Fetal and Maternal Medicine Review 2002; ***13****:4 249–259* © *2002 Cambridge University Press*
DOI:10.1017/S0965539502000426

ULTRASOUND BIOMETRY AND FETAL GROWTH RESTRICTION

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INTRODUCTION

With the ascendancy of biophysical assessment with Doppler velocimetry, and the establishment of routine scan dating in early pregnancy, there needs to be a radical re-think of the role of ultrasound biometry in the definition and assessment of fetal growth restriction (FGR).

Doppler flow velocimetry of the umbilical artery has proven its value in defining the FGR fetus.[1] It is more useful than cardiotocography (CTG) or biophysical profile scoring.[2] However, the sensitivity of any test depends on the prevalence of the condition being looked for. While Doppler is of value in fetuses which are small-for-gestational age (SGA), it is less useful in predicting growth restriction or adverse outcome in the general population.[3,4] The question is therefore, how to detect those pregnancies for which further fetal assessment is indicated.

In pregnancies which are 'high risk', serial ultrasound biometry will allow assessment of growth, and both AC and EFW below the tenth percentile have a useful role.[5] Slowing of growth (dropping below an action line like the tenth percentile) would indicate the need for further investigations. Relative slowing within 'normal' limits, e.g. a drop from the 70th to the 20th centile in consecutive measurements, should also be a matter of concern, but the limits of deviation from normal growth have not been defined. There is a limit to the usefulness of frequently performed third trimester scans: if the increment of a biometric parameter is approximately 5% per week, and the random error of a scan measurement is 10% (see below), then more than fortnightly scans are not likely to give valuable information about true growth.

RECORDING ULTRASOUND PARAMETERS

The usual method of recording ultrasound measurements is to plot biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur

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length (FL) on standard population charts which are usually derived from a cross-sectional population sample.[6] Is the plotting of these individual parameters clinically relevant? In pregnancies dated by early scan – as most are in the UK today – plotting BPD or HC in the third trimester appears of limited use, and is often a cause of unnecessary anxiety as the normal limits are relatively narrow and false positives may appear. Microcephaly is usually detected well before the third trimester. In the West Midlands Congenital Anomalies Register, which has high levels of ascertainment, only 7 cases of microcephaly were detected after 24 weeks between 1994–2001; during the same interval, there were 10 cases which were wrongly suspected of microcephaly, including 5 cases which were normal and 5 which had another, unrelated anomaly. Plotting of femur length in the third trimester would also appear to be of limited relevance, as in most instances, the presence of short femur lengths is detected at the time of the mid-trimester scan.

It is often argued that separate plots of individual ultrasound parameters allow assessment of symmetry of growth failure. Asymmetrical growth restriction is conventionally considered to be due to placental failure with 'head sparing', while symmetrical growth restriction is associated with early onset growth failure. However, these distinctions overlap. Symmetrical FGR can be due to misdating, constitutional smallness, or early onset FGR, and separate plotting of fetal head, abdomen and femur measurements will not distinguish between them. Furthermore, it is doubtful whether the distinction between symmetrical and asymmetrical growth failure adds any clinically useful information. In either case, further investigations are necessary – e.g. biophysical assessment by Doppler. If growth restriction is severe, assessment for chromosomal abnormality would need to be considered in both instances. The degree of deviation is more important than the symmetry between abdominal and head measurements. Studies comparing symmetrical and asymmetrical growth restriction have failed to demonstrate differences in aetiology,[7] fetal acid-base status at time of cordocentesis,[8] neonatal morphometry[9] and other indices of outcome.[10,11]

The main uncertainty about individual ultrasound parameters is that their accuracy has never been established. There is no gold standard, as normal measurements of the head, abdomen and femur of the neonate, corresponding to ultrasound measurements of the fetus, have not been defined.

