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Chinese Fetal Growth: A Multicenter Cohort Study Based on Fetal Ultrasound Measurements

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Abstract

Objective: To build a reference fetal growth chart for the Chinese population based on fetal ultrasound measurements.

Methods: This was a multicenter, population-based retrospective cohort study. Longitudinal ultrasound measurement data were collected from 24 hospitals in 18 provinces of China from 1st September through 31st October of 2019. The estimated fetal weight (EFW) was calculated based on head circumference, abdominal circumference, and femur length using Hadlock formula 3. Fetal growth curves were estimated using a two-level linear regression model with cubic splines. All participants were divided into two groups: the northern group (n = 5829) and the southern group (n = 3246) based on the geographical division of China and male fetus group (n = 4775) and female fetus group (n = 4300) based on fetal gender. The EFW was compared by fetal gender and geographical group. All statistical models were adjusted for maternal sociodemographic characteristics.

Results: A total of 9075 participants with 31,700 ultrasound measurement records were included in this study. Male fetuses demonstrated significantly larger EFW compared to female ones starting at 16 weeks of gestation and extending to delivery (global test P < 0.01). The overall geographic difference in EFW was significant (global test P = 0.03), and week-specific comparisons showed that the northern group had a greater EFW starting at 15 weeks of gestation and extending to 29 weeks of gestation, although this difference did not extend to the time of delivery. The Z-score of EFW confirmed that our Chinese fetal growth charts differed from previously published standards.

Conclusion: This study provides EFW and ultrasound biometric reference measurements for Chinese fetuses and reveals differences from other fetal growth charts. The chart is worth promoting in more regions of China but should be tested prudently before use.

Keywords: Growth charts; Fetal development; Epidemiology

Xiaoli Gong and Tianchen Wu contributed equally to this study.

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Introduction

Fetal growth is the foundation of long-term health, as abnormal growth may increase the risk of future diseases. Small for gestational age (SGA) refers to fetuses whose estimated weight or abdominal circumference (AC) is lower than the expected weight for the same gestational age (GA) or AC by ultrasound is <10th percentile, which may include fetal growth restriction (FGR). FGR is a pathological condition in which the fetus does not reach its intrauterine growth and developmental potential due to impaired placental function; the incidence rate is 5%–10%. FGR leads to an increased risk of adverse pregnancy outcomes and long-term complications in offspring, such as nervous system damage and endocrine diseases. In contrast, large for gestational age (LGA), defined as weight >90th percentile at birth, may also increase the risk of adverse pregnancy outcomes, such as intrapartum cesarean section and postpartum hemorrhage.[2] In addition, some congenital diseases also manifest aberrant measurements, such as dyschondroplasia and osteogenesis dysplasia, in which the fetus has short leg bones. Therefore, a suitable fetal growth chart may help in making accurate diagnoses and reduce the frequency of adverse pregnancy outcomes.

Fetal biometry is a reference for assessing fetal growth in the uterus by ultrasound at different times during pregnancy, and the estimated fetal weight (EFW) is calculated using a formula with combined measurements; different formulas produce different results.[3] Three large cohort studies of fetal growth have recently been conducted in different areas and have been widely adopted worldwide, including the National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies in America,[4,5] the Intergrowth-21st Project,[6,7] and the World Health Organization Multicenter Growth Reference Study (WHO Fetal).[8] An expert review described the details and differences among these three studies and suggested that racial/ethnic-specific standards might improve the accuracy of fetal growth assessments.[9]

The WHO fetal study identified that the EFW differs significantly among countries after adjusting for fetal gender and several characteristics of the mother. The NICHD prepared the standards for four racial/ethnic groups in the USA, including Asians (20%). In China, the latest expert consensus on FGR showed that compared with the Intergrowth-21st Project, the NICHD (Asians) and the semi-customized growth curve of the Chinese population[10] improved the accuracy of SGA during a prenatal screen. However, the NICHD study (Asians) had a small sample size *(n* = 460), and the semi-customized growth curve included only an EFW curve; hence, it is necessary to establish a fetal growth standard for Chinese fetuses. Previous studies presented the domestic fetal growth standard.[11,12] Nevertheless, the data came mainly from the southern area of China,[12] which did not represent the majority of China, and the data have not been updated for about 10 years. A recent multicenter study reported Chinese fetal biometry reference charts. Unfortunately, they did not calculate EFW, and few observations during early and late gestations were collected,[13] and meanwhile, the statistical methods were flawed.

This study aimed to establish an ultrasound-based fetal growth chart and EFW reference data based on monitoring several biometric parameters throughout pregnancy, including biparietal diameter (BPD), head circumference (HC), AC, and femur length (FL). In addition, we also compared our charts with previous reference charts.

Material and methods

Study design and participants

This was a multicenter, retrospective cohort study from China. Singleton pregnant women from 24 hospitals in 18 provinces who delivered between September 1 and October 31, 2019, were included in this study. The 24 partner hospitals are listed in Supplementary Digital Content, Table S1, http://links.lww.com/MFM/A11. This study was approved by the Peking University Third Hospital Medical Ethics Committee (approval number: 2021 No. 336–02), and the ethical review exempted the signing of informed consent. We recruited three physicians in each partner hospital to evaluate all included pregnant women; two of them conducted independent evaluations using the same inclusion and exclusion criteria; the disagreements were evaluated by the third physician. The inclusion criteria were single pregnancy and natural pregnancy. The exclusion criteria were as follows: ultrasound frequency less than three times; abnormal prenatal diagnosis (including Edward's syndrome, Down's syndrome, Turner's syndrome, and intrauterine infection); hyperthyroidism/hypothyroidism; fetal congenital anomalies; diabetes; autoimmune disease; hypertension or other non-communicable diseases before pregnancy; previous pregnancy complicated with pre-eclampsia/eclampsia; or hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome; preterm birth or birth weight <2500 g or >4500 g; smoking or drinking within 3 months before pregnancy or the first trimester; history of exposure to toxic, harmful, or radioactive materials; and long-term medication history (except conventional folic acid, calcium, vitamins, or iron). Pregnant women who met any one of the exclusion criteria were excluded from this study. In addition, although pregnant women complicated with gestational-associated hypertensive disorders (including gestational hypertension, chronic hypertension, and pre-eclampsia/eclampsia), gestational diabetes mellitus, sub-clinical hypothyroidism, or underwent assisted reproduction were included in the original cohort, they were still excluded in the present study.

GA in our study was calculated according to the last menstrual period (LMP) with a regular cycle of 21–35 days, which was confirmed by ultrasound in early pregnancy. If the difference was >7 days or the LMP was unclear, the gestational week was determined by ultrasound examination.

