Intrauterine growth restriction

Diagnosis and management

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BACKGROUND Fetal growth disorders are an important cause of perinatal morbidity and mortality with long term health implications for the survivors of intrauterine growth restriction (IUGR). The accurate assessment of fetal growth during pregnancy is difficult, but recent advances have improved this important aspect of obstetric care with positive implications for antenatal patients and their babies.

OBJECTIVE This article provides an overview of the detection of fetal growth problems in pregnancy, the determination of the likely cause, and the antenatal and intrapartum care of women with pregnancies identified as being affected by IUGR. The role of customised fetal growth assessment in the detection of IUGR is considered and followed by an outline of the appropriate monitoring and management of these pregnancies based on the underlying pathophysiology.

DISCUSSION Accurate assessment of fetal growth is improved by early clarification of gestational age and the use of customised fetal growth charts. Once infections and anomalies have been excluded, it is imperative to distinguish the healthy small fetus from the growth restricted fetus. While treatment options are limited, the optimal management of the IUGR affected fetus aims to achieve the delivery of the newborn in the best possible condition, balancing the risks of prematurity against those of continued intrauterine existence.

One of the most important goals of effective antenatal care is the detection of the fetus at risk from suboptimal growth.

Fetuses identified during pregnancy as being small for gestational age (SGA) comprise a heterogeneous group in regard to aetiology, management and prognosis.[1] Causes include:

- incorrect dating of the pregnancy
- constitutionally small size
- genetic/chromosomal defects in the fetus
- intrauterine infection, and
- intrauterine growth restriction (IUGR) related to an inadequacy in the supply of nutrients and/or oxygen to the fetus through the uteroplacental unit.[1,2]

Fetuses affected by IUGR form an important subset of the cases of SGA, given the short and long term health risks faced by these infants.[3–6]

In accurately dated pregnancies, approximately 80–85% of fetuses identified as being SGA are constitutionally small but healthy, 10–15% are 'true' IUGR cases, and the remaining 5–10% of fetuses are affected by chromosomal/structural anomalies or chronic intrauterine infection.[1] The correct classification of a fetus as being either a normal but small fetus or IUGR requires both an accurate assessment of gestational age and appropriate fetal growth charts. The use of standard population charts frequently leads to misclassification of some babies who are constitutionally small as growth restricted while other babies who are truly growth restricted by anthropometric indices as within the normal range.[3]

In attempting to overcome the limitations of standard antenatal and birth weight charts in assessing fetal and neonatal development, charts have been

developed that adjust for the maternal variables of height, weight, parity and ethnic group.[5,7] Customised antenatal growth charts plot the weeks of pregnancy on the 'x' axis, and symphysis fundal height (SFH) and/or ultrasound derived fetal weight on the 'y' axis.[3] Software that allows generation of customised charts – based on an Australian dataset – is freely available on the internet (www.gestation.net). Two examples using these customised fetal growth curves, based on the variables of maternal height, weight, parity, and ethnic group are shown in *Figure 1a, b*. A baby born at 37 weeks weighing 2500 g is within normal limits for Mrs Small (51st centile), but the 5th centile for Mrs Large as the latter's predicted optimal growth curve is steeper.

The incidence of IUGR varies according to the reference population (with higher rates of IUGR in developing countries) and the percentile determined as indicating clinically significant growth restriction.[7] While <10th centile is usually considered to indicate SGA, it may be that <3rd to 5th centile is more relevant in indicating the group with an increased risk of an adverse perinatal outcome.[8]

Suboptimal fetal growth is an important cause of perinatal mortality and morbidity.[6,9–12] The sequelae of IUGR include stillbirth, detrimental effects on neuro-developmental progress in childhood, and higher risks of degenerative diseases (eg. hypertension, vascular disease, diabetes) in adulthood.[13,14] The aim of detecting IUGR is to reduce perinatal morbidity and mortality, primarily by optimising the timing of the delivery of the affected fetus.[15] Additionally, and especially of relevance in the rural setting, the early identification and close surveillance of IUGR cases should enable local paediatric staff to be ready for the elective delivery of a baby affected by IUGR or, in some cases, enable the pregnant woman to be transferred to a larger centre for delivery.

