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Defining Normal and Abnormal Fetal Growth: Promises and Challenges

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Abstract

Normal fetal growth is a critical component of a healthy pregnancy and influences the long-term health of the offspring. However, defining normal and abnormal fetal growth has been a long-standing challenge in clinical practice and research. The authors review various references and standards that are widely used to evaluate fetal growth, and discuss common pitfalls of current definitions of abnormal fetal growth. Pros and cons of different approaches to customize fetal growth standards are described. The authors further discuss recent advances towards an integrated definition for fetal growth restriction. Such a definition may incorporate fetal size with the status of placental health measured by maternal and fetal Doppler velocimetry and biomarkers, biophysical findings and genetics. Although the concept of an integrated definition appears promising, further development and testing are required. An improved definition of abnormal fetal growth should benefit both research and clinical practice.

Keywords

biomarker; definition; Doppler; fetal growth; restriction; standard

Normal fetal growth is a critical component of a healthy pregnancy and influences the long-term health of the offspring. Common adult diseases such as type 2 diabetes and cardiovascular conditions have been linked to abnormal fetal growth, particularly fetal growth restriction (FGR).[1] However, the latter has not been clearly defined. The American College of Obstetricians and Gynecologists Practice Bulletin2 states: "*Intrauterine growth restriction is one of the most common and complex problems in modern obstetrics. Diagnosis and management are complicated by the use of ambiguous terminology and a lack of uniform*

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diagnostic criteria.…… Size alone is not an indication of a complication. As a result of this confusion, underintervention and overintervention can occur." Therefore, an objective assessment of normal and abnormal fetal growth has enormous utility in prenatal and neonatal care and outcome-based research. The purpose of this review is to summarize literature on the definition of abnormal fetal growth that go beyond simple fetal size.

Currently, estimated fetal weight (EFW) or birthweight below the 10th percentile of certain reference at a given gestational week is commonly defined as small for gestational age (SGA).[3] EFW or birthweight < 5th or < 3rd percentiles are also used. Regardless of which percentile is applied, a reference or standard is required. A population reference is often established based on a large sample size (ideally representing the underlying population) using a study population including both low-risk and high-risk pregnancies, and both normal and abnormal perinatal outcomes. On the other hand, a standard is usually based on low-risk pregnancies with a normal outcome. When the *population reference* and the *standard* are applied to an individual fetus or infant, interpretation of the findings differs. Use of a *population reference* will yield a relative fetal size in relation to the total population, while a *standard* will assess a fetal size in comparison to normally-grown fetuses. Thus, a *standard* may have more clinical utility than a *population reference.*

1. Commonly used population references and standards

In most clinical and epidemiologic research, birthweight-for-gestational-age references have been commonly used.[3–8] These population references were developed with very large, mostly population-based databases. They provide birthweight percentiles by each gestational week. However, evidence has shown that infants born preterm are more likely to be growth-restricted.[9–17] Thus, their birthweight does not represent all fetuses *in utero* at a given gestational week in preterm. The 10th percentile of the birthweight reference in preterm, for example, is substantially lower than the 10th percentile of the ultrasound-based fetal weight reference.[17–21] Consequently, a population birthweight reference will significantly under-diagnose SGA infants in preterm births.

Numerous ultrasound-based fetal weight references have been published since the early 1980s.[18,19,22–38] Most of them were cross-sectional references based on either retrospective databases[27,29–30,33,37] or prospective data collection.[24,26,32,36,38] In these studies, each pregnant woman contributed data from only one observation. The relatively large sample sizes in these studies provided relatively stable estimates.

However, the quality of the data in retrospective studies remains uncertain. Selection bias (e.g., why a woman received an ultrasound exam at a gestational week when a routine ultrasound exam is not given) may have affected the representativeness of these references to an unknown degree. Prospective studies improve the data quality by confirming gestational age early, scheduling exams systematically and having more strict protocols with the measurements taken by fewer highly trained sonographers. Nonetheless, cross-sectional studies can provide a reference only for fetal size, not fetal growth velocity. Longitudinal studies with repeated measurements on the same fetus are required to study true fetal growth, which can be important for serial ultrasound measurements.[39]

Several longitudinal ultrasound studies have been conducted in the past 25 years. While some of them were rather small[19,22–23,25], others had a reasonable sample sizes, ranging from around 200 [28,31,40] to 634 women.[34–35] Most of the larger studies were performed in Europe, predominantly in white women.

