Advances in mathematical models of fetal growth: implications for ultrasound practice

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This editorial article reviews some of the mathematical foundations which form the basis of ultrasound screening for fetal growth anomalies and the estimation of gestational age in the first trimester. Recent developments are discussed including individually fitted crown rump length (CRL) curves, customized antenatal growth charts, fetal growth velocity, and computer simulation for fetal growth screening. There is considerable scope for research on improving current clinical practices, as the detection rate for the small for gestational age (SGA) fetus remains at around 50% even in the best units.

Accurate mathematical modelling of fetal growth is a critical aspect in developing clinically useful obstetric ultrasound services. The two main applications are in estimating gestational age and in monitoring fetal growth.

The norms for commonly measured ultrasound parameters such as the CRL, fetal abdominal circumference (FAC), femur length (FL) and biparietal diameter (BPD) are well established, yet relatively few studies specifically address the issue of intrauterine weight gain. This is partly because for the purposes of growth monitoring, many ultrasound departments plot the individual measurements rather than weight estimates. However, several studies suggest that the estimated fetal weight (EFW) is at least as good as the FAC for the detection of the SGA fetus.[1,2]

In this paper we discuss advances in the mathematical modelling of fetal growth and their relevance to ultrasound-based clinical practice.

Gestational age estimation

A first trimester fetal growth curve was first described as a quadratic function of gestational age in Scotland by Robinson and Fleming[3,4] in 1973. This was developed from regression analysis of 214 CRL measurements in women with certain menstrual dates:

GA = 8.052 SQRT(CRL) + 23.73

Using this formula, a single ultrasound measurement of the CRL could estimate the menstrual age of a fetus within a 95% confidence interval of ± 5 days. This continues to be the most widely used formula programmed in ultrasound equipment for gestational age estimation.

Recently we described a novel algorithm derived from the Robinson formula that allows to individually fit CRL growth curves on the basis of two measurements: the K-P algorithm[5]. This model postulates that early fetal growth is a power function of gestational age as follows:

CRL = ((GA – k)/s)^P

Where CRL is in mm, GA is the menstrual age in days, "s" is a scaling constant, "k" is a dating adjustment variable and "P" is the growth coefficient.

The advantage of this method is that it holds the potential to detect deviations from normal early fetal growth, which could be predictive of adverse outcomes. It could also be used to improve the accuracy of gestational age estimation.

Alternative models of fetal growth

Rossavik and Deter[6] proposed a sigmoid function to describe fetal growth of any parameter, including weight. This function is of the form:

$$P = c(t)^{k+st}$$

where P is the ultrasound parameter, t is the duration of growth, k a fixed coefficient determined by the anatomical characteristics, c and s constants related to growth regulatory processes. This function allows the prediction of individual 'normal' growth channels based on two separate ultrasonic examinations before 27 weeks. This model was applied prospectively by Simon et al[7] to a number of parameters including fetal weight. They found a small but significant systematic error of overestimation for most of the parameters and fetal weight; the standard deviation of the errors for fetal weight ranged from 6.7 % to 9.4% , depending on gestation. This is well within the range of the published errors of weight estimation formulae. The advantage of this model is that reference charts are no longer needed; instead, growth disturbances may be detected as deviations from the individually projected standard. The main drawbacks are the need for two ultrasound examinations before 27 weeks' gestation, spaced at least 5 weeks apart, and the need for appropriate computer equipment and software to carry out complex calculations.

Fetal growth velocity has also been studied as a method for detecting intrauterine growth restriction (IUGR). Mondry, et al[8] introduced the concept of z-velocity (or dz/dt) as the change in the z-score over time, as an additional criterion for diagnosing IUGR . This should be zero for normal growth, a negative figure

for IUGR and a positive figure for macrosomia.