Causes of SGA (including IUGR)

Small for gestational age early in pregnancy is usually associated with the development of a symmetrically small fetus. Causes include:

- severe maternal vascular disease (early onset IUGR)
- fetal infection (notably, the TORCH infections: toxoplasmosis, rubella, cytomegalovirus, varicella, HIV), and
- chromosomal or structural anomalies (especially cardiac and renal conditions).[2,16]

The later onset of SGA (>32 weeks) usually results from uteroplacental dysfunction (late onset IUGR) and is characterised by a relatively greater decrease in abdominal size (liver volume and subcutaneous fat) than that of the head circumference and length, resulting in an asymmetric reduction in fetal size. The differentiation of early and late onset SGA is linked to the three phases of fetal growth: cellular hyperplasia (first 16 weeks of gestation), concomitant hyperplasia and hypertrophy (16–32 weeks), and cellular hypertrophy (32 weeks to term).[16] Early SGA results when early fetal cellular hyperplasia is impaired, producing a proportionate decrease in all fetal organs. By contrast, late SGA is associated with a fetus able to adapt to a variable extent to a hostile intrauterine environment by redistributing blood flow to the vital organs of brain, heart and placenta, thereby preserving head circumference.[16]

The causes of 'true' IUGR are many and include those related to the fetus (eg. multiple pregnancy, especially monozygous twins), the mother:

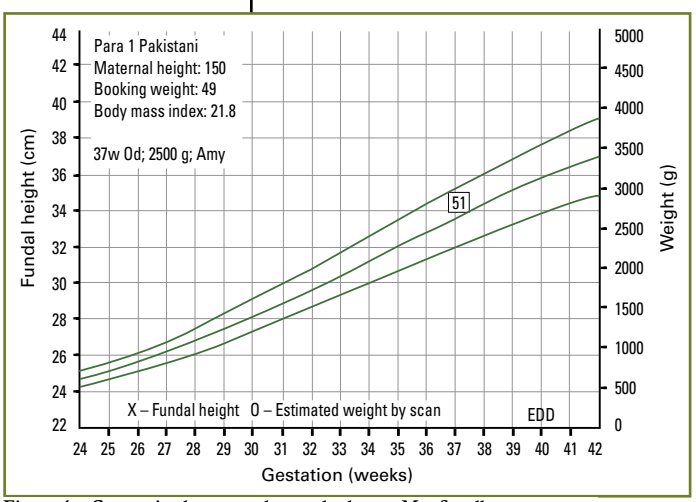

Figure 1a. Customised antenatal growth chart – Mrs Small

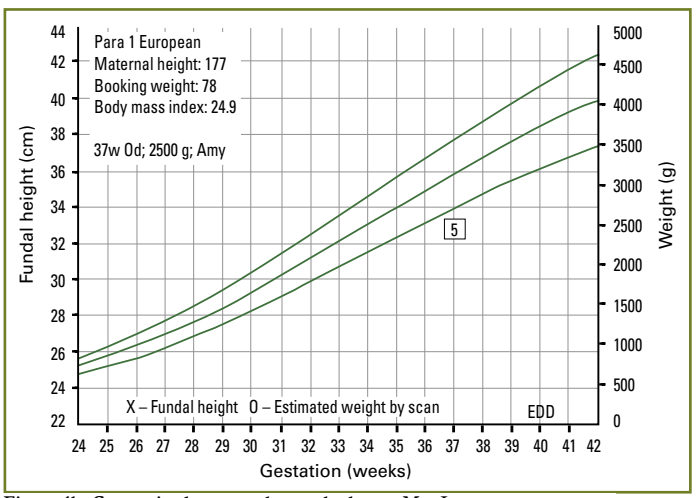

Figure 1b. Customised antenatal growth chart – Mrs Large

- medical factors (hypertension, diabetes and immunological disorders, eg. systemic lupus erythematosus)
- socioeconomic and nutritional factors
- drugs including alcohol, tobacco, cocaine, and amphetamines
- prescription medications (eg. anticonvulsants, warfarin, steroids), and

placental factors including abnormalities of placental morphology, recurrent abruption/placenta praevia, and immunological disorders affecting the quality of placentation.[7,10,17]

