IUGR has been accepted.

The effect of recreational drugs, from nicotine and alcohol to opiates and cocaine has been investigated in relation to fetal growth. Smoking and IUGR are unequivocally linked. The association is dose and gestation dependent and studies have consistently shown a reduction in birthweight of 150–300 g (Ellard et al, 1996). A study in the USA states that smoking is responsible for 10% of all perinatal mortality. Maternal alcohol consumption is associated with IUGR when fetal alcohol syndrome is present. More recent studies have also confirmed an odds ratio of 2.3 for IUGR even with intakes as low as 3 units/day (Windham et al, 1995), although the effect of smoking is three times greater.

The use of opiates and cocaine is increasing in the UK, especially in inner city populations. Evidence of a link with IUGR is less conclusive than for alcohol or smoking as there are often confounding socio-economic factors present. It is likely that opiate use is associated with IUGR but that this effect is less than smoking. A similar lack of conclusive data exists for cocaine.

PLACENTAL PATHOLOGY AND IUGR

It is beyond the scope of this review to discuss the current understanding of normal and abnormal placentation and the subsequent effects on fetal growth. In summary there are at present two theories as to the placental cause of IUGR. The first and more established is that IUGR is associated with reduced placental perfusion secondary to a limited migratory capacity of the extra-villous trophoblast. This results in failure of the conversion of spiral arterioles into low capacitance uteroplacental blood vessels and thus a reduction in the ability of the mother to supply nutrients and oxygen to the fetus. This picture is classically seen in IUGR associated with the maternal syndrome of pre-eclampsia, although it is also seen in IUGR pregnancies where poor placentation alone is present.

The second theory suggests that there is a defect in placental function at the cellular level in relation to the transport of oxygen and nutrients to the fetus. This theory has arisen from the observation that while IUGR may be associated with fetal hypoxia there is not placental hypoxia. As such it is hypothesized that this hyperoxia reduces the angiogenic drive within the placenta resulting in fewer terminal villi for gas transfer and thus impaired placental function. It may be that these two theories are complimentary and further studies are awaited to determine the exact contribution that each mechanism makes to the growth-restricted fetus (Fox, 2000).

THE ROLE OF ULTRASOUND IN IUGR

Pregnancy dating

It is imperative for a diagnosis of either SGA or IUGR to be made that a pregnancy is accurately dated. There is now good evidence that ultrasound dating provides an improvement in dating and it should be used in preference to menstrual dates for pregnancies scanned before 20 weeks gestation (Gardosi, 1997). Crown rump length (CRL) has a 95% prediction to within ± 4.7 days when between 6 and 11 weeks (Wisser et al, 1994).

Fetal biometry and estimated fetal weight

Bi-parietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL) are the routinely performed measurements of fetal size. It is important to always make comparisons to appropriate reference ranges as the charts for estimating fetal size are different to those for fetal age (i.e. dating charts) (Owen et al, 1996). Such charts are constantly being revised to account for improved patient recruitment, better equipment, larger samples and better epidemiological data. It is important that charts are validated among the population that is to be investigated, as there are known to be marked racial differences in growth patterns (Gardosi, 1995; Owen et al, 1996).

The assessment of fetal growth requires a least two measurements to be taken and a change noted. It has been conclusively shown by Chang et al (1993) that serial measurements of AC and estimated fetal weight (EFW) are superior to either single estimates of these parameters or umbilical artery pulsatility index (PI) or aortic-middle cerebral artery PI in the prediction of abnormal neonatal morphometry indicative of IUGR, namely reduced ponderal index, and skinfold thickness (*Figure 1a*). Furthermore, these parameters are also better at predicting perinatal morbidity although the sensitivities and

specificities for this prediction are low (*Figure 1b*) (Chang et al, 1994).