ESTIMATED FETAL WEIGHT

In contrast, the predictive accuracy of fetal weight assessment can be measured easily against birthweight. The delay between scan measurement and weight at birth is best adjusted for by projection of a proportional weight equation[12] or, at term, by an approximate addition of 25g per day.[13]

Various fetal weight formulae exist, using combinations of individual ultrasound parameters. Chien and colleagues[13] recently assessed estimated fetal weight (EFW) at term, using 4 formulae and found that the validity was high for all. The mean

(systematic) error is small but tends to vary depending on the biometric parameters used. Formulae using head, abdomen and femur length measurements reported standard deviations (random error) of between 7.1% in Malmö, Sweden[14] and 7.3% in Houston, Texas.[15] The random error may be higher in routine clinical use. An audit of standard care from Denmark suggested a standard deviation (SD) of 11%, with an agreement between projected weight estimate and actual birthweight of $r = 0.87$.[16] Fetal weight – only curves have been in standard use in Sweden for a number of years.[17]

SHOULD FETAL WEIGHT FORMULAE BE SPECIFIC TO FETAL SIZE?

The assessment of weight formulae also needs to include performance in different populations, and at the extremes of weight, i.e large and small fetuses. A recent comparative analysis of 12 different formulae applied to a South East Asian population found the Hadlock formula[15] using head, abdomen and femur measurements to be the most accurate.[18] For large babies, the accuracy of fetal weight formulae is known to be reduced, and additional soft tissue indices (e.g. upper arm or thigh measurements) appear to add little in accuracy.[19]

In small babies, assessment of weight may also be less accurate, increasing the SD from 7.3 to 9.7.%[15] Sabbagha and colleagues[20] examined specific formulae for large – for- gestational age (LGA), average – for- gestational age (AGA) and SGA babies, based on a previously described model for fetal weight, and found them to be more accurate than a single formula[15,21] applied across all three weight categories. However, the study did not report on systematic and random error separately, and the interval between last scan measurement and delivery was up to 10 days and not adjusted for. More recent, larger studies found that targeted formulae for small fetuses are not better than general i.e. across-the-range formulae.[22,23] Jouannic and colleagues[23] examined 10 formulae in 119 fetuses weighing < 1250 g at birth and found that Hadlock's formula using HC, AC and FL had the smallest systematic error (-0.25%) and one of the smallest random errors (13.0%). Campbell's weight formula[24] which relies on AC only, had a systematic error of +2.56% and the largest random error, 19.3%.

Even if formulae specific for small babies were found to improve weight prediction, they would have to be substantially better to overcome the inherent advantage of using a single formula across the whole range of weights and gestational ages when considering longitudinal i.e. prospective assessment. Changing formulae between sequential assessments may obscure the magnitude of altered growth.

To improve accuracy, a fetal weight formula needs to contain a measure such as the abdominal circumference to assess liver and fat stores; a measure of the head – head circumference in preference to biparietal diameter, as the latter can be affected by head compression – and of the femur, to assess 'tallness'. It would appear that Hadlock's formula for HC, AC and FL,[15] in itself a refinement from an earlier analysis on a smaller sample,[25] has stood the test of time, and has been applied successfully in different populations:

Log 10 weight = 1.326–0.00326 ACxFL + 0.0107 HC +0.0438AC + 0.158 FL

Three-dimensional ultrasound has allowed the calculation of fetal volume which improves the prediction of fetal weight.[26] However, 3D ultrasound is not in routine use. Several volumetric formulae based on conventional ultrasound have been proposed, but their accuracy is still uncertain: some studies consider them to be more consistent across different gestational ages[27] while others suggest that they add little to conventional fetal weight assessment.[28,29]

CONSTITUTIONAL AND PATHOLOGICAL SMALLNESS

There is no clear agreement on the definition of fetal growth restriction. However, it is often referred to as the 'failure of the fetus to reach its growth potential'. This begs the question as to what the individual potential is, ie. what weight should a baby be expected to reach at the end of a normal pregnancy. A general population standard is unlikely to account for constitutional variation.

