Review

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Establishing Chinese Fetal Growth Standards: Why and How

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Abstract

Choosing a fetal growth standard or reference is crucial when defining normal and abnormal fetal growth. We reviewed the recently published standards and compared them with a customized fetal growth chart based on a nationwide population in China. There were substantial discrepancies in the fetal growth pattern, suggesting that these standards may not be applicable to Chinese fetuses. Developing a Chinese-specific standard may better meet our clinical requirements. We also discuss the steps to establish a Chinese fetal growth standard and the potential challenges, including regional disparities and accuracy of sonographic estimated fetal weight. Standardized ultrasound measurement protocol and the introduction of new ultrasonography technology may be helpful in developing a more precise standard than existing ones for the Chinese population.

Keywords: Growth charts; Fetal; Standard; Accuracy; Estimated fetal weight

Introduction

Normal fetal growth is crucial to a healthy pregnancy and the long-term outcomes of the offspring. Abnormal fetal growth is associated with perinatal mortality and morbidity.[1,2] It is also a risk factor for late-onset chronic diseases such as cardiovascular conditions and type 2 diabetes mellitus later in life.[2] Abnormal fetal growth is usually diagnosed as small-for-gestational age (SGA), large-for-gestational age (LGA), fetal growth restriction (FGR), or macrosomia.[3,4] SGA and LGA are commonly defined as fetal size , e.g., estimated fetal weight (EFW) < the 10th percentile or > the 90th percentile of a reference population.[4] Therefore, the choice of a reference or standard will influence the proportion of fetuses that are identified as SGA or LGA and the accuracy of defining normal and abnormal fetal growth.[5] Currently, there is no universally accepted growth chart, especially when it comes to different ethnicities and countries. The objective of this review is to compare the recently published fetal growth standards and answer the following two questions: (1) Is it necessary to develop a Chinese standard?, and (2) What are the necessary steps to establish our own standard?

Recently published international fetal growth standards

Numerous fetal weight references and standards have been published since the 1980s.[6–20] More recently, three contemporary, longitudinal growth charts were developed: the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Fetal Growth Standard, International Fetal and Newborn Growth Consortium for the 21st Century Fetal Growth Standard (INTERGROWTH-21st), and the World Health Organization (WHO) Fetal Growth Charts.[18–20] These three standards share some common features. They were all based on multi-center, prospective studies which included low-risk pregnancies with a normal outcome, though the specific inclusion and exclusion criteria varied. To establish fetal growth trajectories, serial ultrasound measurements were taken, rigorous quality assurance and quality control were performed, and flexible analytic approaches were adopted.[18–20]

The main differences among the three fetal growth standards are presented in Table 1. One of the key differences lies in the philosophical belief on whether fetuses with various genetic and environmental backgrounds have the same normal fetal growth trajectory. The NICHD standards highlighted the racial/ethnic variation and established separate curves for four U.S. racial/ethnic groups (White, Black, Hispanic, and Asian).[19] The INTERGROWTH-21st and WHO fetal growth studies started with the same premise that there would be a single curve for international use but concluded with different recommendations for clinical management.[18,20] The WHO standard demonstrated variations between countries and suggested that growth

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Table 1

Main differences among the NICHD, INTERGROWTH-21st, and WHO fetal growth charts.