There have been numerous modifications made to attempt to improve the predictive values of growth velocities by controlling for such contributory factors as maternal weight and height, fetal sex, and ethnicity. The effect of each of these variables has been described along with modifications to the growth charts based on these data thus creating 'customised growth charts' (Hadlock et al, 1985; Gardosi et al, 1992).

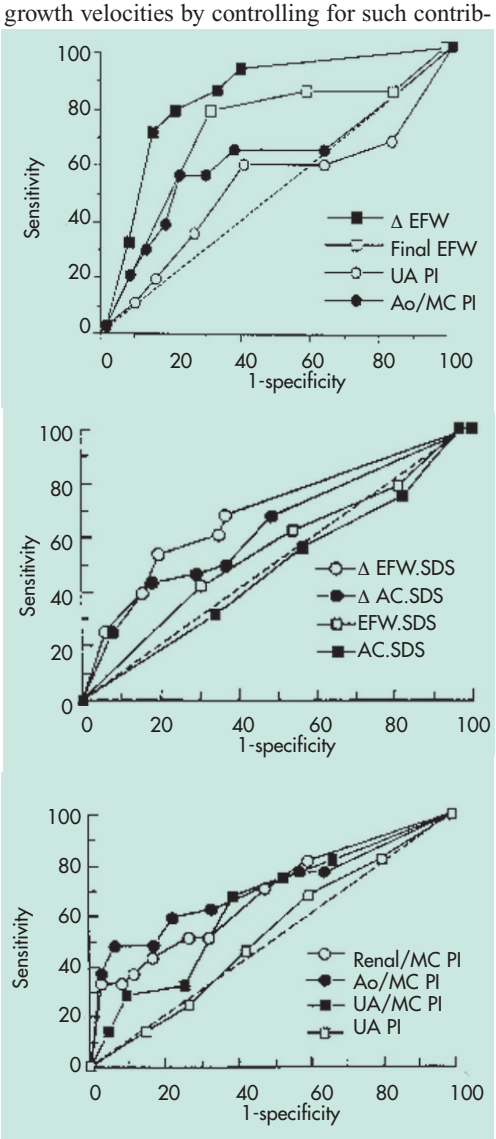

Figure 1. a. Receiver operating characteristic curves in the prediction of abnormal mid arm circumference: head circumference ratio. From Chang et al (1993). EFW = estimated fetal weight; DEFW = change in standard deviation score of estimated fetal weight; UA = umbilical artery; PI = pulsatility index; Ao = aortic; MC = middle cerebral. b. Receiver operating characteristic curves of measurement of fetal growth (change in (Δ) standard deviation score (SDS) values of abdominal circumference (AC) and estimated fetal weight (EFW)) in the prediction of adverse perinatal outcome. c. Receiver operator characteristic curves of SD score of final fetal doppler waveform indices in the prediction of adverse perinatal outcome. From Chang et al (1994). Ao = Aortic; MC = middle cerebral; UA = umbilical artery; PI = pulsatility index.

Screening for malformations

As already discussed, malformations and chromosomal anomalies are often associated with IUGR. The detection rate for major abnormalities is typically 36–77%, depending on the pattern of abnormality (Saari-Kemppainen et al, 1990).

Placental morphology

Grannum and Hobbins (1979) described a grading system for placental morphology. This never gained popularity but recent reports suggest that careful ultrasound examination of a placenta can reveal abnormalities that can be subsequently confirmed histologically (e.g. haematomas and ischaemic areas). Placental grading in the third trimester may be of value as one trial has shown that when performed there is a significant reduction in the stillbirth rate (Bricker and Neilson, 2001). As such in a case of suspected IUGR placental abnormalities should alert the obstetrician to the possibility of the diagnosis.

Amniotic fluid

In the process of fetal growth restriction there is reduced fetal renal perfusion and as such oligohydramnios is associated with such pregnancies. The estimation of amniotic fluid relies on the calculation of the amniotic fluid index, this is the sum of the deepest pool of liquor from the four uterine quadrants. Reference ranges exist for the normal population (as defined by birthweight) and the amniotic fluid index is a useful adjunct to biometry and Doppler assessment (Owen and Ogsten, 1996).