Data collection

To improve the quality and efficiency of multicenter data collection, we designed a standardized data collection form and established an online data acquisition system based on the electronic data capture (EDC) system. To avoid errors caused by staff who were not medical professionals, we recruited two clinicians from each partner hospital for data collection and trained them based on the research protocol. All records in the EDC were reviewed and checked by our researchers, and unqualified records were returned for reverification. All data were obtained from outpatient and inpatient medical records, including the demographic characteristics of the pregnant women, reproductive history, ultrasound bio-metric measurements, and perinatal outcomes.

Ultrasound measurements

We evaluated the ultrasound diagnostic capabilities of each hospital following national guidelines. Only hospitals that met the national guidelines were included. This guaranteed the quality of the ultrasound data in our study. All ultrasound measurements were performed by sonog-raphers qualified for prenatal diagnosis. All ultrasonic measurement operating procedures were based on the "Prenatal Ultrasound Guide (2012)".[14] Each ultrasound measurement contained four biometric parameters: BPD referred to the outer edge of the proximal skull to the inner edge of the distal skull, AC referred to cross-section at the level of the stomach and bifurcation of the portal vein, HC referred to the outer margin of the fetal skull, and FL referred to the longest straight distance between the metaphyseal edges of the ossification on both sides of the backbone. Each parameter was measured twice, and the average value was calculated. All measurements were obtained from the ultrasonic images with the largest magnification. The original values of each measurement and the ultrasonic images were preserved for random quality control spot checks, and outliers were traced back. All participants received at least three ultrasound measurements during the first, second, and third trimesters. The numbers of ultrasound measurements at each week are listed in Supplementary Digital Content, Table S2, http://links.lww.com/MFM/A11.

Statistical analysis

Continuous variables are presented as means ± standard deviation (*SD*), and categorical variables are presented as frequencies and percentages. Comparisons of continuous variables were tested by Student's *t*-test, comparisons of categorical variables were tested by Pearson's Chi-squared (χ^2) test. The EFW was calculated based on HC, AC, and FL using the Hadlock formula 3.[15] Ultrasound measurements were used to estimate reference curves for individual ultrasound biometric parameters (AC, HC, BPD, and FL) and the EFW. Log-transformation was used for each fetal growth parameter and EFW to stabilize variance across GAs and to improve normal approximations for the error structures.

We used a two-level linear regression model with cubic splines to determine the relationship between fetal growth and GA in which the ultrasound measurements were the first-level units and the pregnant women were the second-level units. This method has been used in several previous studies[5,16] and has been confirmed to ensure unbiased percentile estimates.[5] Three knots at the 25th,50th,and 75th percentiles were chosen at the GA that evenly split the distributions.[17] The percentiles of EFW and four biometric parameters were calculated based on the assumed normal distribution of the random effects and error structure. We further analyzed the influence of geographical area and fetal gender on the EFW.

Table 1

Overall and geographical-specific maternal characteristics and perinatal outcomes.

Maternal characteristics/Perinatal outcomes	All (*n* = 9075)	North (*n* = 5829)	South (*n* = 3246)	*P*
Maternal age (years), mean ± *SD*	29.5 ± 4.0	29.4 ± 4.0	29.5 ± 4.1	0.316*
Height (cm), mean ± *SD*	161.2 ± 4.9	161.9 ± 4.8	159.8 ± 4.8	<0.001*
Pregestational weight (kg), mean ± *SD*	55.5 ± 8.4	56.8 ± 8.7	53.1 ± 7.4	<0.001*
Ethnic group, *n* (%)				
Han	8451 (93.1)	5460 (93.7)	2991 (92.1)	0.006†
Minority	624 (6.9)	369 (6.3)	255 (7.9)	
Education, *n* (%)				
Primary school and below	39 (0.4)	28 (0.5)	10 (0.3)	<0.001†
Junior high school	777 (8.6)	504 (8.6)	265 (8.2)	
Senior high school	1455 (16.0)	845 (14.5)	609 (18.8)	
Bachelor degree	6098 (67.2)	3917 (67.2)	2197 (67.7)	
Master degree and above	706 (7.8)	535 (9.2)	165 (5.1)	
Parity, *n* (%)				
0	5663 (62.4)	3828 (65.7)	1835 (56.5)	<0.001†
≥1	3412 (37.6)	2001 (34.3)	1411 (43.5)	
Neonatal gender, *n* (%)				
Male	4775 (52.6)	3049 (52.3)	1726 (53.2)	0.429†
Female	4300 (47.4)	2780 (47.7)	1520 (46.8)	
Mode of delivery, *n* (%)				
Spontaneous	5694 (62.7)	3511 (60.2)	2183 (67.3)	<0.001†
Vacuum	62 (0.7)	56 (1.0)	6 (0.2)	
Forceps	124 (1.4)	73 (1.3)	51 (1.6)	
Cesarean section	3195 (35.2)	2189 (37.6)	1006 (31.0)	
Premature rupture of membranes, *n* (%)	1695 (18.7)	1023 (17.6)	672 (20.7)	<0.001†
Premature, *n* (%)	222 (2.4)	153 (2.6)	69 (2.1)	0.140†
GA at delivery (weeks), mean ± *SD*	39.5 ± 1.2	39.5 ± 1.3	39.5 ± 1.2	0.038*
Birth weight (g), mean ± *SD*	3318.0 ± 407.6	3338.4 ± 404.7	3281.4 ± 410.4	<0.001*
Birth length (cm), mean ± *SD*	50.1 ± 1.8	50.2 ± 1.6	50.0 ± 1.9	<0.001*

GA: Gestational age; *SD*: Standard deviation.

*Comparisons of continuous variables were tested by Student's *t* test.

†Comparisons of categorical variables were tested by x^2 test.

According to the geographical areas of China, we divided the participants into a southern group and a northern group (as shown in Supplementary Digital Content, Table S1, http://links.lww.com/MFM/A11). Geographical- or gender-specific overall comparisons were conducted using a likelihood ratio test. When the overall difference was significant, the Wald test was used to test the week-specific difference in EFW at each week of gestation. We also conducted multivariate linear regression (for GA at delivery, birth weight, and birth length) and logistic regression (for premature rupture of membranes and premature birth) to analyze the influence of the geographical group on perinatal outcomes.