2. The common approach to defining fetal size abnormality

Most clinicians and researchers use SGA and FGR interchangeably. However, this practice is problematic. Fetuses with a weight less than the 10th percentile are not necessarily growth-restricted (they may be constitutionally small but healthy). On the other hand, a weight above the 10th percentile does not necessarily denote "normal" fetal growth. For example, the rate of fetal growth may undergo pathological decline in late gestation. In such a case, the birthweight may still be above the 10th percentile but the fetus may have suffered from growth restriction and incurs an increased risk of perinatal mortality and morbidity.[41–42]

Furthermore, it is well established that normal fetal size at birth varies significantly by race/ethnicity, sex, parity, and maternal size, as well as other genetic and physiological factors.[4, 6] Some studies even suggest that the fetal growth pattern may differ by these factors. For example, based on birthweight data, Overpeck et al.[43] showed that Mexican-American fetuses seem to grow at a similar (or even faster) rate as white fetuses before term but substantially slower after term. This observation is consistent with findings in a longitudinal ultrasound study in Peruvian women.[40] The authors speculated that this phenomenon might be due to the shorter stature of Mexican-American women, which possibly constrains the uterine environment in late gestation.43 Therefore, ultrasound standards, which are mostly based on non-Hispanic white populations, might not be applicable to other races/ethnicities. Likewise, a given fetal size may be considered normal for a short, thin woman but may reflect FGR for a tall, large woman.

3. The individualized approaches to define fetal size abnormality

The key to solving these problems is to develop a method that can identify the growth potential for individual fetuses. Several approaches have been proposed over the past 20 years. Rossavik and Deter [44] first proposed a mathematical model for fetal growth. This model assumes that all fetal biometric parameters follow a definable growth pattern throughout pregnancy. Regression analysis can be used to obtain optimal coefficient estimates for the Rossavik function [$P = c(t)^{k+s(t)}$ where P is the growth of the biometric parameter to be estimated, t is the time in pregnancy when the observation is made, and c, k, and s are the model coefficients]. In a series of papers, the authors demonstrated that this mathematical model fit the growth of several fetal biometric parameters quite nicely.[44–47] Based on this model, the authors developed an individualized growth assessment, in which an individualized fetal growth curve is created based on early ultrasound exams. The assessment requires a minimum of two ultrasound exams separated by 4 to 8 weeks before 26 weeks of gestation.[48–49] This curve is used to predict late fetal growth in the same fetus, i.e., each fetus becomes its own control. Implicitly, this model assumes that fetal growth is not affected by external factors (pathological or environmental) before 26 weeks.

Concerns regarding this approach have been raised that fetal growth abnormality can be demonstrated as early as in the first trimester.[50–52] Although measurements taken early in fetuses with abnormal growth may still be used to predict the weight at term, such a prediction ignores the fact that the fetus has failed to reach its growth potential because the individualized growth curve has been artificially lowered.[53] In addition, ultrasound measurements have inherent errors, random as well as systematic. Such errors can occur in the first and/or second scans, which may affect projection of the weight at term. More importantly, when the errors occur in the opposite directions in two scans in early pregnancy, the deviation of term projection is amplified.[53] So far, the literature has not provided convincing evidence that the Rossavik model is superior to computationally simpler models.[25,28,54,55]

In the 1990s, Gardosi et al.[53,56] proposed a method using customized birthweight norms that incorporated information about fetal growth potential. Based on the premise that birthweight

varies with maternal and fetal physiological parameters (e.g., race/ethnicity, parity, sex, prepregnancy or early pregnancy body mass), they defined a new methodology to calculate optimal fetal weight at each gestational week customized by individual profile. The authors combined birthweight data at 40 weeks of gestation with estimated fetal weight based on the Hadlock estimated fetal weight curve.[24] The ultrasound EFW curves were proportionately adjusted upwards or downwards according to the birthweight at 40 weeks for specific maternal and fetal profiles.

