Should We Customize Fetal Growth Standards?

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Key Words

Intrauterine growth restriction • Small for gestational age • Birth weight

Abstract

Several maternal and fetal physiological characteristics account for a substantial proportion of the variation in birth weight. These characteristics can be used to calculate an individualized optimal birth weight and to adjust or 'customize' the birth weight standard. Customized birth weight standards improve the distinction between constitutional and pathological smallness, and there is evidence that this finding can be extrapolated into the fetal period to evaluate intrauterine growth, but further studies are required to evaluate and quantify the effectiveness of customized versus conventional charts in improving the diagnosis of pathological smallness before birth.

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Introduction

Intrauterine growth restriction (IUGR) is defined as a failure of the fetus to reach its growth potential. It is a major contributor to perinatal mortality, being etiologically responsible for 50% of perinatal deaths occurring preterm and 20% at term [1]. This condition is also associated with intrapartum distress, metabolic acidosis, cerebral palsy

[2] and with a wide range of neurocognitive and neurobehavioral disruptions that persist into childhood [3]. Finally, there is growing evidence of the association between growth restriction and metabolic syndrome in adulthood [4]. However, the identification of IUGR remains elusive, since the growth potential could not be precisely quantified. Because most cases of growth restriction are also small for gestational age (SGA), birth weight or estimated fetal weight is used as surrogate. Nevertheless, this could be misleading, since not all small babies are growth restricted and not all growth-restricted infants are small [5]. Thus, the differentiation between IUGR and SGA represents a major challenge in modern obstetrics.

Most instances of true growth restriction correspond with cases of placental insufficiency [6]. Thus, intrauterine placental function evaluation by umbilical artery Doppler is the clinical standard to distinguish between SGA and IUGR [7–9], and there is evidence that umbilical Doppler ultrasound use in these pregnancies improves many obstetric care outcomes and reduces perinatal deaths [10]. While abnormal umbilical Doppler is associated with adverse perinatal and neurodevelopmental outcome [11–14], small fetuses with normal umbilical artery Doppler are considered to represent one end of the normal size spectrum, and the importance of managing them completely differently from true IUGR babies has been stressed [15, 16]. However, growing evidence suggests that a considerable proportion of fetuses with the diagnosis of SGA have true growth restriction in spite of a normal um-

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bilical artery Doppler [11, 12, 17]. This contention seems to be more relevant near term, when most instances of adverse outcome attributable to growth restriction occur in babies with normal umbilical Doppler [18].

The adjustment of the expected birth weight by its determinants has been called 'customization', and it has been proposed to improve the distinction between SGA and IUGR. This paper aims to review the evidence for incorporating customization into clinical practice as a primary tool to better define IUGR both prenatally and in the neonatal period.

Physiological Factors Influencing Birth Weight

Gestational age is a major determinant of fetal growth, with an almost linear effect throughout the third trimester resulting in an average weight gain of about 25 g per day [19, 20]. When pregnancies are not dated by ultrasound, growth modeling results in an artifactual flattening beyond 40 weeks, because the proportion of misdated pregnancies in this period is substantial. Apart from the length of gestation, fetal growth is significantly influenced by many other fetal and maternal physiological factors such as sex, parity, maternal height and weight and ethnicity. The effect of fetal gender on birth weight differs across studies (232–310 g at 280 days) [21–28]. Most of this variability is secondary to absolute differences in the average birth weight of the population on which each study was carried out. The effect of maternal weight at booking has also been found positively associated with birth weight [21–28], with a negative effect at both extremes (underweight and obesity) [26]. Similarly, maternal height also has a positive correlation with a plateau effect at the upper extreme. On average, women with a previous delivery have babies 87–110 g heavier [21–28], but this effect decreases at higher parities, and some series have even demonstrated a negative effect in grand multiparae women [22]. Ethnicity has also an important effect on fetal growth [29] and birth weight [21–26, 28, 30]. Graafmans et al. [30] compared birth weights in 7 Western European countries and found substantial differences between countries. They concluded that to improve the identification of growth-restricted infants, population-specific standards for birth weight should be developed. However, deriving standards based on geography or ethnicity alone would neglect the effect on fetal growth of other maternal and fetal characteristics secondarily associated with ethnicity. Not only ethnicity could be considered a measure of 'biological' difference,

since other social and environmental variables greatly differ between different ethnicities.

Overall, gender, parity, maternal height, weight and ethnicity explain a 20–35% of the variability of birth weight at term [21–26]. In addition, other maternal physiological variables such as age [22], educational [31], socioeconomic [32] and marital status [33] or altitude of the area of residence [34] also have a significant albeit less relevant effect on birth weight. Similarly, paternal height has been demonstrated to affect birth weight [35], but this effect is relatively minor and the information is often not available.