We adjusted for maternal age, parity (0 *vs*. ≥1), prepregnancy weight, height, ethnic group (Han *vs*. minority), education (primary school and below, junior high school, senior high school or equivalent, bachelor's degree, or master's degree and above), and gender of the infant (male *vs*. female) in the linear mixed models above. All covariates were treated as continuous variables except for the ethnic group, education, parity, and the gender of the infant. We used multiple imputations to impute missing covariates with 20 imputations.[18] All analyses were implemented using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA.). All statistical tests were two-tailed, and $P < 0.05$ was considered significant.

In addition, we calculated *Z*-scores to compare our EFW reference chart with previous fetal growth curves from the NICHD (Asians),[5] the Intergrowth-21st Project,[7] the WHO fetal growth charts,[8] Hadlock's fetal growth standard,[19] and a Chinese study[12] (Hong Kong, China), as well as a semi-customized fetal growth curve[10] for the Chinese population. *Z*-scores were calculated using the following formula: *Z*-score = (XGA-MGA)/SDGA, where XGA is the data from the comparative populations with a known GA, and MGA and SDGA are the mean and *SD* values at this GA, respectively, calculated using the reference equation for our population. We have presented the 5th,50th, and 95th percentile *Z*-scores across different GAs for a visual comparison.

Results

Maternal sociodemographic characteristics and perinatal outcomes

We enrolled 11,891 participants in the original study, from whom a total of 2816 (23.7%) participants were excluded due to complicated with gestational diabetes mellitus (1660, 14.0%), pregnancy-associated hypertensive disorders (395, 3.3%), subclinical hypothyroidism (433, 3.6%), or underwent assisted reproduction (328, 2.8%), the numbers of these diseases overlap each other. Finally, 9075 (76.3%) participants with 31,700 ultrasound measurements were available for our analyses. The characteristics and perinatal outcomes of all included pregnant women are listed in Table 1. The average age of the participants was 29.5 ± 4.0 years. The pre-pregnancy weight of the pregnant women was 55.5 ±

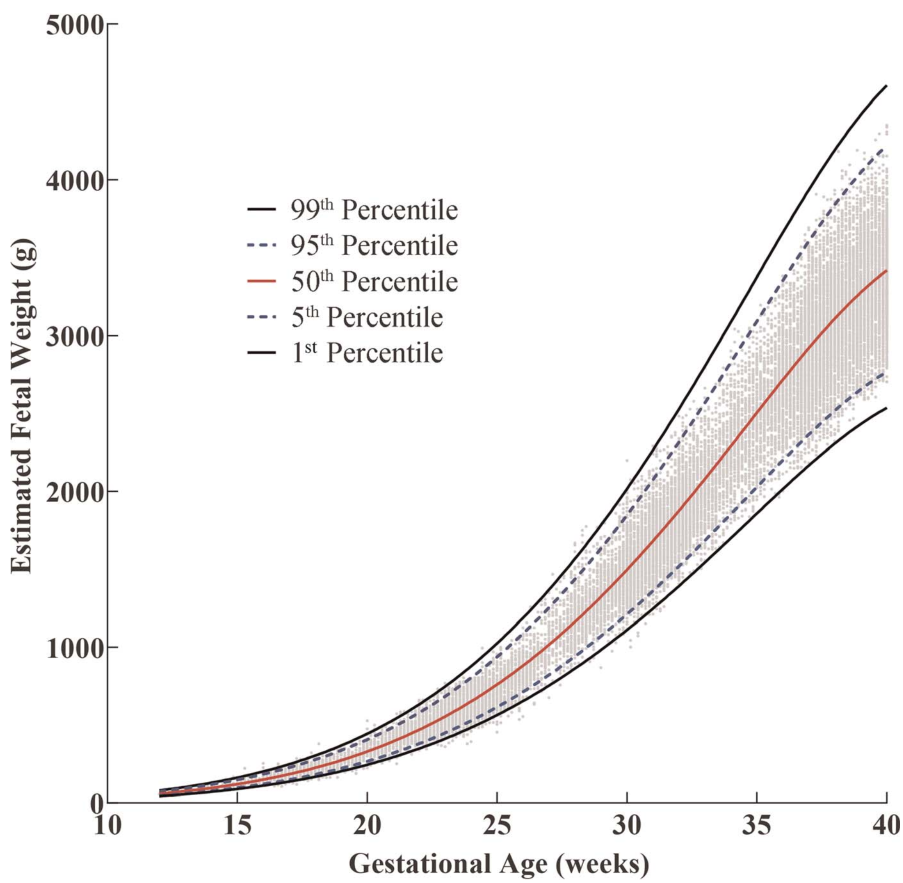

Figure 1. Nationwide EFW curve. EFW: Estimated fetal weight.

8.4 kg. The average GA at delivery was 39.5 ± 1.2 weeks, and the average birth weight was 3318.0 ± 407.6 g. For the geography-specific comparison, 5829 and 3246 participants were in the northern and southern groups, respectively. Pregnant women in the northern group were taller and heavier and had a higher proportion of primiparas than those in the southern group. The neonatal gender ratio and proportion of premature birth were not significantly different between the two groups. Pregnant women in the northern group had a higher proportion of cesarean section and a lower proportion of premature rupture of membranes than those in the southern group. For the fetal gender-specific comparison, 4775 and 4300 participants were in the male and female groups, respectively.

Reference charts for EFW and four biometric parameters

We show the fitted nationwide fetal growth curves for the EFW and four biometric parameters (BPD, HC, AC, and FL) in Figures 1 and 2 including the 1st, 5th, 50th, 90th, and 99th percentiles. We listed the percentiles (including the 1st, 3rd, 5th, 10th, 50th, 90th, 95th, 97th, and 99th) of reference values for EFW and the four biometric parameters in Tables 2–6.