A possible association between maternal thrombophilia and IUGR has been postulated but not proven.[18] There is an increased risk of IUGR in the pregnancies of those women who:

- were themselves growth restricted at birth
- have previously had a pregnancy associated with IUGR, and
- who have a sister who has had an IUGR pregnancy.[7]

The recurrence risk was found in one study to be 29% if the first pregnancy was affected, and 44% if two pregnancies have been affected.[19] Recent research has shown that insulin-like growth factor 1 receptor (IGF-1R) gene mutations – leading to disordered function of IGF-1 receptors – may result in restricted intrauterine growth and suboptimal development in postnatal life.[19]

While some maternal risk factors such as hypertension, abuse of tobacco and other substances, and malnutrition may be amenable to change through health care interventions, the problem of IUGR remains difficult to predict or prevent.[17] There is some evidence that treatment induced reductions in maternal blood pressure for women with mild to moderate hypertension may actually adversely affect fetal growth.[20] Similarly, while treatment of significant hypertension in pregnancy is important for protection of the mother, there is no evidence that such treatment improves fetal growth in these pregnancies.[8]

Detection of IUGR

The recognition of IUGR involves both a consideration of risk factors and the careful clinical assessment of fetal growth throughout the pregnancy.[1] Accurate surveillance of fetal growth requires certainty of gestational age and this is ideally established through first trimester ultrasound scanning (USS) with an accuracy to within 5 days, while second trimester scanning should be accurate to within 10 days.[21] Once gestational age is known, antenatal assessment aims to determine if fetal growth is progressing normally over time.[1]

Table 1. Main points regarding SFH measurement

Step	Procedure
1.	The care provider should ensure that the woman lies supine with legs extended, the bladder empty and the uterus relaxed[36]
2.	The fundus of the uterus should be found by palpation caudally from the xiphisternum and the distance to the upper edge of the pubic symphysis ascertained by laying a nonelastic tape (with the scale face down) along the uterine axis (which should not be corrected if deviated from the midline)[3]

Symphysis fundal height

At each antenatal visit, the attending practitioner should aim to assess fetal growth by one or more means. Traditionally, the primary method has been by palpation of the uterus and fetus, and more recently, by also measuring the SFH as a surrogate measure of fetal size.[22–24]

Symphysis fundal height measurement should ideally provide a reproducible, objective measure to ensure reliable assessment across the differing practitioners many women see during their pregnancies (*Table 1*). It is low cost, convenient and readily available, especially in developing countries where more sophisticated assessment is either unavailable or very limited. The simplicity and affordability of SFH measurement allows fetal assessment within primary heath care, enabling triage of pregnancies identified as being higher risk to a better equipped centre.[23]

Given the potential usefulness of SFH measurement, it is disappointing that the introduction of this measurement into obstetric care has not led to consistent improvements in the detection of disorders of fetal growth. In part, this failure may relate to variation in the measurement techniques between different practitioners.[25,26] Studies have suggested that training in a standardised method of SFH measurement may reduce inter-observer variation and thereby improve the performance of antenatal care in the detection of fetal growth disorders.[23,24]

In addition, there is evidence that SFH measurement performs better if the charts used to plot SFH are customised to match particular variables affecting fetal growth in fetuses of different mothers.[3,5,27–32]

Further assessment

In cases in which clinical assessment, including

SFH measurement, leads to clinical concerns about potentially suboptimal fetal growth, further assessment of the fetus is indicated.[21] The assessment modalities comprise:

- USS evaluation of fetal growth
- the amniotic fluid index (AFI)
- Doppler studies, and
- fetal behavioural analysis through the biophysical profile (BPP).[21]