Pathological Factors Influencing Fetal Birth Weight

Cigarette smoking during pregnancy is a strong dose-dependent risk factor for SGA [36]. Smoking alone independently explains 9 and 12% of preterm and term cases of SGA [37] and has been highlighted as the single largest modifiable risk factor affecting the growth of unborn infants in developed countries [38]. Other major prenatal pathological conditions that have relevant effects on fetal growth are diabetes and hypertensive disorders [22, 39]. In addition, congenital malformations are frequently associated with impaired fetal growth [40]. Finally, infants born preterm have a higher incidence of SGA than infants born at term. This is not only because IUGR is a common indication for delivery before term. Indeed, spontaneous preterm delivery or premature rupture of membranes are consistently associated with SGA [27, 41–43] and both conditions share many risk factors, such as obesity, smoking or black ethnicity [42]. It has been speculated that the initiation of parturition is a fetal adaptive response to placental insufficiency.

This latter aspect makes it important to construct standards on fetuses rather than on neonates. The need to base preterm weight standards on fetal rather than on neonatal weights is illustrated in figure 1. Ultrasound-estimated fetal weights are plotted from 480 low-risk pregnancies having a routine third trimester ultrasound. Whereas population-based standards [44] only show 1.7% of the population as SGA (below the 10th centile), fetal standards [23] identified 9.7% as SGA.

Methodological Aspects

The adjustment of the expected birth weight by its physiological and pathological determinants has been called 'customization' since the original report of this

Fig. 1. Plot of 480 estimations of fetal weight measured at routine third trimester ultrasound in a low-risk Spanish population, with 10th and 90th centile lines based on the local neonatal weight standard (dotted lines) and the fetal weight standard, adjusted to a Spanish population average (maternal height 161 cm, weight 59 kg). The graphs show that while only 8 cases (1.7%) were found to be SGA by the neonatal weight standard, the fetal weight standard identified 45 cases (9.4%) as SGA.

method [45]. Several standards for birth weight customization have been published, and some methodological aspects are noteworthy.

Design

Ultrasound dating is much more accurate than menstrual dating [46]. Because the distribution of menstrual dating error is positively skewed, and it is more frequent to have a long first menstrual phase than a short one, there is a systematic overestimation of gestational age by menstrual dating. This results in many birth weight points at term appearing at later gestational ages than they actually should be, leading to an artifactual flattening of the growth curve at term and setting artificial low standards that result in an underestimation of growth restriction in this period. Most published standards have included only ultrasound-dated pregnancies [22–24, 26–28].

The importance of using standards free from pathology has been stressed; otherwise, assessment of fetal growth is done against an inaccurate optimal weight. Therefore, exclusion of mothers with known risk factors for either low (hypertension, congenital anomalies, multiple pregnancies and preterm deliveries) or high birth weight (diabetes) is warranted. Controversy exists whether smokers should be excluded. While it seems logical to exclude these women to get standards reflecting optimal

rather than real birth weight, most series [22, 24, 28, 45, 47] have included smoking in the model since it is highly correlated with several of the other covariates [48]. Hence, its exclusion may skew the population towards a non-smoker profile that may not be representative of the general population. Despite its inclusion to construct standards, it is agreed [49] that the smoking coefficient should not be used to prospectively adjust the optimal weight. Although including this negative coefficient would likely improve the prediction, not adjusting for this factor improves the identification of growth restriction due to smoking or other causes. Thus, the expected optimal weight is calculated as if each mother is a non-smoker.

Analysis

Although several standards have been published [22–28, 50], methodological approaches to construct customized standards have remained very similar to the original report [45]. In short, optimal birth weight at term is modeled by linear regression, which takes into account the above-mentioned biological characteristics. The formula of Hadlock et al. [51], a model that predicts fetal weight for gestational age, has been the most widely used standard to individually derive optimal fetal weight for each gestational age. Other authors have used other formulae to extrapolate backwards the optimal weight with very similar results [22]. From that optimal fetal weight, the

Fig. 2. Examples of customized charts using Gestation Related Optimal Weight software version 7.5.1 (www.gestation.net). The charts can be used to plot previous baby weights and ultrasound-estimated fetal weights in the current pregnancy (right Y axis) as well as fundal height measurements for serial assessment (left Y axis). The horizontal axis shows the day and month of the start of each week of gestation, calculated by the software on the basis of the estimated date of confinement. The 3 curves on the chart are the 50th centile and the 10th and 90th centile limits, representing the predicted range of optimal growth for each pregnancy, after adjustment for maternal height, weight, parity and ethnic origin. The pregnancy details are shown on the top left of the chart, with maternal height in cm and maternal weight in kg. The example shows 2 mothers – ‘Mrs. Small’ and ‘Mrs. Large’ – with 2 different sets of characteristics. A previously born baby girl weighing 3,000 g at 40.0 weeks is illustrated as being of average size (49th birth weight centile) for Mrs. Small (**a**), but SGA (5th centile) for Mrs. Large (**b**). DOB = Date of birth; EDD = expected date of delivery.

limits are calculated as a proportion of the standard variation at term, which assumes normal distribution and constant standard deviation throughout the third trimester.

