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Femur and humerus length in trisomy 21 fetuses at 11–14 weeks of gestation

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KEYWORDS: chromosomal defect; femur length; first trimester; humerus length; nuchal translucency; screening; trisomy 21

ABSTRACT

Objective *To determine the value of measuring fetal femur and humerus length at 11–14 weeks of gestation in screening for chromosomal defects.*

Methods *Femur and humerus lengths were measured using transabdominal ultrasound in 1018 fetuses immediately before chorionic villus sampling for karyotyping at 11–14 weeks of gestation. In the group of chromosomally normal fetuses, regression analysis was used to determine the association between long bone length and crown–rump length (CRL). Femur and humerus lengths in fetuses with trisomy 21 were compared with those of normal fetuses.*

Results *The median gestation was 12 (range, 11–14) weeks. The karyotype was normal in 920 fetuses and abnormal in 98, including 65 cases of trisomy 21. In the chromosomally normal group the fetal femur and humerus lengths increased significantly with CRL (femur length* $= -6.330 + 0.215 \times CRL$ *in mm,* $r = 0.874$, $P < 0.0001$; *humerus length* $= -6.240 + 0.220 \times CRL$ *in mm,* $r = 0.871$, $P < 0.0001$*). In the Bland–Altman plot the mean difference between paired measurements of femur length was 0.21 mm (95% limits of agreement −0.52 to 0.48 mm) and of humerus length was 0.23 mm (95% limits of agreement −0.57 to 0.55 mm). In the trisomy 21 fetuses the median femur and humerus lengths were significantly below the appropriate normal mean for CRL by 0.4 and 0.3 mm, respectively* ($P = 0.002$)*, but they were below the respective 5th centile of the normal range in only six (9.2%) and three (4.6%) of the cases, respectively.*

Conclusion *At 11–14 weeks of gestation the femur and humerus lengths in trisomy 21 fetuses are significantly reduced but the degree of deviation from normal is too small for these measurements to be useful in screening for trisomy 21.*

INTRODUCTION

Trisomy 21 is characterized by short stature and in the last decade several ultrasonographic studies have reported that during the second trimester the condition is associated with relative shortening of the femur and more so the humerus[1–5]. In the combined data from two leading centers of obstetric ultrasound, shortening of the femur was observed in 5.2% of 9331 normal fetuses and 41.4% of 319 trisomy 21 fetuses; the respective values for short humerus were 1.5% and 33.4%[6,7].

The aim of the present study was to determine the potential value of measuring fetal femur and humerus length at 11–14 weeks of gestation as a screening test for trisomy 21.

METHODS

We measured the fetal femur and humerus lengths at the routine ultrasound scan carried out before fetal karyotyping, by chorionic villus sampling (CVS), in 1018 consecutively examined fetuses at 11–14 weeks of gestation. There were 992 singleton pregnancies and 13 twin pregnancies in which each fetus was examined. The study was carried out in our center during a 5-month period (November 2002–March 2003). In all cases there was prior screening for chromosomal defects by a combination of maternal age and fetal nuchal translucency (NT) and the patients included in this study were those that after counseling elected to have invasive testing[8].

The fetal femur and humerus were examined by transabdominal sonography and the aim was for the angle between the ultrasound transducer and the bone

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examined to be about 45° since in this position a sharp image of the edges of the bones is obtained (Figure 1). Bone length was measured with calipers on the screen and the magnification of the image was such that each increment in the distance between calipers was only 0.1 mm. The fetal NT and crown–rump length (CRL) were also measured[8]. Examination of the fetal femur and humerus was successfully achieved in all cases and this added 1–3 min to the overall time of about 15 min for the 11–14-week scan.

Demographic characteristics and ultrasound findings were recorded in a fetal database at the time of the examination. In all cases CVS was carried out and when the fetal karyotype results were made available they were entered in the database also.

Statistical analysis

In the chromosomally normal group, regression analysis was used to determine the significance of the association between femur and humerus length with CRL. Each measurement of the long bones' length was then expressed as a difference from the expected mean for CRL (delta value) and the Mann–Whitney *U*-test was used to determine the significance of difference in the delta values between the chromosomally normal and trisomy 21 fetuses. Regression analysis was used to determine the significance of the association between delta femur and humerus length and delta NT thickness both in the chromosomally normal and trisomy 21 fetuses. In the 70 cases with paired measurements, the Bland–Altman plot (the difference between the two paired measurements versus the average of the two measurements) was performed and the 95% tolerance interval for paired observations was calculated[9].