Influence of geographical areas and fetal gender on EFW

Figure 3 shows the gender- and geography-specific EFW curves, and we list the reference values with percentiles (1st, 3rd, 5th, 50th, 95th, 97th, and 99th) in Supplementary Digital Content, Tables S3-6, http://links.lww.com/MFM/A11. The P values from Wald tests for the weekly gender-and geography-specific comparisons are listed in Supplementary Digital Content, Table S7, http://links.lww.com/MFM/A11. Male fetuses had larger EFW values than female ones starting at 16 weeks of gestation and extending to delivery (global test $P < 0.01$). The overall test of geography-specific difference in EFW was significant (global test $P = 0.03$), and week-specific comparisons showed that

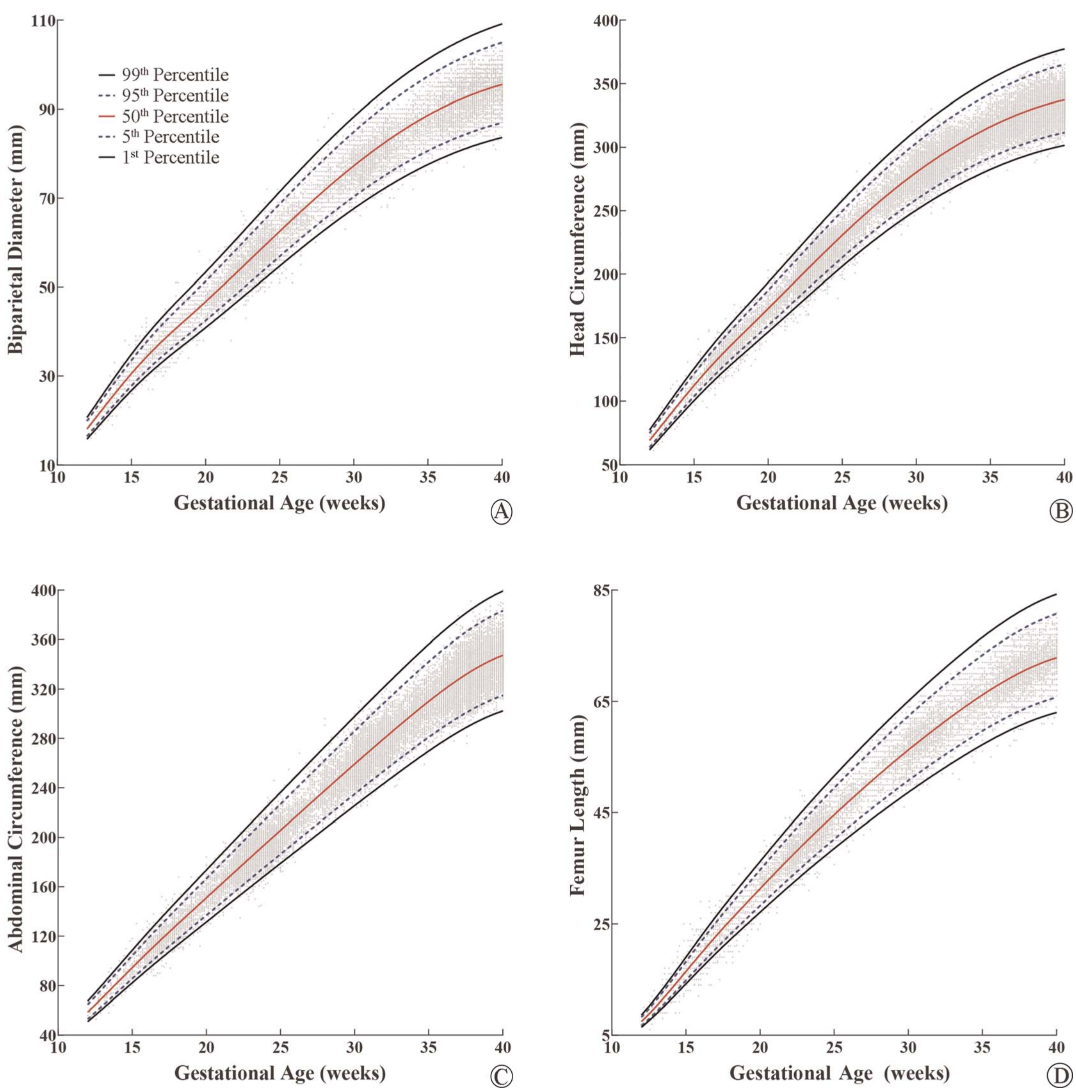

Figure 2. Nationwide ultrasound biometric measurement curves for BPD (A), HC (B), AC (C), and FL (D). AC: Abdominal circumference; BPD: Biparietal diameter; FL: Femur length; HC: Head circumference.

Table 2

Percentiles of fetal growth chart for BPD (mm).

GA (weeks)	1^{st}	3^{rd}	5^{th}	10^{th}	50^{th}	90^{th}	95^{th}	97^{th}	99^{th}
12	15.8	16.2	16.4	16.8	18.1	19.5	19.9	20.2	20.7
13	19.5	20.0	20.3	20.7	22.3	24.0	24.5	24.9	25.5
14	23.2	23.8	24.2	24.7	26.5	28.6	29.2	29.6	30.3
15	26.7	27.4	27.8	28.4	30.5	32.9	33.6	34.0	34.9
16	30.0	30.7	31.2	31.8	34.2	36.9	37.6	38.1	39.1
17	32.9	33.8	34.2	34.9	37.6	40.5	41.3	41.9	43.0
18	35.6	36.5	37.0	37.8	40.7	43.8	44.7	45.3	46.5
19	38.2	39.2	39.8	40.6	43.7	47.0	48.0	48.6	49.9
20	40.9	41.9	42.5	43.4	46.7	50.3	51.3	52.0	53.4
21	43.6	44.7	45.3	46.3	49.8	53.6	54.7	55.5	56.9
22	46.4	47.6	48.2	49.2	53.0	57.0	58.2	59.0	60.5
23	49.1	50.4	51.1	52.2	56.1	60.4	61.7	62.5	64.1
24	51.9	53.3	54.0	55.1	59.3	63.9	65.2	66.1	67.8
25	54.7	56.1	56.9	58.1	62.5	67.3	68.7	69.6	71.4
26	57.5	58.9	59.7	61.0	65.6	70.6	72.1	73.1	75.0
27	60.1	61.7	62.5	63.8	68.7	73.9	75.5	76.5	78.5
28	62.7	64.4	65.2	66.6	71.7	77.1	78.7	79.8	81.9
29	65.2	66.9	67.8	69.3	74.5	80.2	81.9	83.0	85.1
30	67.6	69.4	70.3	71.8	77.3	83.1	84.9	86.0	88.3
31	69.9	71.7	72.7	74.2	79.9	85.9	87.7	88.9	91.2
32	72.0	73.9	74.9	76.5	82.3	88.6	90.4	91.6	94.0
33	74.0	75.9	77.0	78.6	84.6	91.0	92.9	94.2	96.6
34	75.9	77.8	78.9	80.5	86.7	93.3	95.2	96.5	99.0
35	77.6	79.6	80.6	82.3	88.6	95.3	97.3	98.7	101.2
36	79.1	81.1	82.2	84.0	90.4	97.2	99.3	100.6	103.2
37	80.5	82.5	83.7	85.4	91.9	98.9	101.0	102.4	105.0
38	81.7	83.8	84.9	86.7	93.3	100.4	102.5	103.9	106.6
39	82.7	84.9	86.0	87.8	94.5	101.7	103.8	105.2	108.0
40	83.6	85.8	86.9	88.8	95.5	102.8	105.0	106.4	109.1