Software for calculating customized fetal growth standards for different populations are freely available at www.gestation.net [52]. Figure 2 shows customized fetal growth charts for 2 different women, illustrating the concept of customization.

Evidence for Customizing the Birth Weight Standard

The use of customized birth weight standards has been demonstrated to be superior over population-based standards in the prediction of an abnormal 5-min Apgar score, hospital stay length, admission to the intensive care unit, hypoglycemia, need for neonatal resuscitation, neurological adverse outcome and perinatal death [22, 27, 41, 47, 50, 53, 54]. On the other hand, those neonates with a normal customized birth weight have been found to have a perinatal outcome comparable with the general population [27, 47, 54, 55], even in those SGA cases only according to population standards. The inference of these findings is that SGA according to customized standards and growth restriction are equivalent, and it has been claimed that customized SGA could be used as reliable proxy of growth restriction [49]. Figueras et al. [12] analyzed the relationship between umbilical artery Doppler and customized standards and concluded that normal antenatal umbilical artery Doppler cannot be taken as an indicator of low risk in pregnancies where the fetus is SGA according to customized standards. The adverse effects associated with customized SGA have also been demonstrated for long-term consequences such as cerebral palsy [56] and metabolic disturbances as impaired insulin secretion [57].

It has been suggested that the superiority of customized over population-based standards is mainly due to the former method classifying more preterm deliveries as SGA, which could account to a large extent for the adverse perinatal outcome [41, 58]. However, this argument fails to explain the reported increased risk of stillbirth of customized SGA [27, 47, 53]. It has also been argued that the limitation of population standards in the prediction of adverse outcome in preterm neonates is overcome when fetal instead of neonatal standards are used [58]. However, in pregnancies with neonatal morbidity, customized standards identified 34% more pregnancies as abnormally grown than fetal growth standards [22], fur-

ther supporting the concept that customized SGA babies are intrinsically at increased risk, regardless of gestational age. In a recent study of customized and uncustomized fetal weight standards, various maternal size and parity subgroups were examined, with the finding that SGA by the customized standard shows a consistently and significantly higher perinatal mortality risk than when SGA is defined by the population standard [59].

In conclusion, there is good quality evidence (grade II) to recommend adjusting birth weight for maternal and pregnancy variables to improve the distinction between constitutional and pathological 'smallness'.

Evidence for Customizing Fetal Growth Charts

Although it has been demonstrated that some maternal and fetal characteristics have an association with fetal ultrasound biometry [29, 60], there are no published customized standards derived from estimated fetal weight. However, the predicted 'term optimal (birth)weight' can be backwardly extrapolated into the intrauterine period, by combining it with a 'proportionality' curve derived from an in utero fetal weight standard [7]. Such antenatal growth curves have been found to reflect variation in population subgroups in low-risk [19] as well as high-risk [61] populations. By adjusting for individual variation, customized growth curves reduce false-positive diagnoses of fetal growth restriction [62] and are likely to reduce intervention: in a multi-ethnic population in the UK, 109 women were induced for suspected IUGR diagnosed on the basis of conventional fetal growth charts; retrospective application of customized charts found that the majority of cases (58%) were in fact pregnancies where the babies' weight was within the normal weight range if assessed by customized charts [63]. In a Dutch study of 220 women with an elevated risk of placental insufficiency, serial ultrasound estimations of fetal weight plotted on customized standards resulted in a sensitivity for growth restriction of 83% for a false-positive rate of 11% [55]. However, no comparison was made with uncustomized, population-based standards. Another uncontrolled study [64] found customized centiles only moderately useful (sensitivity 42%, specificity 90%) in the prediction of IUGR, using a lower-quartile neonatal ponderal index as outcome indicator. However, the investigators did not use the customized growth chart for serial assessment, but only calculated a centile from the last measurement. Thus, the accuracy of prediction was likely to have been a function of the accu-

racy of ultrasound-estimated fetal weight. Further work is needed to assess the usefulness of customized fetal weight curves.

In many settings, fundus-symphysis height is used as a screening tool for fetal growth assessment. Fundal height measurement has been found to be subject to the same individual variation as birth weight and fetal weight [65]. A prospective nonrandomized controlled trial in the UK [66] found use of customized fundal height assessment improved the antenatal detection of fetal growth restriction (29–48%) and, moreover, reduced the number of unnecessary referrals for ultrasound. The study was not powered to assess the effect on pregnancy outcome, but a larger study in Sweden has shown that increased antenatal detection of SGA per se does result in a lower risk of adverse outcome [67].

Conclusions

Maternal and fetal physiological characteristics have been described which account for a substantial part of the variation in birth weight at term. These characteristics can be used to calculate an individualized optimal weight. There is good quality evidence to recommend adjusting for maternal and pregnancy variables to improve the distinction between constitutional and pathological ‘smallness’ amongst fetuses and neonates. While observational studies also support antenatal application for the assessment of fetal growth, further prospective studies are needed to assess and quantify the effectiveness of customized versus conventional charts in reducing adverse pregnancy outcome.

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