Chinese Fetal Biometry: Establishment of a Formula for Calculating Gestational Age based on Crown–Rump Length Measurements

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Abstract

Background: To develop an ultrasonographic dating formula for predicting gestational age (GA) based on fetal crown–rump length (CRL) in a Chinese population, evaluate its systematic prediction error and compare it with existing formulae.

Methods: This was a prospective cross-sectional study of spontaneously conceived singleton pregnancies among women with a regular menstrual cycle in the preceding year. Ultrasound examinations were performed at 11–14 weeks according to the date of the last menstrual cycle. The CRL was measured three times for each fetus, and the mean was used to derive the best-fit fractional polynomial regression model for estimation of GA in relation to CRL. For each fetus, the GA was compared with the GA calculated using six established dating formulae based on CRL measurements. The means of the differences between estimated and menstrual age were calculated for each formula. All the women were followed up routinely until the birth of the fetus.

Results: Of the 4710 subjects recruited, the mean and standard deviation values of CRL changed linearly with GA. The corresponding regression equation and its correlation coefficient (R^2) was GA = 59.361513 + 0.461425 ´ CRL (R^2 = 0.8028). The mean difference between estimated and menstrual age was 0.22 days (95% confidence interval 0.05–0.21), lower than that of the six existing CRL dating formulae.

Conclusions: We have derived a CRL-based dating formula suitable for naturally conceived pregnancies for GA between 11+0 and 13+6 weeks. The formula has no systematic prediction error, comparing favorably with the existing published dating formulae.

Background

During pregnancy, accurate evaluation of gestational age (GA) is essential for predicting the delivery date and measuring neonatal maturity [1–3]. For the overall population, GA estimation can be used to assess the proportion of small-for-GA and premature infants accurately [4]. GA is often calculated from the date of the last menstrual period (LMP), but the LMP date is unreliable in some pregnant women [5]. In the past 30 years, many formulae have been published on the use of ultrasound measurements to estimate GA for naturally conceived fetuses and those derived from assisted reproductive technology (ART). Clinically, ultrasound parameters, such as crown–rump length (CRL) or biparietal diameter, are often used to predict GA, and are widely used in the first trimester [6–7]. During the first 9–13 weeks of gestation, GA can be calculated accurately from the CRL, because the linear growth rate in this measure is very rapid with a low standard deviation (SD). However, in the second and third trimesters, the CRL measured by ultrasonography is not available or no longer accurate, leading to inaccurate estimations of GA [8]. Many studies have reported formulae for estimating GA using the CRL [9–13], but there has been heterogeneity in the study designs, statistical methods, presentation of results and other aspects [14]. In addition, some formulae have been designed for the calculation of GA before 12 weeks of gestation, and become inaccurate if extended beyond this period [10]. Moreover, some authors have proposed the potential

impacts of ethnicity on CRL. Most previously published CRL dating formulae were based on Western populations. but no large-scale prospective ultrasound evaluation data in the first trimester have been published for fetuses in the mainland of China.

Methods

This study was approved by the Ethics Committee of Peking Union Medical College Hospital and other relevant hospitals. All pregnant women participating in this study signed informed consent forms. All methods were carried out in accordance with relevant guidelines and regulations.

Design

This was a prospective, cross-sectional, multi-center study conducted in 14 tertiary hospitals in the mainland of China from 2008 to 2015. The study was conducted by the Chinese Fetal Growth and Prenatal Screening Consortium, which is a large-scale project about fetal growth and prenatal anomaly screening and diagnosis [15]. The study included pregnant Chinese women in their first trimester. Maternal, paternal, socioeconomic, and pregnancy characteristics were self-reported prospectively by questionnaire. The GA was calculated from the LMP, and ultrasound examinations were performed at the 11^{+0} to 13^{+6} weeks of gestation. The ultrasound examinations were arranged specifically for this study, and each woman was examined only once during the first trimester. All of them underwent continuous ultrasound follow-up during the second and third trimester, and were hospitalized for delivery. Follow-up results were obtained mainly by case review or telephone follow-up records.