BPD: Biparietal diameter; GA: Gestational age.

the northern group had a larger EFW starting at 15 weeks of gestation and extending to 29 weeks of gestation, but this difference did not extend to the time of delivery. At 32 weeks, when an obstetrical ultrasound could be obtained to evaluate fetal growth, the 5^{th}, 50^{th}, and 95^{th} percentile EFWs were 1677.0 g, 1877.4 g, and 2101.7 g for the northern group and 1662.7 g, 1865.1 g, and 2092.1 g for the southern group, respectively. At approximately full term (39 weeks), 5^{th}, 50^{th}, and 95^{th} percentiles for EFW were 2929.2 g, 3279.1 g, and 3670.9 g, respectively, for the northern group and 2896.6 g, 3249.3 g, and 3644.9 g, respectively, for the southern group.

Influence of geographical areas on perinatal outcomes

To further compare fetal growth between the southern and northern groups, we conducted multivariate analyses on the impact of geographical factors on perinatal outcomes (as listed in Supplementary Digital Content, Table S8, http://links.lww.com/MFM/A11). Fetuses in the southern group were at a significantly higher risk of premature rupture of membranes than those in the northern group (odds ratio (OR) = 1.28, 95% confidence interval (CI): 1.13–1.44, $P < 0.001$). Besides, birth length was shorter for fetuses in the southern group than that in the northern group ($\beta = -0.09$, 95% CI: –0.17 to –0.02, $P = 0.02$). Multivariate analyses did not find any significant effect for the geographical area on birth weight, the proportion of premature birth, or GA at delivery.

Comparisons with previous fetal growth charts

Figure 4 shows the Z-scores of the 10^{th}, 50^{th}, and 90^{th} percentiles to compare our EFW values with those of six previously published studies.[5,7,8,10,12,19] The results from comparing reference values of EFW between our charts and these previous studies are showed in Supplementary Digital Content, Figure S1, http://links.lww.com/MFM/A11. The Z-scores in the six populations revealed different patterns. The NICHD (Asians)[5] and Intergrowth-21st Project[7] had higher EFW values than ours during the first trimester; their 50^{th} percentile was close to our 90^{th} percentile and the 5^{th} percentile reached the level of the 50^{th} percentile. The other four charts were quite compatible with our EFW charts in the second and third trimesters for all percentiles.

Also, we compared the proportion of EFW values <10^{th} percentile calculated using different reference standards (Supplementary Digital Content, Figure S2, http://links.lww.com/MFM/A11). The proportion of fetuses classified as having an EFW <10^{th} percentile ranged from 2% to 15% and exhibited similar patterns across gestation using our fetal growth chart and the other standards, except for the Intergrowth-21st Project standard. The proportion calculated based on the Intergrowth-21st Project standard decreased rapidly from 22 to 27 gestational weeks, which was >15% before 25 gestational weeks and <1% after 29 gestational weeks. The WHO fetal study and Hadlock standards classified more fetuses as <10^{th} percentile compared

Table 3

Percentiles of fetal growth chart for HC (mm).

GA (weeks)	1^{st}	3^{rd}	5^{th}	10^{th}	50^{th}	90^{th}	95^{th}	97^{th}	99^{th}
12	61.7	63.0	63.8	64.9	69.1	73.5	74.8	75.7	77.4
13	74.8	76.4	77.3	78.6	83.7	89.0	90.6	91.6	93.6
14	87.8	89.7	90.8	92.4	98.3	104.5	106.4	107.6	109.9
15	100.4	102.6	103.8	105.6	112.4	119.5	121.6	123.0	125.7
16	112.4	114.8	116.1	118.2	125.7	133.7	136.1	137.6	140.6
17	123.5	126.2	127.6	129.9	138.2	147.0	149.6	151.3	154.6
18	134.0	137.0	138.5	141.0	150.0	159.5	162.3	164.2	167.8
19	144.3	147.4	149.1	151.7	161.4	171.7	174.7	176.7	180.6
20	154.6	157.9	159.7	162.6	172.9	183.9	187.2	189.3	193.5
21	165.0	168.6	170.5	173.5	184.6	196.3	199.8	202.1	206.5
22	175.4	179.2	181.3	184.5	196.2	208.8	212.4	214.9	219.5
23	185.8	189.8	192.0	195.4	207.9	221.1	225.0	227.6	232.6
24	196.1	200.3	202.6	206.2	219.4	233.3	237.5	240.2	245.4
25	206.1	210.6	213.0	216.8	230.6	245.3	249.6	252.5	258.0
26	215.8	220.5	223.1	227.0	241.5	256.9	261.4	264.4	270.2
27	225.2	230.1	232.7	236.8	251.9	268.0	272.7	275.8	281.8
28	234.1	239.2	241.9	246.2	261.9	278.6	283.5	286.7	293.0
29	242.5	247.8	250.6	255.0	271.3	288.6	293.7	297.0	303.5
30	250.4	255.9	258.8	263.4	280.1	298.0	303.3	306.8	313.4
31	257.8	263.4	266.4	271.2	288.4	306.8	312.3	315.8	322.7
32	264.7	270.5	273.6	278.4	296.2	315.1	320.6	324.3	331.3
33	271.1	277.0	280.2	285.2	303.3	322.7	328.4	332.2	339.4
34	277.1	283.1	286.3	291.4	310.0	329.7	335.6	339.4	346.8
35	282.5	288.6	291.9	297.1	316.0	336.2	342.1	346.0	353.5
36	287.4	293.6	297.0	302.2	321.5	342.0	348.0	352.0	359.7
37	291.7	298.0	301.5	306.8	326.3	347.2	353.3	357.3	365.1
38	295.5	301.9	305.4	310.8	330.6	351.7	357.9	362.0	369.8
39	298.7	305.2	308.7	314.2	334.2	355.5	361.8	366.0	373.9
40	301.4	308.0	311.5	317.0	337.2	358.7	365.1	369.2	377.3

GA: Gestational age; HC: Head circumference.

Table 4

Percentiles for AC(mm) by GA.