Items	Fetal growth charts		
	NICHD	INTERGROWTH-21st	WHO
Aims	Developing fetal growth standards for four U.S. racial/ethnic groups	Providing international EFW standards available for use worldwide	Providing fetal growth charts intended for worldwide use
Dates	2009–2013	2009–2014	2009–2015
Location	12 U.S. sites (New York (2 sites), New Jersey, Delaware, Rhode Island, Massachusetts, South Carolina, Alabama, Illinois, and California (3 sites))	Eight countries (Brazil, China, India, Italy, Kenya, Oman, United Kingdom, and United States)	Ten countries (Argentina, Brazil, Democratic Republic of the Congo, Denmark, Egypt, France, Germany, India, Norway, and Thailand)
Sample size	1737 (Non-Hispanic white: 481; Non-Hispanic black: 426; Hispanic: 488; Asian/Pacific Islander: 342)	2404	1362
Ultrasound scans	The first screen was at 8^{+0} week to 13^{+6} week. Then women were randomized among four ultrasound schedules with measurements taken at five visits from 16 week to 41 week	Every five weeks from 9–14 weeks' until 40 weeks' gestation	The first visit was between 8^{+0} and 12^{+6} week, and subsequent visits were at approximately 4-week (±1 week) intervals at 14, 18, 24, 28, 32, 36, and 40 week
EFW formula	1985 Hadlock formula	$\log(EFW) = 5.084820 - 54.06633 \times (AC/100)^3 - 95.80076 \times (AC/100)^3 \times \log(AC/100) + 3.136370 \times (HC/100)$, where EFW is expressed in g, AC and HC in cm, and the log function designates the natural logarithm	1985 Hadlock formula
Suggestions for clinical use	Racial/ethnic-specific standards improve the precision in evaluating fetal growth	INTERGROWTH-21st standards describe optimal growth and can be used to assess both individuals and populations	WHO charts may need to be adjusted for local clinical use

AC: Abdominal circumference; EFW: Estimated fetal weight; HC: Head circumference; INTERGROWTH-21st: International Fetal and Newborn Growth Consortium for the 21st Century; NICHD: The Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO: The World Health Organization.

charts should be adjusted and refined to fit diverse populations. However, INTERGROWTH-21st argued against using local references for a given country or ethnic group in multicultural societies[18,21] despite its own data showing that under optimal nutritional and socioeconomic conditions, birthweight at term could differ by several hundred grams from country to country.[22]

The need for establishing Chinese fetal growth standards

Although INTERGROWTH-21st advocated a one-size-fits-all approach, there were doubts about its suitability for diverse populations. When applied to a Chinese population in Hong Kong(China), the INTERGROWTH-21st standard led to over-diagnosis of fetal smallness, particularly when using head circumference and femur length measures.[23] On the contrary, when compared with the proportion identified as SGA in a Canadian population based on the Canadian reference, the proportion considered as SGA by INTERGROWTH-21st was lower.[24] On the other hand, for LGA, the proportion was considerably higher for the Canadian population when adopting INTERGROWTH-21st standard.[24] An Australian population-based study evaluated three international standards (Hadlock, INTERGROWTH-21st and WHO) and revealed significant differences in the SGA and LGA classifications, and poor performance of these standards in predicting adverse outcomes.[25] Thus, the one-size-fits-all approach may result in misclassification of fetuses as SGA and LGA in local populations.

As well-controlled, prospectively measured fetal growth parameters in a representative sample of fetuses in China are still not available, it is challenging to ascertain if the growth of Chinese fetuses follows the global fetal growth curves. Therefore, we borrowed the adjustable global reference proposed by Zhang *et al*.[26] to create a prototype of EFW standard for comparison and illustrative purposes. Specifically, Zhang *et al*. made a generic reference that could be easily adapted to local populations based on the fetal-weight reference developed by Hadlock *et al*. and the notion of proportionality proposed by Gardosi *et al*.[9,26,27] Customization can be readily achieved by determining the mean birthweight and the standard deviation of birthweight at 40 weeks (40^{+0} to 40^{+6}).[26] Data from the China Labor and Delivery Survey (CLDS) was used in this customized curve. The CLDS was a multi-center, hospital-based cross-sectional survey conducted throughout China between March 1, 2015, and December