One method is to prospectively predict each baby's growth potential on the basis of ultrasound biometry in the second trimester. The Rossavik model[30] calculates a projected growth curve on the basis of two scans at about 18 and 24–26 weeks. There are two potential problems with this approach:

1 ultrasound error at each of the sequential scans can lead to substantial variation when forward projecting the growth curve calculated on the basis of these measurements
2 the scans, especially the second one, can already be affected by early onset FGR, resulting in these values then being falselyprojected as the 'norm'.

This mathematical modelling failed to show improved prediction of fetal growth.[31]

Ultrasound measurements can also be used to calculate 'conditional centiles' and assess growth at the subsequent ultrasound scan in relation to these predicted limits.[32] Compared to conventional, population based assessment, conditional centiles of fetal abdominal area were found to improve the prediction of a low ponderal index.[32] In view of the above discussion of the inherent errors of ultrasound measurements, it will be interesting to see whether the calculation of normal limits on the basis of a scan will affect the accuracy of this method in routine practice.

CUSTOMISING THE STANDARD FOR GROWTH

Another method is to extrapolate the expected birth weight backward into the antenatal period to define intrauterine weight standards, using a 'proportionality growth curve'.[33] Thus an optimal birthweight is defined, from which the optimal intrauterine growth is delineated.

The calculation of the optimal weight at term uses coefficients to adjust for

constitutional variation. This requires accurately dated data, and adjustment for variables including maternal height, weight in early pregnancy, parity, and ethnic group. Pathological factors which show significance in the analysis need to be excluded – e.g. smoking – as the standard should calculate the growth potential. Next, the growth curve to this optimal weight end-point is delineated, using a 'proportional' fetal growth function.[34,35] This avoids using a birthweight curve, as the latter is derived from abnormal (and usually negatively skewed) data in the preterm period.

As there are an infinite number of possible combinations to produce an individual fetus' growth curve, the method requires a computer. The software (GROW – Gestation Related Optimal Weight) is freely available for download from *www.gestation.net*. Examples of customised growth charts are shown in figure 1,

EVIDENCE FOR CUSTOMISED ASSESSMENT

There is evidence that assessment against a customised, individually adjusted standard improves the distinction between normal and abnormal smallness, in the antenatal assessment of estimated fetal weight as well as the postnatal assessment of birthweight.

Intrauterine weight

Fetal weight curves reproduce differences between physiological/constitutional characteristics, in low risk[36] as well as high risk[37] populations. The use of fetal weight instead of individual scan biometry parameters allows adjustment of normal intrauterine growth limits, as there is insufficient data to 'customise' ultrasound scan values by multivariate analysis of all the non-pathological factors which influence fetal growth. However, the variables can be determined from larger, population based birthweight databases, and then applied to intrauterine growth curves.

Customised limits reduce false positive 'FGR' in a normal population.[38] Receiver-operator curves suggest that the 10th percentile is a suitable cut-off limit to detect those babies who will develop perinatal complications.[39]