Doppler studies of the fetal circulation

The commonest method in clinical practice is Doppler waveform analysis of pulsatile flow in the fetal circulation. This has been extensively reviewed elsewhere (Neilson and Alfirevic, 2001). The development of pulsed and colour Doppler techniques has allowed the mapping of flow velocity waveforms in most of the major fetal vessels (arterial and venous). Chang et al (1994) described various Doppler ratios thought to reflect 'brain sparing' and their ability to predict adverse perinatal outcome. They concluded that only the renal:middle cerebral PI and aortic:middle cerebral PI has specifici-

ties above 70% and odds ratios that were significant for the prediction of perinatal morbidity (*Figure 1c*). These measurements, although superior to umbilical artery PI, have such low sensitivities that they are unlikely to be useful in late pregnancy.

Doppler screening of the uteroplacental circulation

Doppler studies have focused on the application of PI or resistance index (RI) values of the uterine arteries at 20–24 weeks gestation and more recently the reporting of diastolic notching of the waveform (*Figure 2*). Some centres use this technique to screen high risk populations to identify a group of pregnancies that require increased surveillance (for either pre-eclampsia, IUGR or both).

In a recent systematic review looking at the predictive value of uterine artery Doppler or the prediction of IUGR, Chien et al (2000) found that in the low risk population the pooled likelihood ratio was 3.6 (95% confidence interval (CI) = 3.2–4.0) for a positive test result and 0.8 (95% CI = 0.8–0.9) for a negative test result. A likelihood ratio of >10 or <0.1 is required for a conclusive positive and negative test result respectively. Even in a high risk population the pooled likelihood ratio was 2.7 (95% CI = 2.1–3.4) for a positive test and 0.7 (95% CI = 0.6–0.9) for a negative test result. They conclude that uterine artery Dopplers have limited diagnostic accuracy and as such interventional decisions should not be based on this test alone.

CLINICAL MANAGEMENT OF IUGR

We have already seen that there are many factors associated with IUGR (*Table 1*). Some of these can be influenced by obstetric management. Because the underlying pathophysiology is often multifactorial preventative measures may be more effective than treatments once the process is established. Smoking habits, maternal nutrition, teenage pregnancy, single mothers and co-

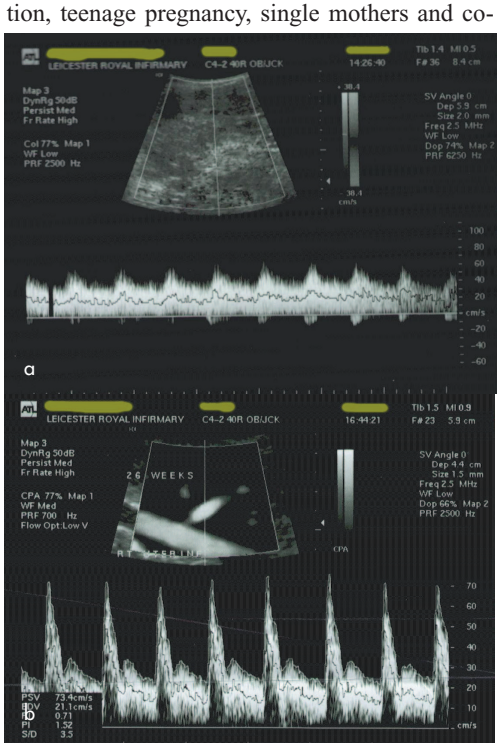

Figure 2. Images of (a) normal uterine artery waveform and (b) uterine artery waveform showing marked notching.

existent maternal disease are all associated with reduced fetal growth and may be amenable to intervention (Scholl and Hediger, 1995; Ellard et al, 1996).