Data collection

Ethnically Chinese woman, whose husband was also ethnically Chinese, were recuited when they were first documented at our prenatal diagnosis center. Spontaneously conceived singleton pregnancies were included for low-risk women with good nutritional status, and regular menstrual cycles of 28–30 days in the 12 months before pregnancy, were included.

Exclusion criteria were applied as follows: an unclear LMP; irregular menstrual cycles; maternal diseases that might affect fetal growth (e.g., diabetes mellitus, renal or immunological diseases); multiple pregnancies; severe complications of pregnancy (such as pre-eclampsia, pregnancy-induced hypertension, gestational diabetes, or late pregnancy hemorrhage); spontaneous abortions; fetal deaths; congenital malformations; chromosomal abnormalities; or neonatal deaths. No fetuses were excluded because of abnormal biometry or birth weight.

Commercial available ultrasound equipment (GE Healthcare Voluson E8, GE Healthcare Voluson 730, and Philips IU22) were used with curvilinear transabdominal sector probes (C5-2, C6-3 and V7-3, respectively). All sonographers received rigorous standardized training [15, 16]. CRL measurement followed the guidelines of the Fetal Medicine Foundation [17]. The central sagittal section of the fetus was selected for each CRL measurement. The fetal body was flexed naturally, the top of the head and the sacral tail were

displayed clearly, and the trunk showed a full sagittal section of the spine. The image was enlarged to display the fetal body, which occupied two-thirds to three-quarters of the screen. The cursor was placed on the image of the outer edge of the skin on the top of the fetal head to the outer edge of the sacrococcygeal skin, avoiding the limbs and yolk sac. Each CRL was measured three times, and the mean value was used for analysis.

Analysis of data

The original data are displayed as a scatter diagram of GA versus CRL (Fig. 1) [18]. A simple fractional polynomial regression model was derived to establish the regression formula and an optimal mean prediction formula was selected based on the correlation coefficient R^2. Among the published GA prediction formulae, papers with similar sample sizes and high quality were selected for comparison [10]. The mean of the difference between the GA predicted by these established CRL formulae and that estimated from the LMP were calculated to evaluate the systematic prediction error. The 95% confidence interval (CI) and quartile intervals of these differences were calculated to reflect the random prediction error [19]. All statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA); $P < 0.05$ was considered statistically significant, and unless otherwise stated data are shown as the mean ± standard deviation (SD).

Results

In total, 4710 pregnant women were included in the study, with a mean maternal age of 29.4 ± 3.7 years (range 18.2–47.5) and a mean maternal BMI of 20.5 ± 2.6 kg/m^2. There were 4527 women with Han ethnicity (96.11%) and 183 from minority ethnic groups (3.89%); 4255 primiparas (90.34%), and 455 multiparas (9.66%). The mean GA for ultrasound examinations was 88.7 ± 4.5 days, and the mean CRL was 63.48 ± 8.70 mm. A total of 1892 patients (40.17%) with natural deliveries, and 2818 patients (59.83%) with cesarean section deliveries were followed up. There were 2430 male fetuses (51.59%) and 2280 female fetuses (48.41%). Normal neonates were followed up until 1 month after birth, and all physical pediatric examination results were normal.

Figure 1 shows the raw data, which demonstrated a significant linear relationship between GA and CRL. The corresponding best-fit equation for the estimation of GA was selected as follows: $GA = 59.361513 + 0.461425 \cdot CRL$ ($R^2 = 0.8028$). Table 1 shows the differences in the results between this study and previous ones. The systematic prediction error using our own formula in this study population was 0.12 days (95% CI 0.05–0.21 days). The formulae from Sahota *et al.* [10], Hadlock *et al.* [6], and Papageorghiou *et al.* [13] resulted in systematic errors of 0.28, 0.62 and 0.14 days, respectively. The formulae from Robinson *et al.* [7], Verburg *et al.* [12] and McKenna *et al.* [9], resulted in negative systematic errors of − 0.79 days, − 0.26 days and − 0.99 days, respectively. In terms of random error, the quartile interval of the difference between the predicted and actual GA in this study was 3.01 days, lower than those in the previous six studies described above.