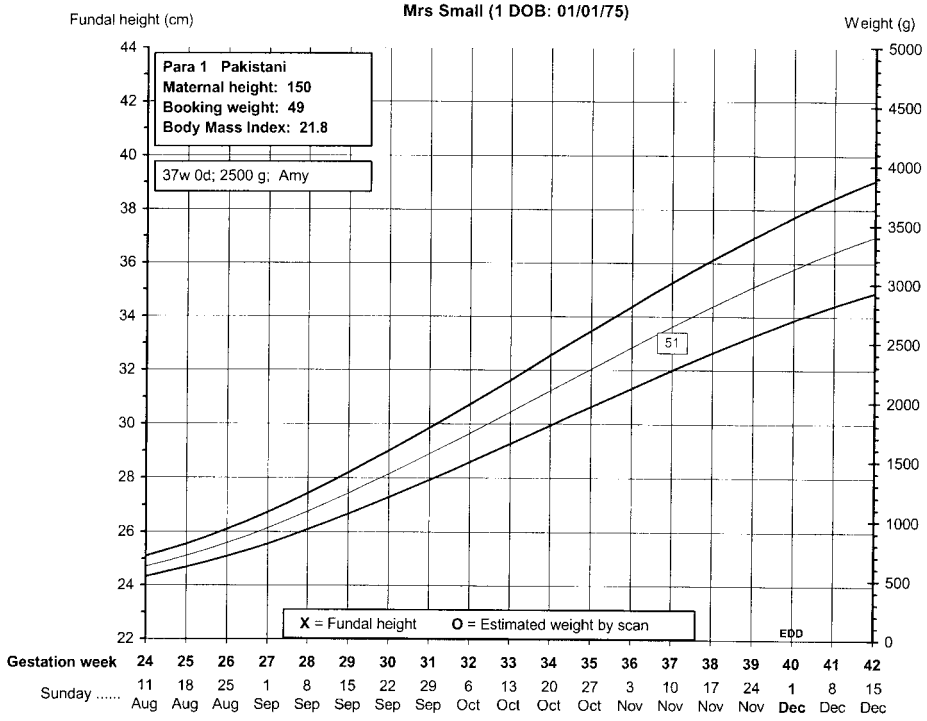
Birth weight

When assessing SGA birthweight, it is clear that a large proportion of the population is misclassified if an unadjusted standard is used. Differences between ethnic groups can be substantial.[40]

Individually adjusted birthweight percentiles are better correlated with Apgar scores[33] and neonatal morphometry indices.[41,42] They also better reflect adverse pregnancy events, even across geographical boundaries. For example, SGA defined by a customised standard derived from an English population is better correlated with operative deliveries for fetal distress and admission to neonatal intensive care in a

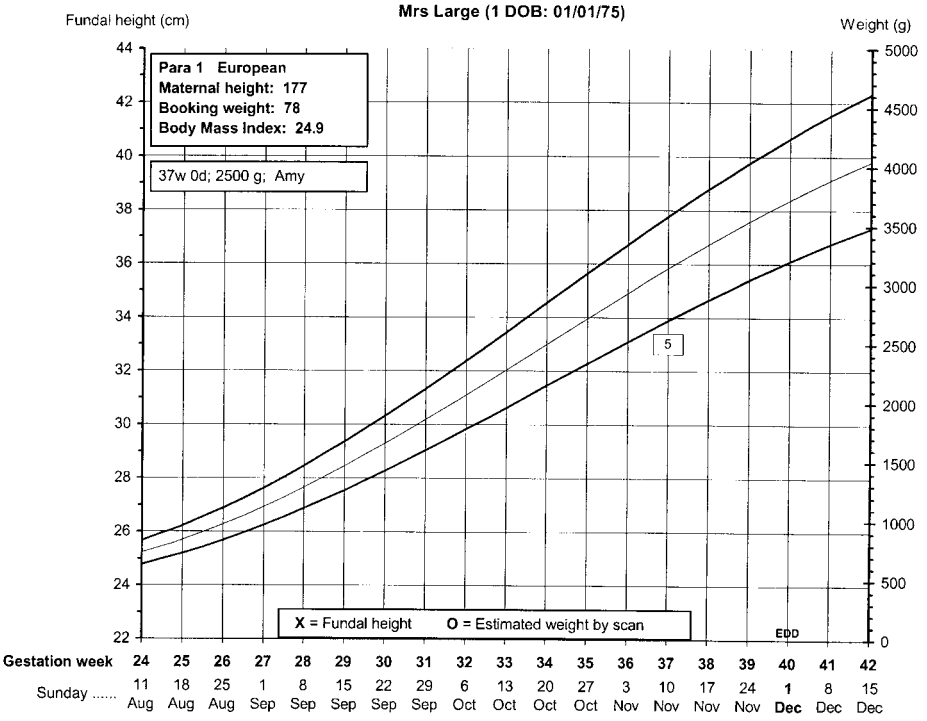
CUSTOMISED ANTENATAL GROWTH CHART

Mrs Small (1 DOB: 01/01/75)



