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Original Research

Femur length in normal fetuses and the correlation between crown-rump length and gestational age at 11–14 weeks in a Chinese Han population: a preliminary study

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Summary

Objective: To establish normative data for the distribution of fetal femur length (FL) with increasing crown-rump length (CRL) and gestational age (GA) at 11–14 weeks, and to construct equations of fetal FL among normal fetuses in a Chinese Han population. *Materials and Methods:* The present retrospective review study included singleton fetuses assessed by ultrasonography between 11 and 14 weeks gestation from March 2015 to May 2016 at the First Affiliated Hospital (College of Medicine of Zhejiang University). The FL and CRL were measured and recorded. The regression models were fitted to estimate the mean at each GA or CRL. *Results*: There were 414 fetuses included. The equations generated to predict the FL from the GA or CRL had a high goodness-of-fit. The regression equations were described as follows: FL=0.479*GA^2-9.15*GA+47.018 and FL=0.001*CRL^2+0.032*CRL+0.424. *Conclusion:* The equations generated can be used to predict FL in a Chinese Han population and can be useful to detect fetal skeletal dysplasia, as well as early growth restriction, but additional clinical data is needed.

Key words: Femur length; First trimester; Crown-rump length; Gestational age; Chinese pregnant women; Ultrasound.

Introduction

To predict whether or not a pregnancy will be normal or have a poor perinatal outcome has been an essential part of obstetric practice for a long time. Fetal femur length (FL) is the only long bone routinely measured during second and third trimester ultrasound examinations. Some studies have shown that a short femur (FL below the 5th percentile) may be associated with skeletal dysplasia [1], chromosomal abnormalities [2], growth restriction [2], and small-for-gestational age neonates [3]. Most of these studies, however, were obtained during mid-pregnancy [4-6]; the growth pattern of the FL in the first trimester has seldom been reported [7-10].

It is well-known that along with the development of medicine and vast improvements in imaging technology, prenatal screening has partly shifted from the second trimester to the first trimester in the past decade. Thus, the aim of the current study was to establish normative data for the distribution of FL with increasing crown-rump length (CRL) and gestational age (GA) at 11–14 gestational weeks. Because the majority of reproductive-age women in China are of Han ethnicity, only the Chinese Han population was included.

Materials and Methods

The current study was approved by the Ethical Review Committee of this hospital. The authors conducted a retrospective review study from March 2015 to May 2016. All pregnant women underwent routine NT ultrasound exams at the First Affiliated Hospital (College of Medicine of Zhejiang University).

The inclusion criteria were as follows: (1) both parents were ethnic Han Chinese, (2) singleton pregnancy at term, (3) GA was determined by the last menstrual period (LMP) and CRL with a discrepancy between the two parameters ≤ 7 days, and (4) neonate information with a known normal outcome (all pregnancies were reviewed from electronic medical records or telephone follow-up).

The exclusion criteria were as follows: (1) maternal chronic diseases, such as type 2 diabetes, hypertension, renal diseases, and systemic lupus erythematosus, (2) fetuses with chromosomal abnormalities or congenital malformations, (3) unknown LMP or LMP suspected to be incorrect, and (4) women with a known history of alcohol, drug, or tobacco abuse.

FL and CRL were measured by three sonographers with > 5 years of experience in obstetric ultrasonography. All ultrasound scans were performed transabdominally with a 2-8 MHz convex transducer. The fetus was in a neutral position with optimum magnification when the CRL was measured and the placement of calipers connected both the crown and rump of the fetus [11]. If it was difficult to properly measure the CRL due to fetal position, the authors repeated the ultrasound after fetal movement or after the mother ambulated. The femoral diaphysis length was meas-

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Table 1. — *Demographic data of 414 pregnant women.*

Characteristics	Value
Maternal ethnicity	Han Chinese
Maternal age (years)	28.7 ± 3.9
Maternal height (cm)	160.2 ± 4.9
Maternal weight (kg)	52.2 ± 7.9
Maternal Body mass index (kg/m^2)	20.4 ± 3.3
Gestational age at visit (days)	89.2 ± 5.5
Nulliparous	295 (71.3)
CRL of fetuses at visit (mm)	65.1 ± 12.5

ured from the greater trochanter to the lateral condyle on a longitudinal scan at an approximate angle of 90° to the insonating beam [9].

Data were carefully checked before transfer to an Excel spread sheet and analyzed with SPSS software (version 19.0). All parameters were expressed as the mean ± SD, and frequencies were expressed as percentages. The FL and CRL were measured in millimeters and the GA was measured in days and calculated in weeks. A $p < 0.05$ was considered statistically significant.