GA (weeks)	1st	3rd	5th	10th	50th	90th	95th	97th	99th
12	50.9	52.3	53.1	54.3	58.6	63.4	64.8	65.7	67.5
13	61.2	62.9	63.7	65.2	70.4	76.0	77.7	78.8	80.9
14	71.7	73.6	74.7	76.3	82.4	89.0	90.9	92.2	94.7
15	82.2	84.4	85.6	87.5	94.4	101.9	104.2	105.7	108.5
16	92.5	95.0	96.3	98.4	106.3	114.7	117.2	118.9	122.1
17	102.5	105.3	106.7	109.1	117.8	127.1	129.9	131.8	135.3
18	112.2	115.3	116.9	119.5	129.0	139.2	142.3	144.3	148.2
19	121.8	125.1	126.9	129.7	140.0	151.1	154.4	156.6	160.9
20	131.4	134.9	136.9	139.9	151.0	163.0	166.6	169.0	173.5
21	141.0	144.8	146.8	150.1	162.0	174.9	178.7	181.3	186.2
22	150.6	154.6	156.8	160.2	173.0	186.8	190.9	193.6	198.8
23	160.1	164.4	166.7	170.4	183.9	198.6	202.9	205.8	211.4
24	169.5	174.1	176.6	180.4	194.8	210.3	214.9	218.0	223.8
25	178.9	183.8	186.4	190.4	205.6	222.0	226.8	230.1	236.3
26	188.3	193.4	196.1	200.4	216.4	233.6	238.7	242.1	248.6
27	197.7	203.0	205.9	210.4	227.1	245.2	250.6	254.2	261.0
28	207.0	212.6	215.6	220.4	237.9	256.8	262.5	266.2	273.4
29	216.3	222.2	225.3	230.3	248.6	268.4	274.2	278.1	285.6
30	225.6	231.6	234.9	240.1	259.2	279.8	285.9	290.0	297.8
31	234.7	241.0	244.4	249.8	269.7	291.1	297.5	301.7	309.9
32	243.7	250.3	253.8	259.4	280.0	302.3	309.0	313.3	321.8
33	252.6	259.4	263.1	268.9	290.3	313.4	320.2	324.8	333.5
34	261.3	268.4	272.2	278.2	300.3	324.2	331.3	336.0	345.1
35	269.8	277.1	281.0	287.2	310.0	334.7	342.0	346.9	356.2
36	277.8	285.3	289.3	295.7	319.2	344.6	352.2	357.2	366.8
37	285.2	292.9	297.1	303.6	327.8	353.8	361.6	366.7	376.6
38	291.9	299.8	304.0	310.7	335.4	362.1	370.1	375.3	385.4
39	297.6	305.7	310.0	316.8	342.0	369.2	377.3	382.7	393.0
40	302.3	310.4	314.8	321.7	347.3	375.0	383.2	388.6	399.1

AC: Abdominal circumference; GA: Gestational age.

with our fetal growth chart. The percentages of all standards increased slightly beginning at 38 gestational weeks.

Discussion

This was the first large-sample fetal growth study covering 18 provinces in China. The current Chinese expert consensus[20] recommended the NICHD Asian group[5] (AC and EFW) and semi-customized fetal growth charts[10,20] for the Chinese population and suggested that these two charts have improved the accuracy of FGR prenatal screening in the Chinese population. However, the Asian group in the NICHD study included both Asian and Pacific Islander women, which cannot represent the genetic background and daily living environment of the Chinese population. The semi-customized fetal growth curve[10,20] used birth weight to estimate EFW values; thus, the huge difference in the 5th percentile would decrease the accuracy of FGR screening, and reference values before 24 weeks of gestation cannot be calculated using this curve. In this study, we included 9075 participants with 31,700 ultrasound measurements from 18 provinces of China to fit the fetal growth reference charts for EFW and four biometric parameters, which were suitable for Chinese fetuses from 12 to 40 gestational weeks nationwide.

Our study found that fetal growth was influenced by fetal gender. The EFW of male fetuses was larger than that of female fetuses beginning at 16 gestational weeks until delivery. Furthermore, the difference was larger for the 95th percentile values and smaller for the 5th percentile values, which was similar to the WHO[8] and Norway[21] fetal growth charts. We also found that the overall geographical difference in EFW was significant, with week-specific comparisons showing that the northern group had a larger EFW starting at 15 weeks of gestation and extending to 29 weeks of gestation but not extending to delivery. The difference in EFW in the second trimester may be related to the significant difference in birth length at delivery, but this hypothesis needs more evidence for verification. An epidemiological survey in China showed that birth weight tends to be lighter in the southern region than in the northern region of China, suggesting that the genetic background of the Chinese population may be different between the northern and southern regions, thereby affecting the fetal growth and birth weight.[22]

We calculated the *Z*-scores of 5th, 50th, and 95th percentiles to compare our EFW values with six previously published fetal growth charts.[5,7,8,10,12,19] The *Z*-scores in the six populations had different patterns; however, the differences gradually decreased with increasing GA. Of note, we found that the NICHD Asian, WHO fetal study, and Intergrowth-21st Project studies and Hadlock standards revealed similar trends, and two studies based on Chinese populations also had similar trends, especially in their 90th percentile values. This finding

Table 5

Percentiles for FL(mm) by GA.

GA (weeks)	1st	3rd	5th	10th	50th	90th	95th	97th	99th
12	6.4	6.6	6.7	6.9	7.5	8.1	8.3	8.4	8.6
13	8.8	9.1	9.2	9.4	10.2	11.1	11.3	11.5	11.8
14	11.4	11.8	11.9	12.2	13.2	14.3	14.7	14.9	15.3
15	14.2	14.6	14.8	15.2	16.4	17.8	18.2	18.5	19.0
16	17.0	17.4	17.7	18.1	19.6	21.2	21.7	22.1	22.7
17	19.6	20.2	20.5	21.0	22.7	24.6	25.2	25.5	26.3
18	22.2	22.8	23.1	23.7	25.7	27.8	28.4	28.9	29.7
19	24.6	25.3	25.7	26.3	28.5	30.9	31.6	32.1	33.0
20	27.1	27.9	28.3	28.9	31.3	33.9	34.7	35.2	36.2
21	29.5	30.3	30.8	31.5	34.1	37.0	37.8	38.4	39.4
22	31.9	32.8	33.2	34.0	36.8	39.9	40.8	41.4	42.6
23	34.2	35.1	35.6	36.5	39.5	42.8	43.8	44.4	45.7
24	36.4	37.4	38.0	38.8	42.1	45.6	46.6	47.3	48.7
25	38.6	39.6	40.2	41.2	44.6	48.3	49.4	50.2	51.6
26	40.7	41.8	42.4	43.4	47.0	51.0	52.1	52.9	54.4
27	42.7	43.9	44.6	45.6	49.4	53.6	54.8	55.6	57.2
28	44.8	46.0	46.7	47.8	51.8	56.1	57.4	58.2	59.9
29	46.7	48.1	48.8	49.9	54.0	58.6	59.9	60.8	62.5
30	48.6	50.0	50.8	51.9	56.3	60.9	62.3	63.3	65.1
31	50.5	51.9	52.7	53.9	58.4	63.3	64.7	65.7	67.5
32	52.3	53.7	54.5	55.8	60.5	65.5	67.0	68.0	69.9
33	54.0	55.5	56.3	57.6	62.4	67.6	69.2	70.2	72.2
34	55.6	57.2	58.1	59.4	64.4	69.7	71.3	72.4	74.4
35	57.2	58.8	59.7	61.1	66.2	71.7	73.3	74.4	76.5
36	58.7	60.3	61.2	62.6	67.9	73.5	75.2	76.3	78.5
37	60.0	61.7	62.6	64.1	69.4	75.2	76.9	78.1	80.3
38	61.2	62.9	63.9	65.3	70.8	76.7	78.4	79.6	81.8
39	62.2	63.9	64.9	66.4	71.9	77.9	79.7	80.9	83.2
40	63.0	64.8	65.7	67.2	72.9	78.9	80.7	81.9	84.3