CUSTOMISED ANTENATAL GROWTH CHART

Mrs Large (1 DOB: 01/01/75)



Dutch population, than the local Dutch population standard.[43] Recent analysis of a large Swedish dataset showed that SGA defined by a customised birthweight centile was more closely associated with stillbirths, neonatal deaths or low Apgar scores (< 4) than the unadjusted population centile.[44] In fact, babies considered small by the general Swedish population standard but not by the customised standard did not have a larger risk of stillbirth, neonatal death or low Apgar scores than the average-for-gestational age group (Figure 2). The inference from these findings is that 'customised' SGA is equivalent to FGR. Furthermore, this study confirms that small-normal babies are not at greater risk than normal size babies.

Hence for epidemiological analysis as well as for prospective assessment of fetal growth, individual adjustments of the weight limits reduce false positives and help to identify those babies who are pathologically small. This should lead to improved detection and further investigation (especially by Doppler) of those babies who are at risk.

THE ROLE OF ULTRASOUND BIOMETRY IN THE DETECTION OF FGR

Most instances of SGA babies are missed during routine antenatal care, and only about a quarter of SGA babies are detected before birth.[45,46] In low risk pregnancies, the rate is even lower, with detection only about 15%.[47,48] This suggests that the assignment of the label of 'low risk' at the beginning of pregnancy puts the fetus in that pregnancy at higher risk of the diagnosis of SGA being missed.

Scanning at every antenatal visit has been suggested as worthy of prospective evaluation.[46] However, routine scans in the third trimester have so far not been shown to improve outcome.[49] It is also doubtful whether serial scanning of the whole population would prove cost effective, or even be acceptable with mothers, against a background of more and more antenatal care being carried out in the community.

Detecting poor fetal growth in the general population requires a good screening test, and it would appear that customised assessment can give the measurement and plotting of fundal height a new lease of life. Fundal height measurements are not well taught, not serially plotted and often only recorded in a haphazard fashion against the

Figure 1. Two examples of customised fetal growth curves, printed out using GROW.exe version 4.6.1. The 90th, 50th and 10th centile lines are shown. The charts can be used to plot previous baby weights and ultrasound estimated fetal weight(s) in the current pregnancy. Serial fundal height measurements can also be plotted. The graphs are adjusted to predict the optimal curve for each pregnancy, based on the variables which are entered (maternal height and weight, parity, ethnic group).

In the example, a baby born at 37.0 weeks weighing 2500 g was appropriate for gestational age for Mrs Small (51st centile) but small for Mrs Large (5th centile) as the latter's predicted optimal fetal growth curve is steeper.

The pregnancy details entered are shown on the top left, together with the (computer-)calculated body mass index (BMI). The horizontal axis shows the day and month of each gestation week, calculated by the software on the basis of the EDD entered.