One of the important assumptions of this approach is that different fetuses follow a similar growth pattern to reach their respective birth weights at the end of the normal pregnancy.[53] The proportionality equation ensures that differences in birthweight at term between white and Hispanic infants, for example, are formed gradually throughout pregnancy. However, findings from the study by Merialdi et al.[40] and Overpeck et al.[43] suggest that this assumption might not necessarily be true.

Earlier studies suggested that the method created by Gardosi et al.[53] appeared to have significantly improved the classification of FGR by using the risk of perinatal morbidity and mortality as the gold standard.[57–60] Infants classified by the customized standard as FGR had a significantly higher overall mortality and morbidity than FGR infants classified by the birthweight standard.[58] However, more recent analyses indicated that the large increase in perinatal mortality risk among infants classified as FGR based on the customized standard is largely due to inclusion of more preterm births.[21,61] Some studies have suggested that the advantages that the customized classification *vs* a simple ultrasound-based standard (without adjustment for maternal and fetal characteristics) are rather limited, based on risk of stillbirth and neonatal death.[17,62] Further studies that use less severe outcomes are warranted to assess the clinical utility of this approach.

Over the years, other methods to individualize the growth standard have been proposed.[63–67] The regression method[66–67], in particular, deserves further attention. This method uses a multivariable linear regression model to predict birthweight based on maternal and fetal characteristics (e.g., BMI, sex, gestational age, etc.). The predicted birthweight is considered as the fetal growth potential based on given maternal and fetal characteristics.[67] One of the appealing features of this approach is that the model can essentially adjust for an unlimited number of variables. Each additional variable can improve the ability of prediction to various degrees. However, decisions about the most influential factors and how many variables should be incorporated into the model have yet to be refined. In addition, similar to the approach by Gardosi et al.,[53] this method also uses the growth pattern that was defined by Hadlock et al. [24] for all fetuses before 280 days.[67] Whether such sophisticated models can result in clinically significant improvement in identifying fetal growth abnormalities remains to be demonstrated.

4. An integrated approach to define abnormal fetal growth

An ideal classification of fetal growth should have the ability to distinguish accurately between normal and abnormal growth determined by perinatal morbidity and mortality or even life-course morbidity. It is well established that at most gestational weeks, perinatal morbidity and mortality increase when the fetal size moves farther away from the “optimal” size.[68] However, fetal size alone cannot accurately predict perinatal mortality and morbidity. Integration of other indicators of fetal and placental health may enhance the accuracy in defining FGR.

Two lines of tools have commonly been used clinically to further improve the diagnosis and management of FGR beyond fetal size: antenatal testing modalities for fetal health and for placental function. The former includes fetal heart rate analysis, amniotic fluid volume assessment, biophysical profile and Doppler fetal and maternal vessels evaluation.[69]

Ott [70] found that SGA fetuses with normal Doppler studies showed no increased morbidity when compared with average-for-gestational-age fetuses. The author concluded that SGA fetuses with normal Doppler studies most likely represent constitutionally small, not pathologically growth-restricted fetuses, a conclusion supported by another study.[71] Combining EFW or abdominal circumference and umbilical artery Doppler finding was, therefore, recommended to improve FGR diagnosis.[72] Baschat[73] proposed to combine multivessel Doppler with biophysical variables in fetal testing for FGR. However, a later study found that although each test alone identified fetal deterioration, the two modalities did not show a consistent relationship with each other.[74] An optimal scheme of integrating these modalities remains to be determined.