The key anatomical indicators of fetal growth are the head circumference (HC) and abdominal circumference (AC). The AC predominantly assesses liver size, thereby reflecting glycogen storage and, hence, fetal nutritional status. An AC <10th centile, preferably based on a customised chart, has a high sensitivity for IUGR while a normal AC has a high negative predictive value for IUGR.[8] Estimated fetal weight assessment, again, preferably based on a customised chart, provides an alternative or additional means of growth assessment.[33] However, the growth velocity is the most sensitive indicator of fetal growth.[3] For those fetuses found to have abnormal growth velocity, Doppler assessment is indicated.

In uteroplacental dysfunction, there is reduced umbilical artery (UA) diastolic flow on Doppler assessment and an increased systolic/diastolic flow ratio.[2] In more severe cases, diastolic flow may be absent or even reversed, although it is noted that such changes may be observed in normal, very pre-term fetuses, complicating assessment in this group.[7]

If UA diastolic flow is abnormal, further Doppler studies are indicated. The fetus adapts to hypoxaemia by redistributing blood flow to the brain and heart and a hypoxaemic fetus may develop:

- reduced middle cerebral artery resistance
- reduced blood flow in the ductus venosus/inferior vena cava or, in more advanced cases
- pulsatile umbilical venous flow (indicating fetal acidaemia and a high risk of intellectual impairment and other postnatal complications).[2]

The assessment of AFI forms an important part of the appraisal of the growth restricted fetus, given the strong association between oligohydramnios and a markedly increased risk of perinatal mortality.[34,35] Conversely, a normal AFI provides a degree of reassurance regarding fetal wellbeing,[35] but should be interpreted in conjunction with the results of other assessment tools.[33]

The BPP is 'a time consuming test and it is not recommended for routine monitoring in low risk/unselected pregnancies or for primary surveillance in SGA fetuses'.[34] The BPP does have a useful role in cases in which UA Doppler has been found to be abnormal, given its high negative predictive value.

Table 2. Diagnostic and assessment tools relating to IUGR[2,35]

Screening

- Biochemical
  - alpha-fetoprotein
    if ↑ in absence of fetal anomaly, risk of IUGR later in pregnancy is ↑ 5–10 x
- Clinical
  - palpation
  - SFH measurement (customised)
- Ultrasound
  - HC
  - AC
  - EFW
    <10th centile on customised charts or reduced growth velocity indicate IUGR

Confirmation of diagnosis

- Ultrasound
  - fetal/placental morphology
  - UA Doppler
  - ± assess for TORCH infections
  - ± fetal karyotyping

Monitoring of IUGR affected pregnancy

- Ultrasound
  - UA Doppler
    ± MCA Doppler
    ± Fetal venous studies
  - AFI
  - ± BPP
- ± cordocentesis (rarely)

Management of an IUGR affected pregnancy

Once abnormal fetal growth has been detected, aetiology should be determined by considering fetal chromosomal or structural anomalies, or intrauterine infection and the other known causes of impaired fetal growth as outlined earlier. Appropriate investigations vary depending on the stage of pregnancy at which the problem is detected and whether the fetus is symmetrically or asymmetrically growth restricted (*Table 2*).

The optimal method of monitoring the fetus affected by IUGR is still the subject of much debate. However, in general, such monitoring aims to ensure

that the primary intervention, that of pre-term delivery, is undertaken at the best possible time[35] (*Table 3*). The goal is to delay delivery as long as possible to achieve fetal maturation and, hopefully, ensure viability while avoiding the sequelae of fetal acidaemia. Useful resources providing guidance and algorithms relevant to this difficult area of clinical care include:

- The RCOG guidelines (No. 31): www.rcog.org.uk
- The UpToDate website: www.uptodate.com
- An excellent algorithm (*Figure 2*) produced by Newcastle University available at their website (www.ncl.ac.uk/nfmmg/guidelines/sga%20guide.htm).