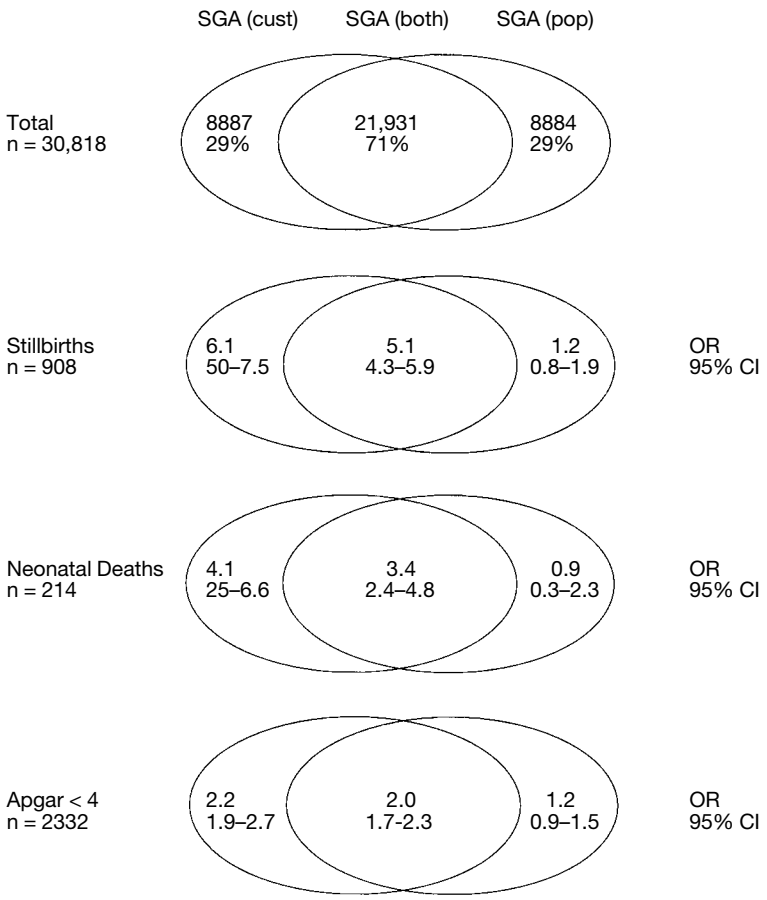


Figure 2 Association between smallness-for-gestational age (SGA) and adverse perinatal outcome in Swedish births 1992-1995.[44] Outcomes: stillbirths, neonatal deaths, and low Apgars (< 4 at 5 minutes). Comparison between definition of SGA as lowest 10 % of births by customised percentile (SGA_{cust}) and the lowest 10% by population based percentile (SGA_{pop}), arranged in three categories: 1: SGA by both methods; 2: SGA by customised centile only; and 3: SGA by population centile only. Odds ratios and 95% Confidence Intervals are shown. Non $SGA_{(cust\ and\ pop)}$ was OR = 1.

number of weeks gestation, under the (false) expectation that fundal height in cm should equal the week of pregnancy. In fact, as is the case with birthweight and fetal growth, fundal height also varies with constitutional factors.[50] A recent study has shown that serial measurement of fundal height in the community, by well trained midwives using a standard measurement technique, plotting on customised growth charts, and clearly defined referral pathways, not only increased the detection of FGR, but also decreased the number of unnecessary referrals for hospital investigations.[51]

The role of ultrasound biometry therefore, in considering the detection of growth restriction in the general maternity population, is to confirm or deny the suspicion of fetal growth problems on the basis of clinical examination including the measure-

ment of fundal height. Amniotic fluid volume is an integral part of the assessment. The scan-based EFW is plotted using a second ordinate axis on the customised fundal height chart. If the EFW is within normal 'customised' limits, surveillance is continued with routine, serial fundal height measurements; if the EFW is below the tenth customised centile line, or if the rate of growth since a previous EFW measurement was slower that that predicted by the customised growth curves, further investigation is recommended. This includes assessment by Doppler and, if the pregnancy continues, serial (i.e. fortnightly) repeat ultrasound biometry. The change in EFW over time is a useful predictor of perinatal outcome.[3]

The timely detection of growth failure is important because of its ever-more apparent links to perinatal morbidity and mortality[52] as well as adverse effects in childhood and later life.[53] Improvements in neonatal care and better surveillance methods of the at-risk fetus place emphasis on better screening and detection of antenatal growth problems. Fetal biometry continues to have an important role, and its most effective use in the third trimester is its provision of an estimated fetal weight which, plotted on customised charts, will give an indication of the growth status of the fetus.

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