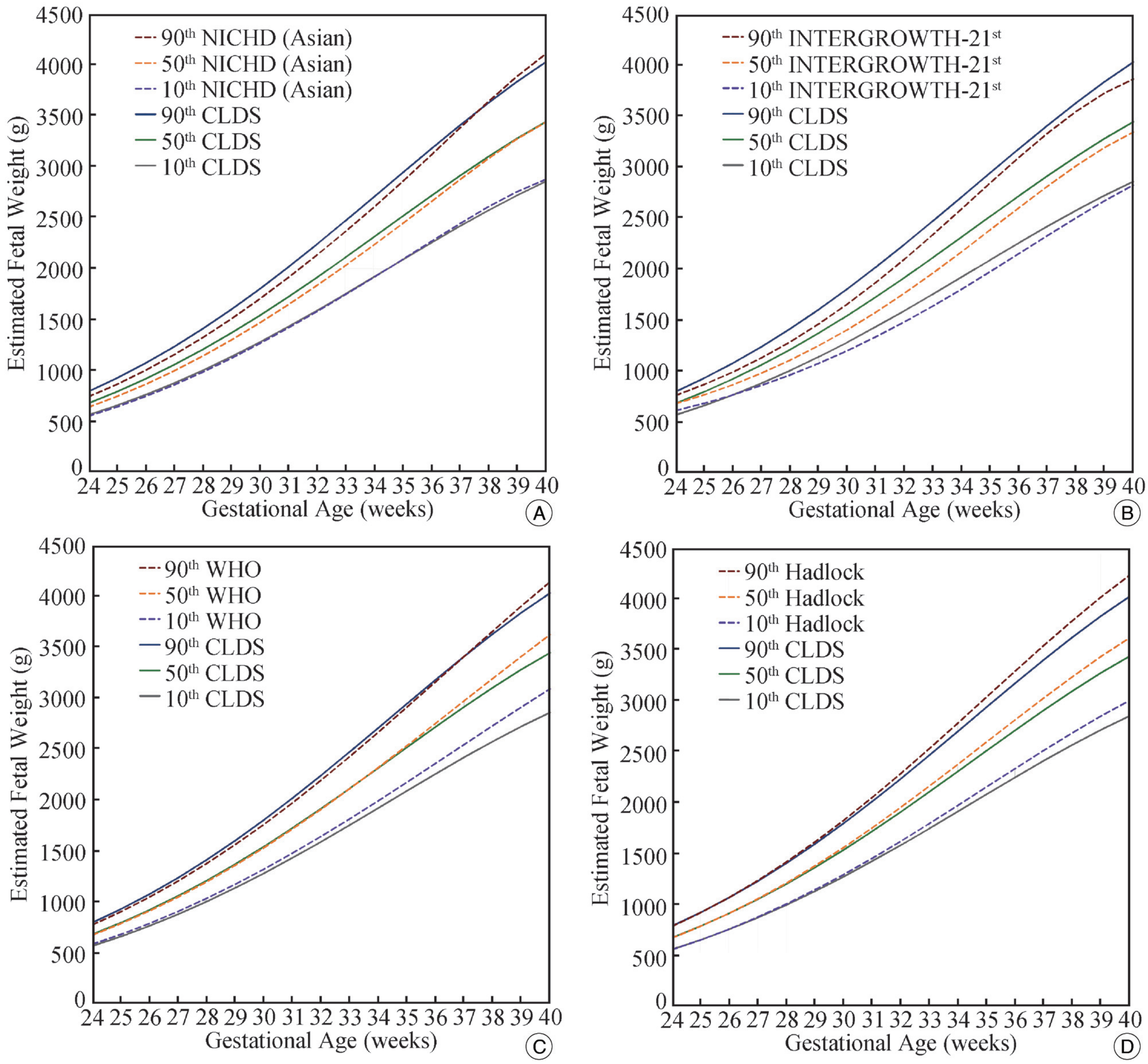

Figure 1. Comparison between the customized fetal growth chart based on the CLDS dataset and A NICHD Asian-specific standard, B INTERGROWTH-21st standard, C WHO standard, D Hadlock 1991 reference. CLDS: The China Labor and Delivery Survey; INTERGROWTH-21st: International Fetal and Newborn Growth Consortium for the 21st Century; NICHD: The Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO: The World Health Organization.

31, 2016. Hospitals with at least 1000 childbirths per year from 25 provinces and autonomous regions across the Chinese mainland were selected to describe the national labor and delivery situation.[28,29] After excluding pregnancies with complications including but not limited to hypertensive disorders and diabetes, the mean birthweight of live-born singleton neonates with an Apgar score > 7 (n=14,793) at 40 weeks in the CLDS was (3438±493) g.[30] The 10th, 50th, and 90th percentiles of the growth charts are presented in Figure 1 and Tables 2–4. Upon comparing the prototype of Chinese fetal growth charts with the aforementioned commonly used standards, we could see the substantial differences in the EFW percentiles (Fig. 1). It should be noted that the differences may result from both the study population and the methodology to establish the charts. The customized curve based on the CLDS data is only an interim step towards better Chinese-specific growth charts. Additionally, the comparison among the curves was constrained by the lack of complete data from other studies. No formal statistical testing could be possible. Therefore, graphical presentation of weight percentiles for visual inspection was adopted in this review and the comparison between curves can only provide a preliminary observation and suggestion, rather than a definite justification.