Antenatal care

There are as yet no trials demonstrating that antenatal care can improve birthweight. Even the impact of optimal care is likely to be marginal. However, population-based interventions aimed at improving pre-pregnancy health should, at least theoretically, improve fetal growth (Gulmezoglu et al, 1997).

Dietary supplementation

The Dutch famine data provide conclusive evidence of the effect of maternal nutrition on fetal growth. Both pre-pregnancy weight and maternal weight gain in pregnancy are associated with fetal growth. However, there are no data to suggest that dietary supplementation can influence perinatal outcome once IUGR is established.

Antenatal treatment

There have been numerous interventions proposed to improve fetal growth.

Bed rest: This has never been evaluated in a randomized controlled trial.

Aspirin: There is as yet no evidence that low dose aspirin therapy can improve fetal growth. CLASP Collaborative Group (1994), the largest study of aspirin in pregnancy to date, found no benefit and recent studies looking specifically at IUGR as a primary endpoint have found no benefit (Caritis et al, 1998).

Oxygen therapy: There are only two small studies to date that allow the assessment of oxygen therapy and they are confounded by gestational age at delivery. As such this therapy is not advocated at present (Gulmezoglu and Hofmeyr, 2001a).

Betamimetic drugs: Two small studies of betamimetic drugs failed to find any difference in birthweight and no firm conclusions can be drawn (Gulmezoglu and Hofmeyr, 2001b).

Plasma volume expansion: This therapy is known to increase placental perfusion and reduce maternal blood pressure in pre-eclampsia. There are at present no clinical trials to assess its role in established IUGR (Gulmezoglu and Hofmeyr, 2001c).

Abdominal decompression: This involves wearing a pressurized suit and depressurizing 2–3 times per day. This has been advocated to improve uteroplacental perfusion although there is no evidence that this is achieved.

Other interventions such as transcutaneous electrostimulation, oestrogen administration and other growth factors such as growth hormone have not been evaluated outside animal models.

If studies comparing immediate delivery with conservative care (Growth Restriction Intervention Trial; GRIT) show that delivery is not beneficial then possible treatments such as oxygen therapy will need to be revisited in larger studies.

There is as yet no good evidence to support any interventional therapeutic measure that might reverse the IUGR. The only means available to an obstetrician at present to potentially influence outcome are resorting to timed delivery after antenatal corticosteroid administration and close collaboration with neonatologists.

TABLE 1.
Factors associated with intrauterine growth retardation

Fetal abnormality
Maternal infection
Drug use in pregnancy
Chronic maternal disease
Low maternal body mass index
Poor maternal nutrition/weight gain
Maternal smoking
Low social class
Teenage pregnancy
Deficient antenatal care

Differentiating IUGR from SGA

Attention has already been drawn to the importance of differentiating the IUGR fetus from the healthy SGA fetus. In general the SGA fetus can be classified as being either a healthy SGA fetus, placental IUGR or aneuploidy.

At the time an SGA fetus is diagnosed a detailed anatomical assessment is performed. Fetal biometry measurements are repeated (BPD, HC, AC, and FL) and can be compared to previous measurements if available. A symmetrically small baby with a normal umbilical artery Doppler is to be considered a healthy, small fetus.

Placental IUGR is a relatively easy diagnosis to make before 32 weeks gestation. Typical findings are shown in *Table 2*. One must note, however, that no one ultrasound finding can be used to establish the diagnosis.

The possibility of aneuploidy is raised by atypical findings such as a very small fetus with normal liquor volume and positive end diastolic

flow velocities in the umbilical artery. Such suspicions may require invasive prenatal diagnosis by either amniocentesis or fetal blood sampling. The greater availability of fluorescent in-situ hybridization has permitted the rapid diagnosis of the major trisomies and triploidy from amniocentesis samples. All such testing is associated with the possibility of procedure-related fetal loss or prematurity and the subsequent decisions regarding possible termination of pregnancy. The diagnosis of lethal abnormalities is important, however, to prevent unnecessary caesarean section with its associated morbidity and implications for future labours.