Table 1
Difference between predicted and actual gestational age (GA) in days.

	Formula for estimating GA based on CRL	Systemetic prediction error (95% CI)[a]	Median difference between predicted and actual GA (upper and lower quartiles).[b]	Random prediction error (interquartile distance).[b]
Our study	59.361513 + 0.461425×CRL	0.12 (0.05,0.21)	0.12 (− 1.48,1.53)	3.01
Papageorghiou et al.[13]	40.9041+(3.21585×$CRL^{0.5}$) + 0.348956×CRL	0.14 (0.04,0.23)	0.14 (− 1.64,1.73)	3.37
Verburg et al. [12]	exp (1.4653 + 0.001737 × CRL + 0.2313 × log(CRL)	−0.26 (− 0.34,−0.16)	−0.26 (− 1.86,1.20)	3.06
Sahota et al. [10]	26.643 + 7.822×$CRL^{0.5}$	0.28 (0.20,0.38)	0.28 (− 1.32,1.78)	3.10
Hadlock et al. [6]	7×(exp(1.684969 + 0.315646×(CRL/10) -0.049306×$((CRL/10)^2)$ + 0.004057×$((CRL/10)^3)$ − 0.000120456×$((CRL/10)^4)$))	0.62 (0.55,0.70)	0.62 (− 1.05,2.19)	3.24
Robinsin et al. [7]	8.052 x ($CRL^{0.5}$) + 23.73	−0.79 (− 0.87,−0.71)	−0.79 (− 2.43,0.74)	3.17
McKennan et al.[9]	32.61967 + 2.62975× CRL − 0.42399 × log(CRL) × CRL	−0.99 (− 1.07,−0.91)	−0.99 (− 2.56,0.50)	3.06

[a]The difference between the actual and predicted GA estimated by our formula showed a skewed distribution, so the median is used to represent the overall prediction error.

[b]For the same reason, in these columns error is expressed as the interquartile distance.

Discussion

Main findings

There has been great heterogeneity in the study design, statistical analysis and presentation of results in reported formulae for calculating GA [14]. Some of the studies included nonselected or low-risk pregnant women, but most of them did not use adequate quality control standards. In other studies, retrospective analyses were used to obtain data from clinical workstations, with a high risk of bias. The purpose of our study was to establish a formula for calculating GA for naturally conceived fetuses at 11–14 weeks of

gestation in the mainland of China. Unified enrollment standards, clinical procedures, data collection procedures and strict quality control procedures were used, so that the examination results could be promoted widely. All data in this study were measured specifically for the purpose of this study, and were obtained from a prospective study rather than a retrospective clinical database. According to the study design recommended by Altman et al. [20], low-risk pregnant women with a naturally conceived singleton pregnancy, and a clear LMP date were selected, and each fetus was measured only once during pregnancy. All pregnant women were followed up until the birth of the fetus, and data were excluded only when the fetus presented with congenital malformations or intrauterine death, to avoid generating an abnormal database.

In this study, GA was calculated according to the first day of the LMP. We selected only pregnant women who had records of regular menstrual cycles of 28–30 days for at least 1 year before pregnancy. They had not taken ovulation-inducing or contraceptives drugs or other estrogenic hormones for at least 6 months before pregnancy. Other methods used previously to calculate the GA have included the date of oocyte collection in ART cycles, serum human chorionic gonadotropin levels, elevated luteinizing hormone levels, the timing of embryo transfer in ART cycles, ultrasound detection of follicular rupture, cervical mucus morphology, basal body temperature increases, and the date of sexual intercourse. Some studies have used the GA of fetuses produced by in vitro fertilization (IVF) as a gold standard. However, fetuses produced through IVF cannot be identical biologically to naturally conceived ones because there might be differences between the dates of ovulation and conception. IVF-derived fetuses might also have growth difference during the first trimester. The biological characteristics of pregnant women following ART might be different from low-risk women with natural conceptions. Therefore, we believe that the application of formulae for evaluating GA derived from ART-conceived fetuses to naturally conceived fetuses is probably invalid.