We tested this model with a computer program that simulated 50,000 FAC measurements, using on published growth formulas. It was found that longer scan intervals generate lower false positive rates (FPR). A scan interval of three weeks with cut off point dz/ dt < -0.5 generated an optimal FPR of about 2%. ROC analysis showed areas under the curve > 0.74 over the complete range of scan intervals. The positive predictive value of growth arrest as the only diagnostic criterion, however, is too low to recommend it as an exclusive or first diagnostic criterion.

Individually adjusted fetal growth charts

Maternal characteristics such as weight, height, parity and ethnic group are strongly correlated with birth weight at term[9]. Some earlier birth weight standards had tables to discriminate by sex and parity and had correction factors for maternal size[10], but these were too unwieldly for routine use. Computer software has been written that calculates individually adjusted fetal size reference curves, by taking into account these maternal variables and gestational age using a multiple regression model [11]. These customised growth chart plots an individualised antenatal growth standard for fetal weight and also symphysis-fundus height. The growth curve kinetics are derived from averaged ultrasound growth standards, rather than birth weight data.

Retrospective analysis of longitudinal data has shown that these maternal variables are correlated with ultrasound estimated fetal weights[12] . These charts allow the individualised assessment of both size and growth velocity. Adjusting for these maternal variables has been shown to generate birth weight percentiles that are better correlated with neonatal morphometric features of IUGR and macrosomia [13,14] , and low Apgar scores [11,15].

Their use is likely to reduce the false positive rate for the diagnosis of IUGR, and thus unnecessary interventions [16]. A 'customised' definition of SGA was found to be better correlated with adverse perinatal events than the local, unadjusted birth weight standard [17]. These charts have been recommended by the UK Royal College of Obstetricians and Gynecologists[18], and the Royal Dutch Midwifery Association for routine clinical use for many years.

In current practice, screening for abnormal fetal growth is usually carried out by serial ultrasound measurements of fetal growth parameters. However, there is considerable uncertainty on the optimal logistics for this screening procedure. One issue is the optimal time interval between ultrasound scans. Difficulties in carrying out research in this field include the lack of an internationally accepted definition of IUGR, and also measurement errors in ultrasound laboratories.

In order to explore these issues we designed a computer simulation model screening for IUGR [19]. Using published growth functions for the FAC and a coefficient of variation for ultrasound error of 5%, computer software was used to estimate false-positive rates in relation to the time interval between ultrasound examinations. IUGR was diagnosed when there was no observed growth in fetal abdominal circumference between two consecutive examinations. We found a steep increase in false-positive rates as the time interval between examinations was reduced. When the initial scan was performed at 32 weeks, the false-positive rate increased from 3.2% for an interval of 4

weeks to 30.8% for a 1-week interval. At a 2-week interval, the error was 16.9%. There was a significant increase in the false-positive rate as the gestational age at the initial ultrasound was increased. At 28 weeks, the false-positive rate with a 2-week interval was 11.8%, increasing to 24.1% at 38 weeks. The effect of ultrasound error in measuring the FAC was also studied. The false-positive rate increased from 0.8% at an error (C.V.) of 2% to 31.9% at an error (C.V.) of 10%.

The predictions from this model were independently verified in a field study by Owens *et al* [20]. They performed serial ultrasound scans at varying time intervals on 274 low risk women, and compared serial FAC measurements with neonatal morphometry. They found that the likelihood ratios for the diagnosis of IUGR were much higher (>10) using a 4-week scanning interval than a 2-week time interval (<5).

The detection and subsequent surveillance of the SGA fetus remains an ongoing challenge in clinical practice. Even with modern techniques and current guidelines, detection rates are no better than about 50% [2,21].

Computer simulation and mathematical modelling hold great promise in advancing the capabilities of clinical ultrasound laboratories. The advantages of computer modeling in this area include the avoidance of biases due to differences between centers and operators, selection bias, avoidance of errors related to time intervals from scanning to delivery, and large sample sizes. Simulation is already well established for a wide range of educational purposes, but its potential in research has not been fully exploited.

Our current research includes improving the detection of abnormal early fetal growth, environmental influences on fetal growth, and improving the sensitivity of fetal weight estimation formulae for the detection of the SGA fetus.

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