The NICHD Asian-specific standard performed closely at the 10th percentile to our Chinese curve but differed at the 50th and 90th percentiles (Fig. 1A). When compared with the INTERGROWTH-21st and WHO standards,

Table 2

The 10th percentiles for estimated fetal weight by gestational age for the customized fetal growth chart based on the CLDS dataset, NICHD Asian-specific standard, INTERGROWTH-21st standard, WHO standard and Hadlock 1991 reference.

	Estimated fetal weight (g), 10th percentiles				
Gestational age (weeks)	CLDS	NICHD (Asian)	INTERGROWTH-21st	WHO	Hadlock
24	559	546	602	576	556
25	652	637	674	673	652
26	756	740	757	780	758
27	871	853	849	898	876
28	995	978	951	1026	1004
29	1130	1114	1065	1165	1145
30	1273	1260	1190	1313	1294
31	1425	1414	1326	1470	1453
32	1583	1574	1473	1635	1621
33	1747	1740	1630	1807	1794
34	1914	1911	1795	1985	1973
35	2082	2085	1967	2167	2154
36	2249	2262	2144	2352	2335
37	2412	2437	2321	2537	2513
38	2568	2604	2495	2723	2686
39	2716	2752	2663	2905	2851
40	2852	2873	2818	3084	3004

CLDS: The China Labor and Delivery Survey; INTERGROWTH-21st: International Fetal and Newborn Growth Consortium for the 21st Century; NICHD: The Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO: The World Health Organization.

neither international chart resembled our curve. The 10th, 50th, and 90th percentiles of the INTERGROWTH-21st standard were consistently lower than those in our local reference (Fig. 1B). In the third trimester, the 10th percentile of the WHO standard was much higher than that determined in our population (Fig. 1C). We also compared our curve with the Hadlock 1991 reference and found that our curve was consistently lower than the Hadlock curve, which was based on a White population in the U.S. (Fig. 1D).[9]

Table 3

The 50th percentiles for estimated fetal weight by gestational age for the customized fetal growth chart based on the CLDS dataset, NICHD Asian-specific standard, INTERGROWTH-21st standard, WHO standard and Hadlock 1991 reference.

	Estimated fetal weight (g), 50th percentiles				
Gestational age (weeks)	CLDS	NICHD (Asian)	INTERGROWTH-21st	WHO	Hadlock
24	673	634	669	665	670
25	786	740	756	778	785
26	912	859	856	902	913
27	1050	990	969	1039	1055
28	1200	1136	1097	1189	1210
29	1362	1293	1239	1350	1379
30	1535	1463	1396	1523	1559
31	1718	1642	1568	1707	1751
32	1909	1830	1755	1901	1953
33	2106	2026	1954	2103	2162
34	2307	2229	2162	2312	2377
35	2510	2438	2378	2527	2595
36	2711	2653	2594	2745	2813
37	2908	2869	2806	2966	3028
38	3097	3077	3006	3186	3236
39	3275	3269	3186	3403	3435
40	3438	3434	3338	3617	3619

CLDS: The China Labor and Delivery Survey; INTERGROWTH-21st: International Fetal and Newborn Growth Consortium for the 21st Century; NICHD: The Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO: The World Health Organization.

Table 4

The 90th percentiles for estimated fetal weight by gestational age for the customized fetal growth chart based on the CLDS dataset, NICHD Asian-specific standard, INTERGROWTH-21st standard, WHO standard and Hadlock 1991 reference.