The formula for calculating GA obtained in this study was based on univariate linear regression analysis, similar to that of McKennan *et al.* [9]. Systematic prediction errors and random prediction errors were used to evaluate the differences in formulae for estimating GA between this study and others. Sladkevicius *et al.* [21] summarized 21 CRL-based dating formulae, among which three were selected from naturally conceived fetuses with relatively large sample sizes, including the studies by Robinson *et al.* [7] in 1975, Hadlock *et al.* [6] in 1991 and von Kaisenberg *et al.* [11] in 2002. However, Sahota et al. [10] pointed out that there was actually no formula for calculating GA in the study by von Kaisenberg *et al.* [11], which was incorrectly derived by Sladkevicius *et al.* [21] based on a size estimation formula. Napolitano *et al.* [14] carried out a systematic analysis on formulae for calculating GA, and four studies with scores higher than 18 points (29-point maximum) were selected: Sahota *et al.* [10], Verburg *et al.* [12], Robinson *et al.* [7], and McKennan *et al* [9]. In 2014, Papageorghiou *et al.* [13] proposed a “worldwide” CRL-based dating formula from data of 4321 fetuses. The results of our study was compared with the above six studies [6, 7, 9, 10, 12, 13] and our formula lay in the middle of them. Three studies overestimated the GA, and three underestimated it, compared with our study. Our results were very consistent with the recent high-quality studies, such as those by Papageorghiou *et al.* [13], Sahota *et al.* [10] and Verburg *et al.* [12]. The prediction differences were + 0.14, + 0.28 and − 0.26 days, respectively.

However, the results of this study had relatively large differences from some relatively old papers, such as those of Robinson *et al.* [7] and Hadlock *et al.* [6], which might be related to the poor resolution of the instruments used in their studies. We believe that there is no clinically significant difference in CRL-based GA formulae derived from Chinese and non-Chinese fetuses [10, 14]. At the same time, this suggests that fetal growth and development are similar between different populations when methodological standards are high and appropriate selection is made.

Strengths and limitations

It should be noted that one disadvantage of estimating GA by measuring fetal CRL alone using ultrasound is the unknown biological variation of this measure during the first trimester of pregnancy. Therefore, we recommend collecting all information (including LMP and assessing its reliability) from pregnant women at their first visit in the first trimester [22]. When the GA calculated by measuring CRL by ultrasound and that from LMP are basically consistent, the GA can be calculated according to the date of the LMP. However, when the timing of the LMP is very accurate and reliable, and there is a big difference from the GA calculated by CRL, clinics should suspect that the fetus might have pathological abnormalities causing disorders of growth and development, which need to be further monitored and diagnosed [23, 24]. At the same time, calculated variabilities in the GA, such as SD values or percentiles, should be explained to pregnant women as estimated prediction error.

Conclusions

A formula for calculating GA among Chinese fetuses based on CRL at 10–15 weeks of gestation with no significant systematic error was obtained in this study. It is highly consistent with formulae for calculating GA obtained from other high-quality studies published in recent years.

Abbreviations

GA: gestational age; LMP: last menstrual period; CRL: crown–rump length.

Declarations

Acknowledgments

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Authors' contributions

HM, YXJ conceived the idea, wrote the protocol, submitted the ethics approval form.FD primarily analysed the data. YXZ analysed parts of the data and drafted the final manuscript for submission. ZHX, YSOY,

SLL, QC, QQW, RL, TR, ALC, XLC, TZY, PC, HNX, HL, QD, MY, XY, JL, JWT, KS, HL checked the patient and got the data. All authors have read and approved the manuscript

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Availability of data and materials

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Peking Union Medical College Hospital and other relevant hospitals. All pregnant women participating in this study signed informed consent forms.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