Since a large proportion of FGR in nonanomalous fetuses is due to placental insufficiency or pathologic lesions[75], the status of placental health may provide some insight on whether the fetus is likely to be constitutionally small or growth-restricted.[76] Furthermore, FGR remote from term is often accompanied by a significant progression in deteriorating placental circulation, redistribution of blood flow and direct cardiac compromise before an abnormal biophysical profile emerges.[77] Thus, the uterine and umbilical artery Doppler ultrasound has been studied as a screening tool for placental and fetal health. The fetal vessels commonly examined include umbilical artery, middle cerebral artery and ductus venosus.[78]

Studies have shown that the ability to predict FGR by 2nd trimester uterine artery Doppler ultrasound may be less than optimal.[79] In the latter study, the sensitivity and specificity of resistance index > the 90th percentile were 53% and 87%, respectively, in low/average-risk population; and 74% and 68%, respectively, in high-risk women. Although assessing the umbilical artery velocity waveform was found to be useful in reducing poor perinatal outcomes in high-risk women[80], the diagnostic performance of the pulsatility index showed a similar level of sensitivity and specificity (45% and 87%, respectively).[81] Issues such as inter- and intra-examiner variations and the location of ultrasound beam proximal to the fetus are likely to decrease the diagnostic performance of the Doppler modality.

Joern and Rath[82] examined both the uterine and umbilical artery Doppler waveforms simultaneously in high-risk pregnancies in the 3rd trimester. They found that if both waveforms were abnormal, the risk of adverse perinatal outcomes was much higher than if only one was abnormal. Kofinas et al.[83] combined umbilical artery resistance and fetal weight deficit and created a compliance-weight deficit index for predicting poor perinatal outcome. They demonstrated that the index had a sensitivity and specificity of 68% and 82%, respectively, in predicting poor perinatal outcomes in high-risk women.

Numerous studies have also shown that certain maternal serum markers are associated with placental function and fetal growth.84 Abnormal levels of alpha-fetoprotein, pregnancy-associated plasma protein A, human chorionic gonadotrophin, estriol, inhibin A and activin A have been associated with not only Down syndrome, but also restricted fetal growth and pregnancy complications.67,[85] More recently, angiogenic and anti-angiogenic factors (vascular endothelial growth factor, placenta growth factor, soluble vascular endothelial growth factor receptor-1 and soluble endoglin) have also been significantly associated with early-onset FGR.[86–88] While the number of studies is still quite limited, combining maternal plasma biochemistry markers with 2nd-trimester uterine artery Doppler measures appears promising for improving prediction of early onset preeclampsia and FGR.[89–90] Abnormal production of these biomarkers may indicate poor placental health status, which is one of the major causes of FGR.[84]

It should be pointed out, however, that most previous studies focused on early “prediction” of pregnancy complications. More research is needed to evaluate whether these biomarkers are

also useful indicators of placental function in late pregnancy and whether they are sensitive and specific enough to be clinically useful. For example, a prospective cohort study showed that pregnancy-associated plasma protein A was a sensitive marker at 17 weeks but not at 25 or 33 weeks, while the level of placental growth factor remained low in FGR pregnancies at all three gestational weeks.[91] Peck et al.[92] found a consistent association between birth weight and estriol levels in the 3rd trimester. Despite a positive correlation (r = 0.32) and strong associations with high estriol levels (odds ratio for highest compared with lowest birth weight quartile = 6.63), the predictive performance of birthweight as a proxy for estriol levels was suboptimal (area under the receiver operating characteristic curve = 0.66).

Finally, new developments in genetic epidemiology could identify DNA polymorphisms potentially associated with fetal growth and size at birth. If valid, these polymorphisms could provide additional markers to improve the predictive ability of screening and diagnostic test aimed at identifying fetuses at risk of abnormal fetal growth. While the literature in this field is still limited, increasing evidence suggests that genetic variations, especially in genes coding for Insulin-like growth factors I and II, Insulin and their receptors might be associated with fetal growth.[93–95]

5. Improving accuracy of estimated fetal weight by ultrasonography

The accuracy of identifying abnormal fetal growth obviously hinges on the accuracy of EFW. Errors in fetal weight estimation may derive from several sources: (1) systematic and random errors in how ultrasound measurements are obtained, which is reflected in inter- and intra-observer variability; (2) combining two dimensional (2-D) measures to approximate three dimensional (3-D) fetal volume, and (3) using fetal volume to estimate fetal weight, which is a measure of mass (volume × density).

Given that lean body mass and fat mass have different densities, it is important to use an appropriate formula to calculate EFW, especially for macrosomia.96 Catalano et al.97 showed that although neonatal fat mass constitutes only 14% of total birthweight, it explains 46% of its variance. Anderson et al.[98] further found that observer error is a relatively minor component of the error in estimating fetal weight (−4.4% to +3.3%); error due to the weight-estimating formulas is a much larger source of error (−18% to +24%). To date, improvements in ultrasound technology have not substantially improved the accuracy of estimating fetal weight.