	Estimated fetal weight (g), 90th percentiles				
Gestational age (weeks)	CLDS	NICHD(Asian)	INTERGROWTH-21st	WHO	Hadlock
24	788	737	751	765	784
25	920	859	858	894	918
26	1067	997	980	1038	1068
27	1228	1149	1119	1196	1234
28	1404	1318	1276	1368	1416
29	1594	1501	1452	1554	1613
30	1796	1698	1647	1753	1824
31	2010	1908	1860	1964	2049
32	2234	2129	2089	2187	2285
33	2465	2360	2332	2419	2530
34	2700	2600	2583	2659	2781
35	2938	2851	2838	2904	3036
36	3173	3111	3089	3153	3291
37	3403	3376	3326	3403	3543
38	3625	3637	3541	3652	3786
39	3833	3884	3722	3897	4019
40	4025	4105	3858	4135	4234

CLDS: The China Labor and Delivery Survey; INTERGROWTH-21st: International Fetal and Newborn Growth Consortium for the 21st Century; NICHD: The Eunice Kennedy Shriver National Institute of Child Health and Human Development; WHO: The World Health Organization.

Collectively, it is imprecise to simply apply these existing standards or references to the Chinese population. Using country as a proxy for the local ethnic mix has been found to be much more important than other variables.[26] Given these discrepancies between the study population in the universal standards and our own population, we suggest that a national fetal growth standard may be constructed for local use.

In the past two decades, several fetal growth charts have been developed for the Chinese population.[31–41] Some of them were created especially for twins[31,32] or for growth velocity trajectories,[33] which are beyond the scope of our review. A comparison of eight other charts is presented in Table 5. Of these eight, two were based on a retrospective design,[34,41] which may be limited by selection bias. Five studies collected data prospectively,[35,36,38–40] but four of them used cross-sectional data that included only one ultrasound examination at a random gestational age,[36,38–40] which can only indicate the size rather than the growth of a fetus. Only the prospective fetal growth standards created by Xu *et al.*[35] used longitudinal measurements. They created both unconditional (cross-sectional) and conditional (longitudinal) standards for use in an ethnic Chinese population, but they did not assess their performance in detecting adverse birth outcomes.[35] Furthermore, their curves were based on a population living in Singapore, where the environmental conditions are not the same as those in China. While three charts were developed from multi-center studies,[37,38,40] two of them were derived from a local population in a specific region or province, which may be insufficient to represent the general Chinese population.[37,38] The remaining one was conducted in 14 tertiary hospitals throughout the country.[40] Nevertheless, the distribution of observations across the reference ranges was uneven in this study, which may impact the quality of data. As such, we suggest that a national fetal growth standard should be derived from a prospective, multi-center, and longitudinal study that takes geographic regions into account.

How to establish a Chinese fetal growth standard

Before discussing how to construct our own standard, it is critical to draw a distinction between fetal growth standards and fetal growth references. References are descriptive charts based on populations that include both low- and high-risk pregnancies with both normal and abnormal perinatal outcomes. On the other hand, standards are normative charts based on low-risk pregnancies with a normal outcome.[3,21,42] A standard may have more clinical utility for a country than a reference, because it describes how fetuses should grow when nutritional and environmental conditions are optimal.[42]

On the basis of this definition, a crucial step in creating a national fetal growth standard is to select healthy pregnant women who are at low risk for adverse maternal and perinatal outcomes. The standard should be derived from a prospective, multi-center study that covers most areas of China. All centers should be under the supervision of an ultrasound quality-control center and a data management center. The sonographers participating in the study need to be trained and certified, and have their scans periodically assessed for quality control. Longitudinal data collection with repeated measurements is required to study true fetal growth. It is important to collect a validation dataset concurrently. Lastly, advanced

Table 5

Comparison among fetal growth charts for Chinese population.