Induction of labour

Determination of the optimal timing of delivery of the IUGR affected fetus requires a careful consideration of the severity of the growth restriction and its impact on fetal wellbeing balanced against the stage of gestation.[2] There is general consensus that delivery is indicated when the risk of fetal death or significant morbidity from continued intrauterine existence is greater than the risk of prematurity.[35] This decision making process has been informed by the findings of the Growth Restriction Intervention Trial (GRIT) which concluded that, in general, at gestations less than 31 weeks, delivery is best delayed if there is any uncertainty about the need for intervention.[35] The GRIT has not provided evidence to date that 'early delivery to pre-empt severe hypoxia and acidosis reduces any adverse outcome'.[34]

Before 36–37 weeks

Delivery should generally be deferred if end diastolic flow is present on UA Doppler and other surveillance findings are normal.[34] Before 34 weeks, if diastolic flow disappears or reverses, 'admission, close surveillance and administration of steroids are required. If other surveillance results (BPP, venous Doppler) are abnormal, delivery is indicated'.[34] If more than 34 weeks, even if other results are normal, delivery may be appropriate.[34]

Table 3. Evaluation and management of the IUGR fetus[7]

	Constitutionally small fetus	**Fetus with structural and/or chromosome abnormality; fetal infection**	**Substrate deprivation: uteroplacental insufficiency**
Growth rate and pattern	Usually below but parallel to normal: symmetric	Markedly below normal: symmetric	Variable: usually asymmetric
Anatomy	Normal	Usually abnormal	Normal
Amniotic fluid volume	Normal	Normal or hydramnios: decreased in the presence of renal agenesis or urethral obstruction	Low
Additional evaluation	None	Karyotype: specific testing for viral DNA in amniotic fluid as indicated	Fetal lung maturity testing as indicated
Additional laboratory evaluation of fetal wellbeing	Normal BPP/UA Doppler	BPP variable, normal UA Doppler	BPP score decreases, UA Doppler evidence of vascular resistance
Continued surveillance and timing of delivery	None: anticipate term delivery	Dependent upon aetiology	BPP and UA Doppler: delivery timing requires balance of gestational age and BPP/UA Doppler findings: fetal lung maturity testing often helpful

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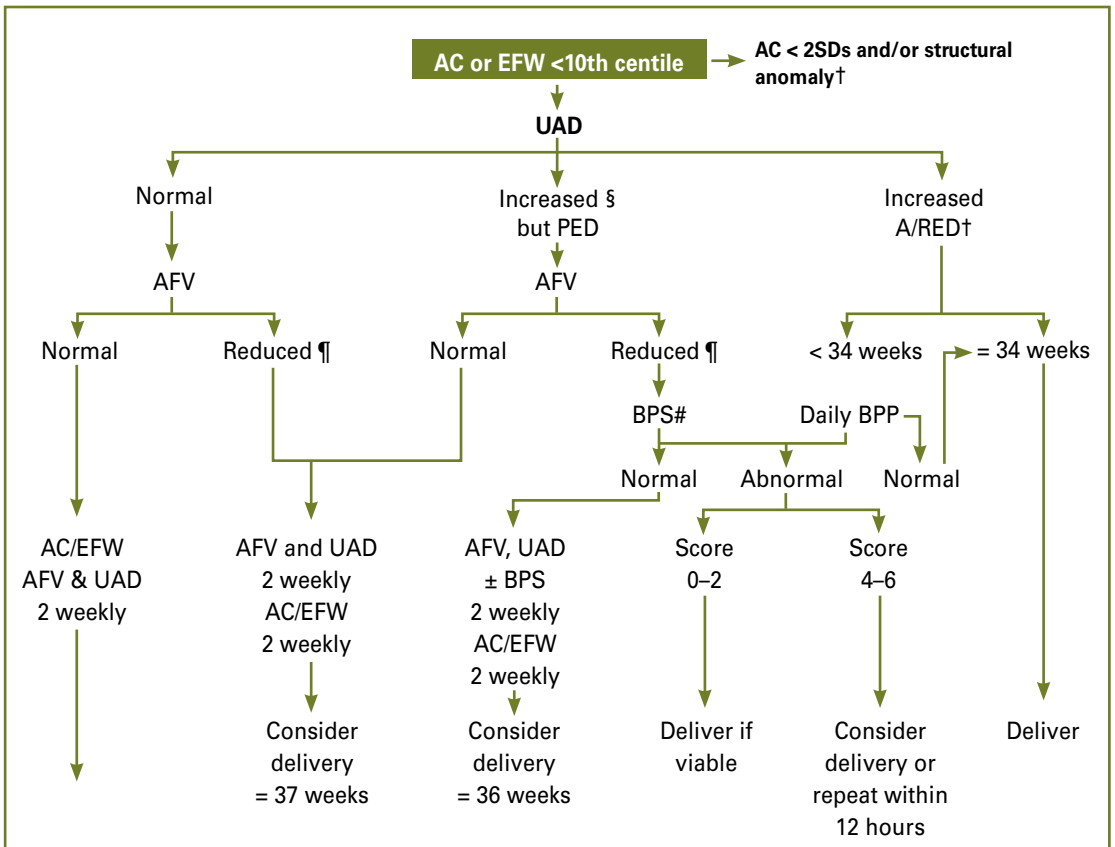