FL: Femur length; GA: Gestational age.

may be due to the four studies all including multi-ethnic populations with relatively similar compositions, particularly those of the WHO and Intergrowth-21st Project studies.

We also compared the proportion of EFW values <10th percentile using different standards (Supplementary Digital Content, Figure S2, http://links.lww.com/MFM/A11). Most fetal charts had similar patterns to ours, which means that ours would give similar diagnostic rates as those from the other EFW reference curves for FGR in our population. However, it was confusing that the diagnosis rate of FGR varies so much in the Intergrowth-21st Project, a similar result was found by Zhang *et al.*,[23] who suggested that approximately 20% of fetuses had FL, AC, or HC values <10th percentile, which would lead to overdiagnosis of FGR in a Chinese population. Also, not every FGR found in each gestational week would be finally diagnosed as FGR, some fetuses would reach the growth standard in the later period. We next plan to focus on and study this aspect of the fetal growth trajectory.

Compared with previous studies, our study had several strengths. First, this was the largest sample study based on ultrasound data from several centers to establish a fetal growth curve in China and represented the majority of fetuses in China. Second, we used multivariate analysis to adjust for potential confounders in each model; therefore, the fitting results truly reflect the EFW growth pattern with increasing GA. However, our research had some limitations. It was a retrospective study, all ultrasound measurement records existed before the data collection, and several ultrasound examinations varied from hospital to hospital; hence, a high percentage of missing values was inevitable. Although the ultrasound measurements were performed by experienced doctors, there were still measurement errors due to personal habits and inconsistent ultrasound instrument models. Finally, although we adjusted for several confounders, there were variables that we could not collect in a retrospective study, such as eating habits, which may have biased our results.

Conclusions

Fetal intrauterine growth affects the delivery outcome and has long-term effects on early childhood development.[24] We used population-based ultrasound measurement data to establish new fetal growth charts for Chinese mainland. These new charts will help to improve the accuracy of fetal intrauterine growth surveillance and in detection of high-risk pregnancies. We consider this curve worth promoting in more regions of China and recommend testing prudently before use.

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Table 6

Percentiles for EFW(g) by GA.

GA (weeks)	1st	3rd	5th	10th	50th	90th	95th	97th	99th
12	43.4	46.0	47.4	49.7	58.7	69.4	72.8	75.1	79.6
13	55.7	59.0	60.8	63.7	75.2	88.7	93.0	95.8	101.5
14	70.7	74.8	77.1	80.8	95.3	112.4	117.7	121.3	128.5
15	88.7	94.0	96.8	101.5	119.6	141.0	147.7	152.3	161.2
16	110.4	116.9	120.5	126.2	148.8	175.4	183.7	189.4	200.5
17	136.1	144.2	148.6	155.7	183.5	216.3	226.6	233.6	247.3
18	166.6	176.4	181.8	190.5	224.5	264.7	277.3	285.8	302.6
19	202.3	214.2	220.8	231.3	272.7	321.4	336.8	347.1	367.5
20	244.0	258.4	266.3	279.0	328.9	387.7	406.2	418.7	443.3
21	292.3	309.5	319.0	334.3	394.0	464.4	486.6	501.5	531.0
22	347.9	368.3	379.6	397.8	468.8	552.6	579.0	596.8	631.9
23	411.2	435.4	448.8	470.2	554.2	653.3	684.4	705.5	747.0
24	483.0	511.4	527.1	552.2	650.9	767.2	803.8	828.5	877.3
25	563.6	596.7	615.1	644.4	759.6	895.3	938.0	966.8	1023.7
26	653.5	692.0	713.2	747.3	880.8	1038.2	1087.7	1121.2	1187.1
27	753.1	797.4	821.9	861.1	1015.0	1196.4	1253.5	1292.0	1368.0
28	862.4	913.2	941.2	986.1	1162.4	1370.1	1435.5	1479.6	1566.6
29	981.4	1039.1	1071.1	1122.2	1322.7	1559.1	1633.5	1683.7	1782.7
30	1109.7	1174.9	1211.0	1268.8	1495.6	1762.8	1846.9	1903.7	2015.7
31	1246.6	1319.9	1360.5	1425.4	1680.1	1980.4	2074.9	2138.6	2264.4
32	1391.4	1473.2	1518.5	1590.9	1875.2	2210.3	2315.8	2387.0	2527.4
33	1542.8	1633.5	1683.7	1764.1	2079.3	2450.9	2567.8	2646.7	2802.4
34	1699.2	1799.1	1854.4	1942.9	2290.1	2699.3	2828.1	2915.0	3086.5
35	1857.7	1967.0	2027.5	2124.2	2503.8	2951.2	3092.0	3187.0	3374.5
36	2014.8	2133.3	2198.9	2303.8	2715.4	3200.7	3353.4	3456.4	3659.8
37	2166.0	2293.4	2363.9	2476.7	2919.3	3440.9	3605.1	3715.9	3934.5
38	2306.6	2442.3	2517.4	2637.5	3108.8	3664.3	3839.1	3957.1	4189.9
39	2431.4	2574.4	2653.5	2780.1	3276.9	3862.5	4046.8	4171.1	4416.5
40	2534.9	2684.1	2766.6	2898.6	3416.6	4027.3	4219.4	4349.1	4605.0

EFW: Estimated fetal weight; GA: Gestational age.