A least squares regression model which estimated the mean FL as a function of GA or CRL was chosen based on the F-test for significance of regression and adjusted R square (R^2). The relationship between the CRL and GA was also assessed by regression analysis. The centiles for the FL were based on the regression model. Percentiles of FL were calculated using the following formula: centile=mean FL± (Z-score×SD), where the Z-score is the normal equivalent deviate (±1.645 for the 5th and 95th centiles). The SD was the standard deviation of the FL. The standard errors of the FL estimate were calculated using the CRL or GA, and compared to determine whether or not the CRL was a better predictor for the FL than the GA. Then, the cases were divided into five groups based on the CRL at 10-mm intervals and three groups based on the GA at one-week intervals. The predicted mean FL was compared with previous studies.

Results

There were 414 fetuses included in the present study based on inclusion and exclusion criteria from March 2015 to May 2016. All examinations of the fetuses were normal throughout the three trimesters and the one-minute Apgar scores were 8–10. The maternal characteristics are shown in Table 1.

The best description of the relationship between the CRL and GA was achieved by the following quadratic function: CRL=0.031*GA^2-3.475*GA+131.006, R^2=0.738, $p < 0.0001$ (the GA is expressed in days and the CRL is expressed in mm). The mean CRL, which was derived by the present equation, was not statistically different than that reported by Robinson *et al.* [12] (Figure 1).

The relationship between the expected FL and CRL, and GA were best-fitted with a quadratic polynomial regression and can be described as follows, in which the FL and CRL are expressed in mm and the GA is expressed in weeks:

FL=0.479*GA^2-9.15*GA+47.018 (R^2=0.675, $p < 0.0001$)

FL=0.001*CRL^2+0.032*CRL+0.424 (R^2=0.842, $p < 0.0001$)

The R^2 is close to 1 and $p < 0.001$, which indicates a high level of goodness-of-fit between the expected data and raw data. The residuals of CRL and GA were fitted by a straight line. Figures 2 and 3 show the mean and 95% data intervals for the FL in relation to the CRL and GA, respectively.

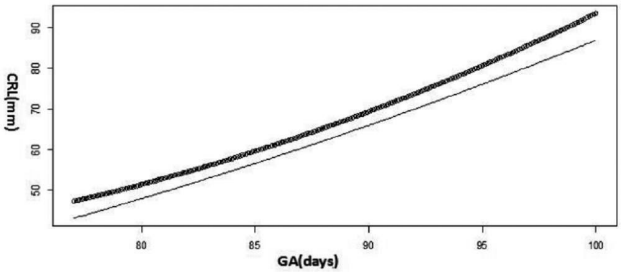

Figure 1. — Comparison of models for predicting the mean femur length between the present study (—) and that reported by Robinson *et al.* (—).

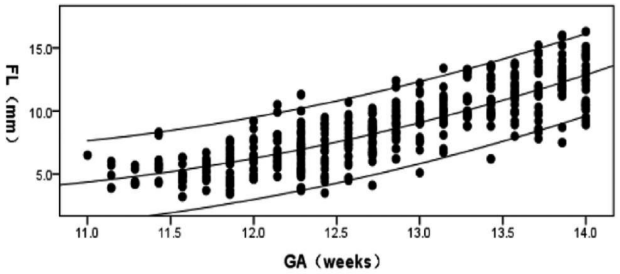

Figure 2. — Mean and 95% reference interval for polynomial model fitted to femur length (FL) in relation to gestational age (GA).

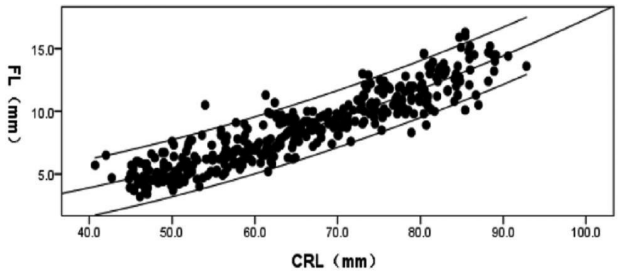

Figure 3. — Mean and 95% reference interval for polynomial model fitted to femur length (FL) in relation to crown-rump length (CRL).

The 95% prediction interval and the standard error for estimating the FL were ±2.65 (0.11) when using the CRL as predictor; the R^2 as a function of the CRL was 0.842. Using GA as a predictor, the values were ±9.5 (0.52) for the FL. According to Wisseret *et al.* [13], the confidence interval for the estimation for GA (±4 days) should be considered. Furthermore, the R^2 as a function of the GA was 0.675.