Fetal growth charts	Aims	Location	Design	Sample size	Ultrasound scans	EFW formula
Lei *et al.* 1998[38]	Constructing growth curves for 13 fetal growth measures	Five obstetric ultrasonography labs in Central-South China	Prospective	5496	Only one routine examination between 16 and 40 weeks was included for each subject	EFW was not calculated
Leung *et al.* 2008[39]	Constructing reference charts for BPD, HC, AC and FL	One university obstetric unit in Hong Kong, China	Prospective	709	For each subject, only one ultrasound scan was arranged randomly between 12 and 40 weeks	EFW was not calculated
Jiang *et al.* 2013[37]	Constructing local reference charts for BPD, AC and FL	Five hospitals in Shaanxi, China	Cross-sectional	6832	One set of biometric measurements between 16 and 41 weeks was randomly selected	EFW was not calculated
Xu *et al.* 2015[35]	Creating unconditional (cross-sectional) and conditional (longitudinal) standards	Two major public hospitals in Singapore	Prospective; longitudinal	313	The first screen was at 11–12 weeks, and subsequent visits were at 19–21, 26–28 and 32–34 weeks	1985 Hadlock formula
Zhang *et al.* 2017[40]	Constructing reference charts for BPD, HC, AC, FL	14 tertiary hospitals in Chinese mainland	Prospective; cross-sectional	7553	Only one examination between 15 and 40 weeks was included for each subject	EFW was not calculated
Cheng *et al.* 2018[36]	Developing EFW references for local population and comparing them against the INTERGROWTH-21st and WHO Charts	One university obstetric unit in Hong Kong, China	Prospective; cross-sectional	970	The first screen was at 11–13 weeks. A second visit was randomly allocated between 20 and 39 weeks	1985 Hadlock formula and INTERGROWTH-21st formula (shown in Table 1)
Bao *et al.* 2021[34]	Establishing a personalized fetal growth curve model	One hospital in Beijing, China	Retrospective	3093	Retrospective analysis of ultrasound results at 22–40 weeks	Gardosi formula
Lun *et al.* 2021[41]	Constructing reference charts for BPD and HC	Two hospitals in Guangdong, China	Retrospective; cross-sectional	18,269	Retrospective analysis of ultrasound results at 13–40 weeks	EFW was not calculated

AC: Abdominal circumference; BPD: Biparietal diameter; EFW: Estimated fetal weight; FL: Femur length; HC: Head circumference. INTERGROWTH-21st: International Fetal and Newborn Growth Consortium for the 21st Century; WHO: The World Health Organization.

statistical methodology is indispensable for appropriate data analysis.

Challenges and future directions

Two main challenges are envisaged while constructing a Chinese fetal growth standard. First, the regional disparities in birthweight are substantial. According to the data from the CLDS, the mean birthweight at 40 weeks varied from 3276 g in Yunnan Province to 3538 g in Heilongjiang Province. In addition, differences were also observed between rural and urban areas and inland and coastal regions.[43–45] Both environmental factors (such as maternal nutrition status and perinatal health care) and genetic backgrounds may have contributed to these regional disparities.[43,44] Consequently, the national chart may need adjustment and refinement to increase their diagnostic and predictive performance. Although separate fetal growth standards for different regions might capture the growth patterns more precisely, the benefit must be balanced with the costs. The development and application of a set of weight charts will be laborious and expensive. With advanced computer programming, an adjustable standard such as the one proposed by Zhang *et al.*[26] may be a reasonable solution.

Challenge can also be expected in terms of the accuracy of sonographic EFW, particularly in cases of suspected LGA in the third trimester.[46] Inaccuracy of fetal weight estimation may be attributed to several causes, including systematic and random errors, combining two-dimensional (2D) measures to approximate three-dimensional (3D) fetal volume, and utilizing fetal volume to estimate fetal weight.[42]

Sonographic measurement errors and inter- and intra-observer variability account for the majority of systematic and random errors, which may be reduced by standardization, rigorous training and quality control.[47] In addition to the inherent random errors, numerous maternal and fetal factors may affect the precision of sonographic EFW, including maternal body mass index, gestational age, parity, maternal diabetes, amniotic fluid volume, fetal presentation, and fetal sex.[48,49] However, a study analyzed over 9000 sonographic fetal weight estimations and concluded that although some of these factors significantly affected EFW, their impact was of questionable clinical value since only up to 10% of the systematic errors could be attributed to these variables.[48]