At this stage additional tests for congenital infections might be prompted dependent upon the specific ultrasound findings.

Management of a non-viable fetus

Some IUGR fetuses are likely to be non-viable. Typical features would be an estimated fetal weight of <500 g after 26 weeks gestation, reversed end diastolic velocities in the umbilical arteries and a pattern of decelerations on a cardiotocograph. Such circumstances require careful counselling with the input of neonatologists as well as obstetricians. At present the GRIT randomized controlled trial is comparing immediate delivery with conservative management until there is deterioration in the fetal condition. This study will address an important question as to whether such infants should be delivered.

In such cases 40% of women will already have or will go on to develop associated pre-eclampsia. As such, appropriate screening is required and should pre-eclampsia develop it would be appropriate to induce labour for maternal reasons. The fetus would not be expected to survive labour and as such it is imperative that intrapartum caesarean section for 'fetal distress' is avoided, as this may need to be a classical section to deliver a small and premature fetus.

TABLE 2.
Features of placental intrauterine growth retardation

Elevated head circumference/abdominal circumference ratio
Abnormal middle cerebral artery pulsatility index/ umbilical artery resistance index
Reduced amniotic fluid index
Abnormal placenta
Notched uterine arteries
Pre-eclampsia

Surveillance of pregnancies complicated by early onset IUGR

The management of pregnancies with an SGA fetus in the authors' unit is summarized in *Figure 3*. Steroids (for fetal lung maturation) are administered to all women who are admitted for intensive fetal surveillance. There is some evidence that steroid administration can improve placental vascular resistance, although it is not yet clear whether this has a beneficial effect on outcome (Wallace et al, 1999).

The decision as to 'when to deliver' is a balance between gestational age (fetal maturity) and fetal size. Draper et al (1999) have produced gestation and birthweight specific survival tables. It can be seen from *Figures 4a–c* that the data are dependent upon the sex, ethnicity and whether the infant is a twin. Predicted survival at