Then, the included fetuses were divided into five and three groups based on the CRL and GA, respectively. The

Table 2. — *Five categories based on the CRL in 10-mm intervals*

CRL	n	5th perentile	Mean	95th perentile	SD
40-50	60	3.5	5.0	6.7	0.9
50.1-60	93	4.2	6.3	8.5	1.3
60.1-70	110	6.3	8.3	9.9	1.2
70.1-80	84	8.6	10.5	12.7	1.3
>80	66	10.0	12.8	15.7	1.7

Table 3. — *Three categories based on the GA in 1-week intervals*

GA	n	5th perentile	Mean	95th perentile	SD
11^{+0}-12^{+0}	91	3.8	5.6	8.2	1.3
12^{+1}-13^{+0}	173	4.6	7.7	10.6	1.9
13^{+1}-14^{+0}	150	8.2	11.4	14.7	2.0

Table 4. — *Comparison of the means of FL (mm) at 12–13 weeks gestation*

		Our study	Chitty's study[9]	Jeanty's study[10]
12-week				
	Number	173	8	8
	Mean±SD	7.7±1.9	7.7±1.8	8.1±2.5
13-week				
	Number	150	18	12
	Mean±SD	11.4±2.0	10.9±1.8	11.0±2.5

expected 5th, 50th, and 95th percentile values for the FL were obtained for a given CRL or GA (Table 2).

Discussion

In this study, reference equations for the CRL from the GA and the FL from the CRL or GA were obtained by fitting polynomial equations to a Chinese Han population between 11 and 14 weeks gestation (CRL, 40–93 mm). All of these equations were well-fitted. Centiles, including the 5th, 50th, and 95th) for the FL at 10-mm intervals of CRL and one-week intervals for the GA were provided.

The CRL was first mentioned by Robinson [14] in 1973, and measuring CRL has since become a routine biometric parameter in most countries. The equation for CRL and the corresponding GA between 11 and 14 weeks gestation was compared with Robinson[13], which was constructed by transvaginal scanning in an unselected population. The mean values were similar, thus the relationship between CRL and GA appears to be uniform among different ethnic populations.

It has been demonstrated that Asian populations have the shortest FL when compared with other ethnic groups [15, 16]. The software programs of reference charts installed in the ultrasound equipment in Chinese hospitals, however, is based on American reports and the FL is less than Caucasian populations, thus misleading obstetricians. The present study only included Chinese. Interestingly, the means of the FL in this study at 12 and 13 gestational weeks were not significantly different from Caucasians when compared with the Jeanty and Romero [10] and Chitty *et al.*'s [9] studies. The reasons were due to the examination method, which was based on transvaginal scans, while the present authors used transabdominal scanning. Furthermore, Jeanty and Romero and Chitty *et al.* did not have as many gravidas in the gestational week range as in the present study [9, 10].

The progress of ultrasound technology has made it possible to detect fetal structural and genetic abnormalities in the first trimester. Early diagnosis of fetal skeletal anomalies in the first trimester has been reported [17, 18] and the association between nuchal translucency and skeletal dysplasia in the first trimester has been described [19]. In the present study the authors generated regression equations in early pregnancy. For a given GA or CRL, the formula helps detect early growth restriction or short extremities and facilitates appropriate intervention in the first trimester[15].

Kustermann *et al.* [8] and Salomon *et al.* [20] showed that the fetal biparietal diameter, head circumference, and abdominal circumference correlate better with CRL than GA, but the FL was not included. In this study, the authors compared the R^2 of equations and standard error for estimating the FL based on CRL or GA, and the results support the finding that the FL is a better estimate in relation to the CRL.

The present authors excluded abnormal cases and all ultrasound exams were performed by three experienced examiners with two apparatuses that avoid the effect of apparatus settings, which served as strengths in this study. The patients were all of Chinese Han origin, which also avoided the effect of race. One of the limitations of the study was the sample size, therefore increasing the number of participants in future studies will strengthen this relationship. The present authors were unable to identify a sufficient number of appropriate studies for comparison because most studies reporting the fetal FL were conducted using pregnancies in the second trimester.

In conclusion, the present authors have established equations using the GA or CRL for estimating the FL between 11 and 14 weeks gestation in the Chinese Han population. Although the equations could be useful in the early assessment of femur abnormalities, monitoring the femur morphology and growth are also essential. The purpose of this study was to determine the normal length of the fetal femur and knowing the normal FL will help us recognize abnormalities.

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