The accuracy of fetal weight estimation equations is another concern. In 1984 and 1985 Hadlock *et al*. introduced an algorithm combining measurements of fetal head circumference (HC), biparietal diameter (BPD), femur length (FL) and abdominal circumference (AC) for weight estimation.[50,51] Since then, various new estimation models have been developed. Nevertheless, the algorithm described by Hadlock *et al*. remains the most accurate prediction of fetal weight.[52] For fetuses suspected to be SGA, Hadlock's AC-BPD-FL function provided an accurate estimation for fetuses with asymmetric growth (HC/AC ratio >95th percentile) before 34 weeks' gestation.[53] While for other subgroups with symmetric growth or beyond 34 weeks' gestation, subgroup-specific models may enhance the accuracy.[53] For instance, among fetuses with suspected SGA beyond 34 weeks' gestation, the model proposed by Scott *et al*. performed better than others if the presence of a brain-sparing effect was identified.[53,54] Likewise, Hadlock's formula remained the top choice for LGA detection.[52,55,56] It has been suggested that the accuracy of fetal weight estimation may have reached a maximum using traditional biometric parameters.[57] Significant advances can probably only come from new ultrasonography technology. For example, several studies have demonstrated that soft tissue measurements and 3D ultrasonography were promising for weight assessment in macrosomia.[58,59]

Measurement of soft-tissue thickness (STT), involving adipose tissue plus lean mass, has shown an advantage over conventional biometric parameters in weight prediction.[60–62] Most of the conventional measurements do not account for increased soft tissue mass, which may give rise to an underestimation of fetal weight.[60] In addition, measurement of mid-thigh STT demonstrated its superiority over head measurements when the fetal head is in a low position in the pelvis.[60] Moreover, rather than assessing circumferences, this approach measures linear parameters, which are more easily measured in obstetric practice.[60] Scioscia *et al*. reported the linear measurement of mid-thigh STT and developed a new formula that had an absolute mean error of <15% in 97% of cases.[60] Abuelghar *et al*.[61] validated Scioscia's formula and proposed a modified one, both of which were considered equally efficient in calculating true fetal weight. For macrosomia or diabetic gestations, the utility of STT was valuable.[62,63] Garabedian *et al*.[63] showed that soft tissue in the upper arm had the best area under receiver operating characteristic (AUROC) value (0.855) along with good sensitivity and specificity (85.7% and 80.0%, respectively) for detecting macrosomia in pregnancies complicated by diabetes.

Fractional limb volume (FLV), measured by 3D ultrasound technology, can also reflect soft tissue development.[64] In 2001, Lee *et al*. introduced the concept of FLV, which provided a new way of evaluating soft tissue for weight prediction.[65] Since then, numerous studies have shown that a combination of 2D and 3D parameters can improve the precision of EFW.[64,66–68] During the second and third trimesters of pregnancy, incorporation of 3D data, such as fractional arm volume (AVol) or fractional thigh volume (TVol), into estimation models reduced the random error to 6.6%.[66] By comparison, the random errors of the original Hadlock model and a modified Hadlock model were 8.5% and 7.6%, respectively.[66] A multicenter study indicated that the inclusion of automated FLV measurements improved the proportion of correctly classified birthweight ± 10% in >80% of cases than 73.8% for the INTERGROWTH-21st model.[64] For Chinese fetuses in the third trimester, particularly newborns weighing <3500 g, the percentage of estimated error ≤ 5% using the automated limb volume estimation software (58.1% for AVol model and 64.5% for TVol model) was significantly higher than that of the traditional 2D model (19.4%).[68]

In summary, the recently published fetal growth standards and one-size-fits-all approach may not be applicable to Chinese fetuses. Developing Chinese-specific charts may better meet our clinical requirements. It is important to emphasize that strict quality control procedures for establishing standards are warranted. Meanwhile, efforts should be directed toward resolving the regional disparities in birthweight and obtaining satisfactory fetal weight estimation. A standardized ultrasound measurement protocol is essential and the introduction of novel weight assessment strategies are conducive to a more precise standard.

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Author Contributions

Conceptualization: Jun Zhang, Xiaojing Zeng; analysis: Xiaojing Zeng, Jing Zhu; writing—original draft preparation, Xiaojing Zeng; writing—review and editing, Jun Zhang, Jing Zhu.

Conflicts of Interest

None.

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