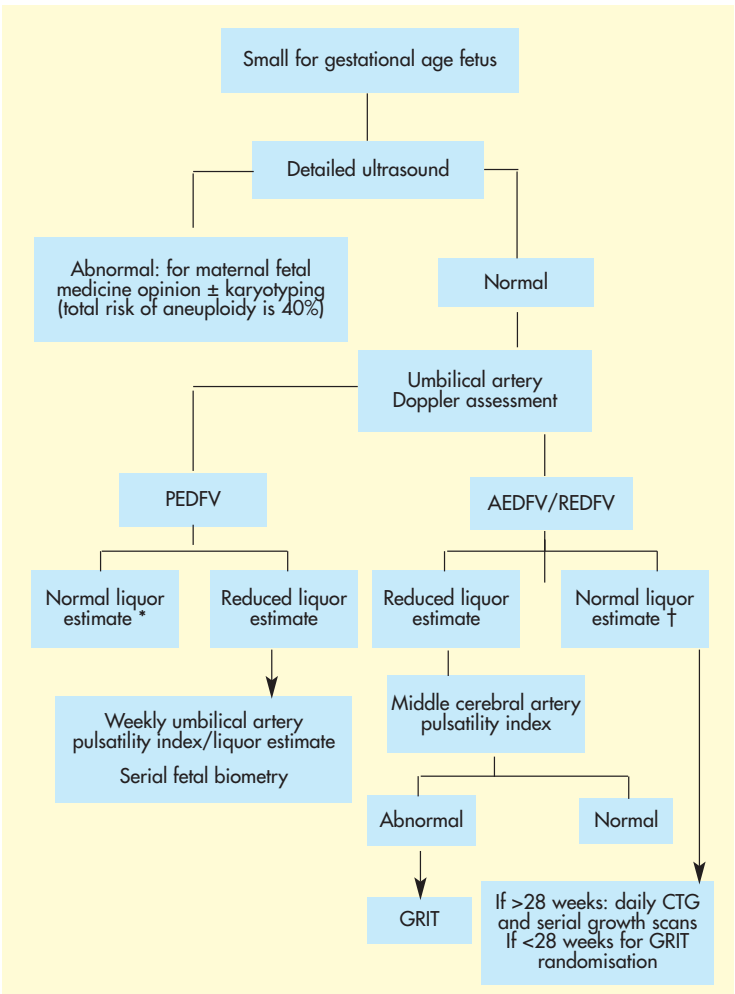

*Figure 3. Algorithm for the management/surveillance of the small for gestational age (SGA) fetus. *If SGA with PEDFV then the risk of aneuploidy is up to 30%. † If SGA with normal liquor volume and AEDFV the risk of aneuploidy is up to 20%. AEDFV = absent end diastolic flow velocities; CTG = cardiotocograph; GRIT = growth restriction intervention trial; PEDFV = positive end diastolic flow velocities; REDFV = reduced end diastolic flow velocities.*

any given gestational age is dependent upon the weight (whether estimated from ultrasound or birthweight) at gestations as early as 24 weeks.

The decision to deliver is central to the management of these pregnancies. The GRIT study hopes to address this difficult clinical issue and to thus provide the evidence on which to base decisions in the future.