Scioscia et al.99 examined the accuracy of 35 formulas used to estimate birthweight; 29 gave an overall mean absolute percentage error ≤ 10%. The percentage of birth weight predictions within ±10% and ±15% of actual birthweight were, on average, 69.2% and 86.5%, respectively. Most formulas provided accurate estimates when the actual birthweight was between 2,500 and 3,500 grams. They tended to overestimate fetal weight in fetuses weighing <2,500 grams and underestimate fetal weight in fetuses weighing >3,500 grams, particularly >4,000 grams. Other studies have shown that the antepartum sonographic estimate was no better than the clinical estimate in predicting macrosomia100, while the intrapartum sonographic estimate performs even worse than the clinical estimate.[101–102] Both methods have a mean percent error about 10% of birthweight and a sensitivity for detecting macrosomia (birth weight ≥ 4,000 g) of 60%.[100] Ironically, a self-estimate of fetal weight by parous women was found to be as good as or even better than both clinical and ultrasound estimates.101

Various attempts have been made to include soft tissue measurements (cheek-to-cheek diameter and upper-arm, thigh, abdominal and shoulder subcutaneous tissues) to improve birthweight prediction.[103–108] Other authors also tried to tailor predictions specifically toward SGA or macrosomia.[109–110] These efforts seem to have improved the accuracy of EFW to various degrees but have not been widely adopted in practice.

With the wide availability of 3-D ultrasonography, it seems appropriate to seek new and improved methods to estimate fetal weight. Several studies have demonstrated that fetal thigh and upper-arm volumes are better predictors of fetal weight than conventional 2-D measurements.[111–118] A multivariable approach that incorporates other maternal and fetal characteristics may further improve the estimation.[119–120] Validation of new formulas in a large prospective cohort of patients is warranted.

In summary, an ideal definition of FGR should take into account the growth potential of the fetus, current fetal size, fetal and placental health, and, if available, fetal growth velocity. However, as FGR has a multifactorial etiology,[84] none of these factors alone seems able to discriminate between constitutionally and pathologically small fetuses with great certainty. An integrated diagnosis with multiple modalities appears a promising concept but requires further development and testing. Many basic issues in assessing fetal growth have yet to be addressed, such as whether fetuses of different race/ethnic groups have a similar growth pattern; how fast a normal fetus is supposed to grow at different stages of gestation; and how to improve fetal weight estimation. To meet these basic needs, the National Institutes of Health in the U.S. and the World Health Organization have recently launched multi-country, multi-race/ethnicity studies. An integrated definition building upon these findings could potentially be a useful tool to improve classification of whether or not a fetus is growth-restricted in various countries, races and ethnicities. An ultimate FGR definition is likely to be multi-dimensional, incorporating findings from several modalities.

Due to the ambiguity of current definitions of FGR in clinical practice, management of pregnancies with a suspected FGR fetus varies greatly among hospitals and obstetricians. Baschat and Weiner [71] suggested that antenatal surveillance may be unnecessary in fetuses with suspected FGR if the umbilical artery systolic/diastolic ratio and amniotic fluid volume are normal. If their findings are confirmed in independent prospective studies, reducing the number of antenatal fetal surveillance tests in these pregnancies could yield significant cost savings. Thus, an improved definition of abnormal fetal growth should benefit both research and clinical practice.

Finally, as FGR and fetal programming have been implicated in the causes of common adult diseases, there is a need to identify suboptimal fetal growth in all pregnancies. Indeed, although SGA fetuses/infants have a higher risk of poor outcomes, the vast majority of adverse perinatal outcomes occur in births with a birthweight above the 10th percentile.[121] Thus, SGA infants may only represent the tip of an iceberg. A substantial proportion of FGR infants may be missed simply because their weight is above the 10th percentile. If the integrated diagnosis works well in pregnancies with an SGA fetus, the method might also be applicable to all suspected FGR fetuses.

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