Abbreviations: AC = abdominal circumference, EFW = estimated fetal weight, UAD = umbilical artery Doppler, AFV = amniotic fluid volume, BPS = biophysical profile score, § = resistance index >95th centile, † = consider referral to fetal medicine specialist, ¶ = amniotic fluid index <5 cm or single pocket <2 cm, # = venous Doppler or computerised CTG may be an alternative

Queries about this algorithum or problems arising from its use should be directed to Professor SC Robson/Dr SN Sturgiss, Royal Victoria Infirmary, Newcastle NE1 4LP. Tel 0191 2825833, Fax 0191 2275194, email s.c.robson@ncl.ac.uk or s.n.sturgiss@ncl.ac.uk

Figure 2. Management of the SGA fetus

Beyond 36–37 weeks

If IUGR is certain, end diastolic flow is present, and AFI is normal, delivery may be deferred until the Bishop's score is adequate for induction.[2] If the AFI is reduced, delivery should be expedited. However, if growth is static between two scans 2 weeks apart in a fetus more than 32 weeks, delivery may be appropriate (once steroids have been administered to those <34 weeks).[2]

Delivery should be undertaken in a unit capable of providing intrapartum monitoring with continuous cardiotocography in labour and appropriate neonatal staff and facilities to care for the IUGR affected newborn.[34] The decision on the best mode of delivery is based on the gestation, fetal condition, and cervical status.[2,34] In cases where there is evidence of fetal acidaemia, caesarean section may be appropriate.[2]

Fetuses with IUGR have an increased risk of meconium aspiration and intrapartum asphyxia/stillbirth. Therefore, meticulous intrapartum care and monitoring is essential with recourse to obstetric intervention if evidence of additional fetal compromise emerges in labour.[2] Given their oxygen and substrate deprivation during intrauterine life, newborns affected by IUGR may develop hypoxic-ischaemic encephalopathy or have meconium aspiration, polycythaemia, hypoglycaemia or other metabolic abnormalities, as well as hypothermia.[2,35] Longer term risks faced by survivors of IUGR, including neuro-developmental problems in childhood and degenerative diseases in adulthood, have been outlined earlier. The prognosis is optimised by the appropriate timing of delivery, close intrapartum surveillance, and skilled neonatal care.[35]

Summary of important points

- Accurate dating is essential to allow careful monitoring and assessment of apparently abnormal fetal growth.
- Customisation of fetal growth assessment assists in distinguishing the healthy small fetus from one affected by IUGR.
- The primary medical intervention in an IUGR affected pregnancy is to ensure delivery of the baby at the optimal time, balancing the risks of fetal compromise from uteroplacental dysfunction against those of prematurity.

Conflict of interest: none declared.

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