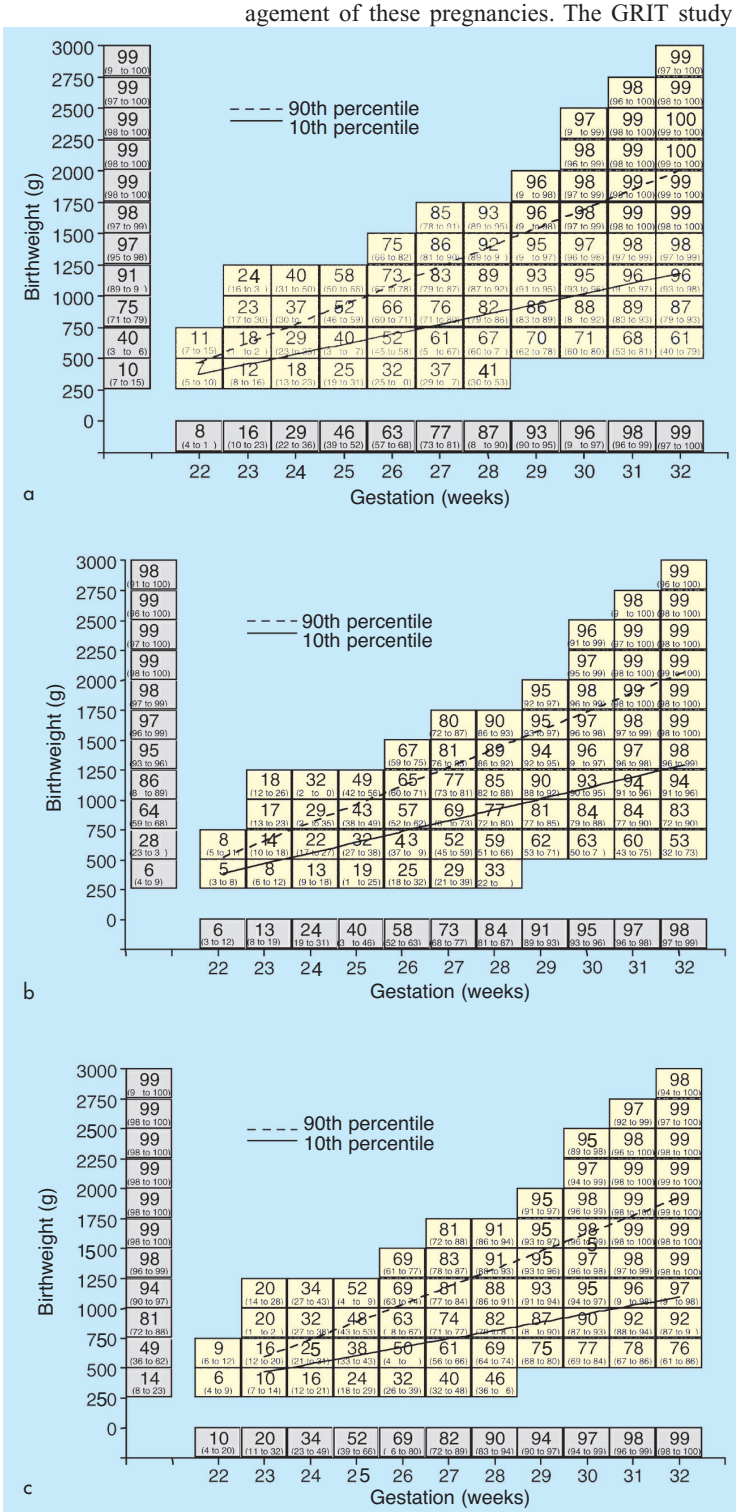

Figure 4. Predicted survival (%) for infants admitted to neonatal care. a. European (female). b. European (male). c. Asian. From Draper et al (1999).

Management of IUGR diagnosed after 35 weeks

Under these circumstances the fetal prognosis is much better and as such delivery is most often for fetal reasons. It is also possible to deliver vaginally following induction of labour rather than needing to deliver by elective caesarean section. Although the GRIT study is addressing the role of timed delivery in the preterm IUGR fetus there are no comparable study data to guide clinicians in IUGR at late gestation.

The consequences of IUGR for the neonate and into adult life

Despite the problem of confounding variables and retrospective data collection both SGA infants and IUGR infants are at increased risk of both minor and major neurological problems (Hackett et al, 1987; Kok et al, 1998). The risk of cerebral palsy increases as the birthweight deficit increases; however, this outcome is rare and as such most SGA infants are not affected (Malcolm et al, 1991). Other conditions associated with IUGR are necrotizing enterocolitis, respiratory distress syndrome, hypoglycaemia, polycythaemia and postnatal growth problems (MacLennan, 1999).

The concept of fetal programming is now well established. The effects of poor fetal nutrition are to reduce cell numbers in certain organ groups depending upon the timing of the insult in relation to development. There is now an accepted association between birthweight and adult hypertension, coronary heart disease and non-insulin dependent diabetes (Barker et al, 1989).

CONCLUSIONS

This review has outlined the current diagnostic tools available to the obstetrician to manage IUGR. At present the authors' main interventional strategy is timed delivery and this is currently undergoing assessment in the GRIT randomized controlled trial due to report in 2001 (GRIT Study Group, 1996). This will provide important answers for obstetricians in an uncertain clinical area. Should we deliver a growth restricted infant at a premature gestation or should we continue with a conservative approach of antenatal surveillance? Furthermore with now well established links to adult disease there is a greater need to understand how the intrauterine environment can influence fetal growth patterns and what effects at a cellular level such environmental changes might have. It is through such

studies that we might develop interventional tools to prevent the sequel of established IUGR. HM

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KEY POINTS

- Intrauterine growth restriction (IUGR) is a pathological condition associated with significant morbidity and mortality for the fetus. As such it should be separated from the term small for gestational age (SGA).
- The aetiology of IUGR is multifactorial and requires antenatal investigation to plan management strategies.
- There is a significant risk of aneuploidy (20–30%) with an SGA infant dependent upon liquor volume and umbilical artery Doppler parameters
- Neonatal mortality is gestation dependent; however, it is also weight dependent even at gestations as low as 24 weeks.
- Management of the IUGR fetus often necessitates timed delivery. At present with limited evidence to guide this decision, the support of ongoing studies into delivery *vs* conservative care is to be recommended.