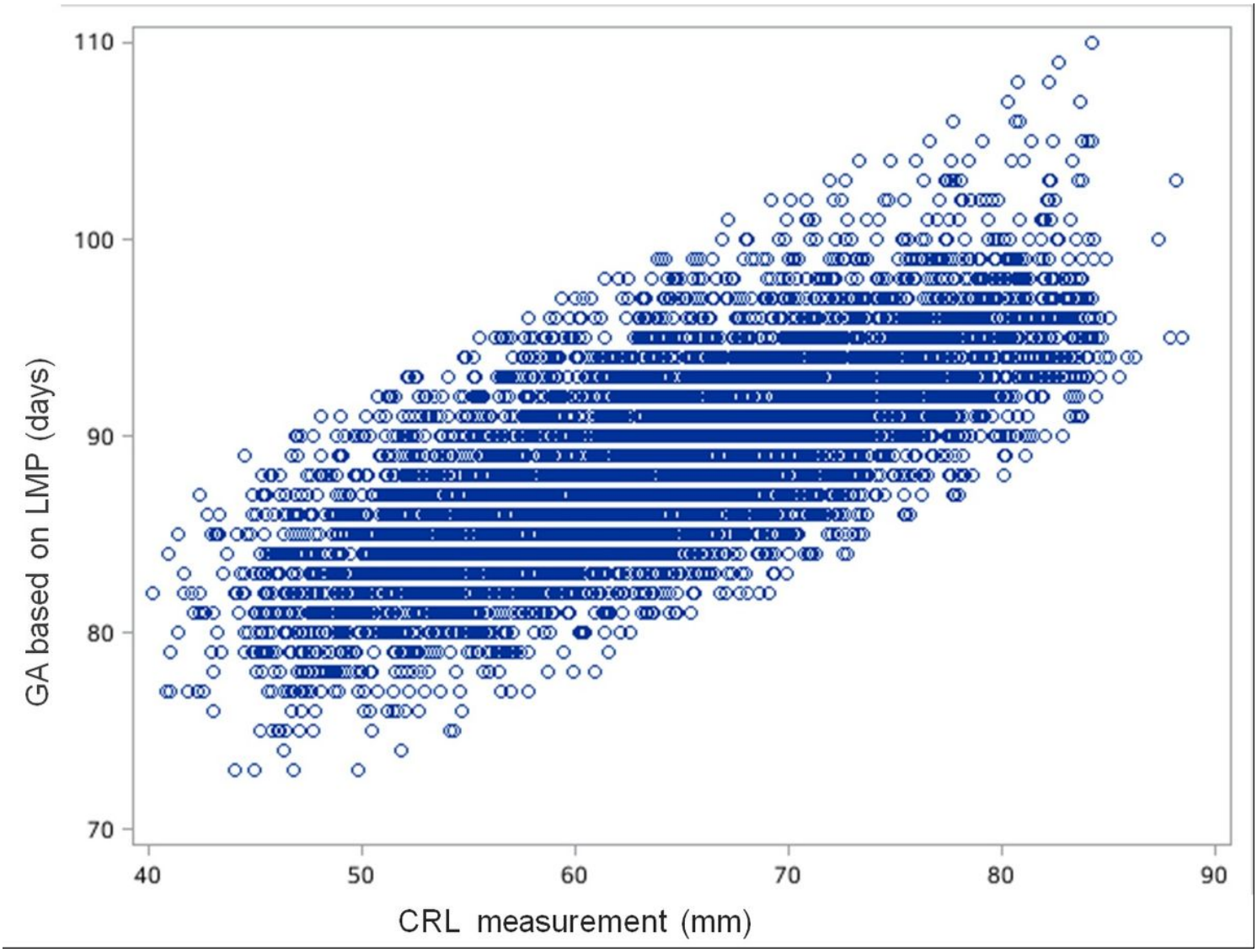

Figure 1

Scatter plot of gestational age (GA) versus crown–rump length (CRL) in 4710 Chinese fetuses.