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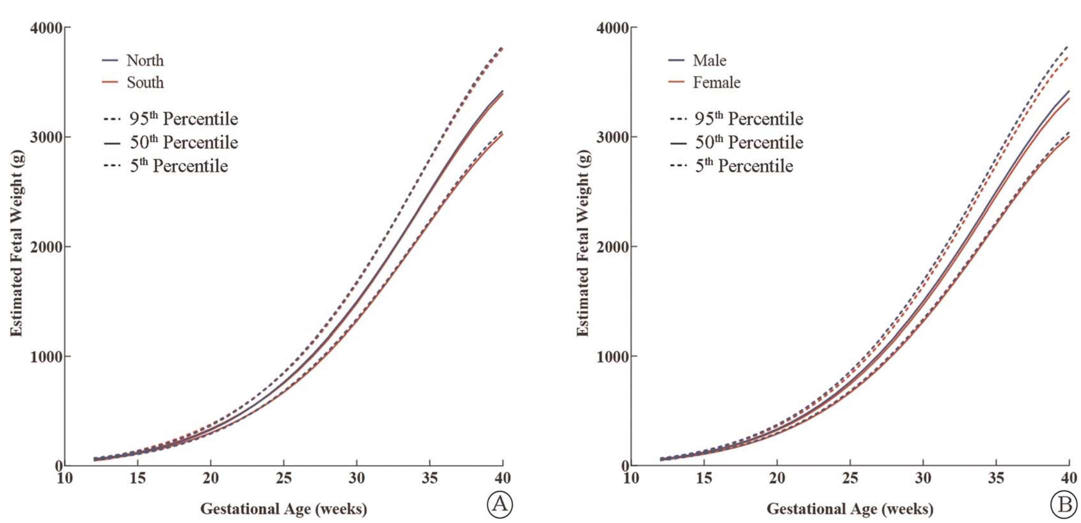

Figure 3. The influence of geographical areas and fetal gender on EFW. A Comparison of EFW between north and south groups. B Comparison of EFW between female and male groups. EFW: Estimated fetal weight.

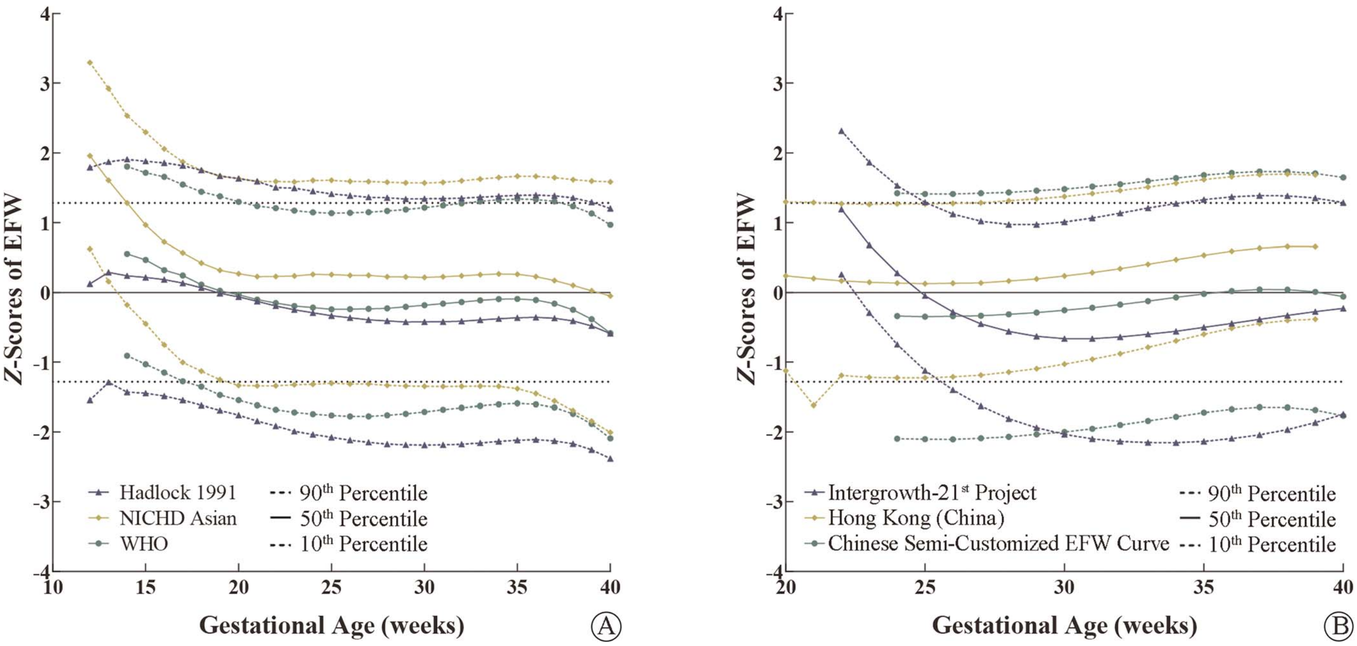

Figure 4. Comparison of EFW between our study and six previously published studies by *Z*-scores. A Comparison between our study and Hadlock 1991, NICHD Asian and WHO study. B Comparison between our study and Intergrowth-21st Project study, Hong Kong (China), and semi-customized fetal growth curve for the Chinese population. EFW: Estimated fetal weight; NICHD: National Institute of Child Health and Human Development; WHO: World Health Organization Multicenter Growth Reference Study.

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Author Contributions

Yangyu Zhao and Yuan Wei designed and implemented the multicenter study. Xiaoli Gong, Tianchen Wu, Xiaoli Wang and Jingsi Chen participated in the study design. Lizhen Zhang, Yiping You, Hongwei Wei, Xifang Zuo, Ying Zhou, Xinli Xing, Zhaoyan Meng, Qi Lyu, Zhaodong Liu, Jian Zhang, Liyan Hu, Junnan Li, Li Li, Chulin Chen, Chunyan Liu, Guoqiang Sun, Aiju Liu, Jingsi Chen and Yuan Lyu were responsible for the collection and upload of data from their respective hospitals. Tianchen Wu and Xiaoli Wang conceived and proceed the analysis. Xiaoli Gong and Tianchen Wu completed the first draft of the article. Yangyu Zhao and Yuan Wei modified the article. All authors read and approved the final manuscript.

Conflicts of Interest

None.

Editor Note

Yangyu Zhao is an Editor of the *Maternal-Fetal Medicine*. The article was subject to the journal's standard procedures, with peer review handled independently of this editor and her research groups.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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