RESULTS

The median maternal age was 37 (range, 17–48) years, the median fetal CRL was 65 (range, 45–84) mm and the median gestation was 12 (range, 11–14) weeks. The maternal ethnic group was Caucasian in 908 (89.2%) cases, Afro-Caribbean in 40 (3.9%), Asian in 39 (3.8%), Chinese or Japanese in 18 (1.8%) and mixed in 13 (1.3%). The fetal femur and humerus were successfully examined in all cases. The fetal karyotype was normal in 920 pregnancies and abnormal in 98, including 65 cases of trisomy 21 and 33 with other abnormalities (14 of trisomy 18, five of trisomy 13, two of trisomy 22, eight of Turner syndrome, two of Klinefelter syndrome, one of triploidy and one partial deletion of chromosome 3).

In the Bland–Altman plot the mean difference between paired measurements of femur length was 0.21 mm and the 95% limits of agreement were −0.52 to 0.48 mm (Figure 2). The respective values for humerus length were 0.23 mm (95% limits, −0.57 to 0.55 mm).

In the chromosomally normal group the fetal femur and humerus length increased significantly with CRL from respective means of 3.3 and 3.7 mm at CRL 45 mm to 11.9 and 12.5 mm at CRL 85 mm, respectively (femur length $= -6.330 + 0.215 \times$ CRL in mm, $r = 0.874$, $P < 0.0001$; humerus length $= -6.240 + 0.220 \times$ CRL in mm, $r = 0.871$, $P < 0.0001$; Figure 3).

In the trisomy 21 fetuses the median femur length was significantly below the normal mean for CRL by 0.386 mm (range, −2.583 to 2.132; $P = 0.002$). Similarly, the median humerus length was significantly below the appropriate normal mean for CRL by 0.338 mm (range, −2.174 to 2.007; $P = 0.002$). In the fetuses with other chromosomal abnormalities the median femur length was not significantly different from the normal mean for CRL (mean difference, 0.236 mm; range, −2.694 to 2.184; $P = 0.212$). Similarly, the median humerus length was not significantly different from the normal mean for CRL (mean difference, 0.078 mm; range, −2.233 to 1.861; $P = 0.582$). In the trisomy 21 fetuses the median femur and humerus lengths were below the respective 5th centile of the normal range in only six (9.2%) and three (4.6%) of the cases, respectively (Figure 4).

There was no significant association between the delta score of bone length and delta NT in either the chromosomally normal fetuses ($r = -0.061$, $P = 0.066$

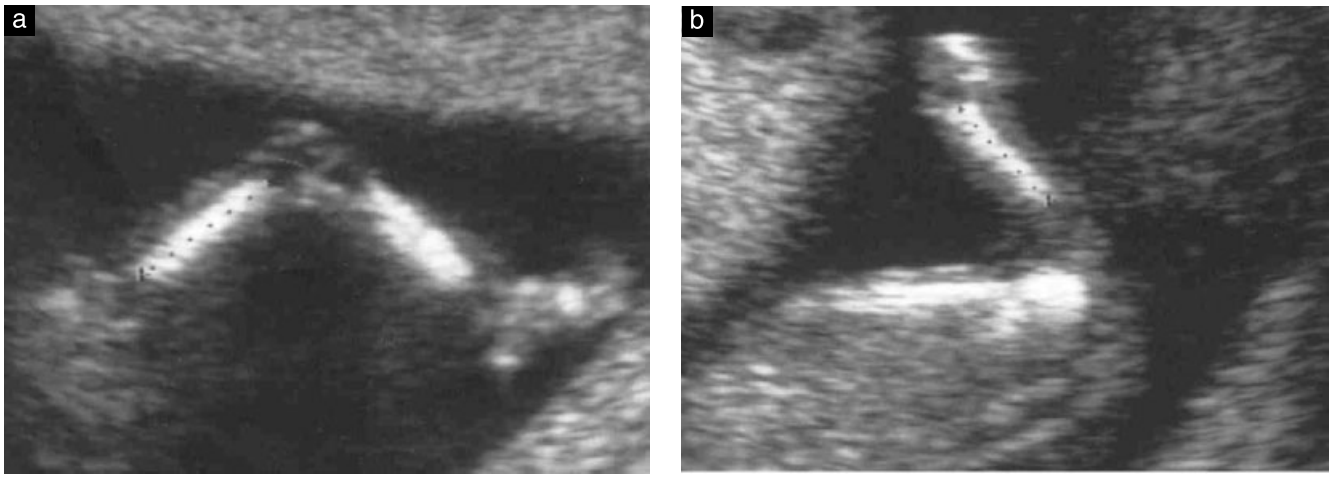

Figure 1 Ultrasound image of a 12-week fetus demonstrating measurement of (a) femur and (b) humerus length.

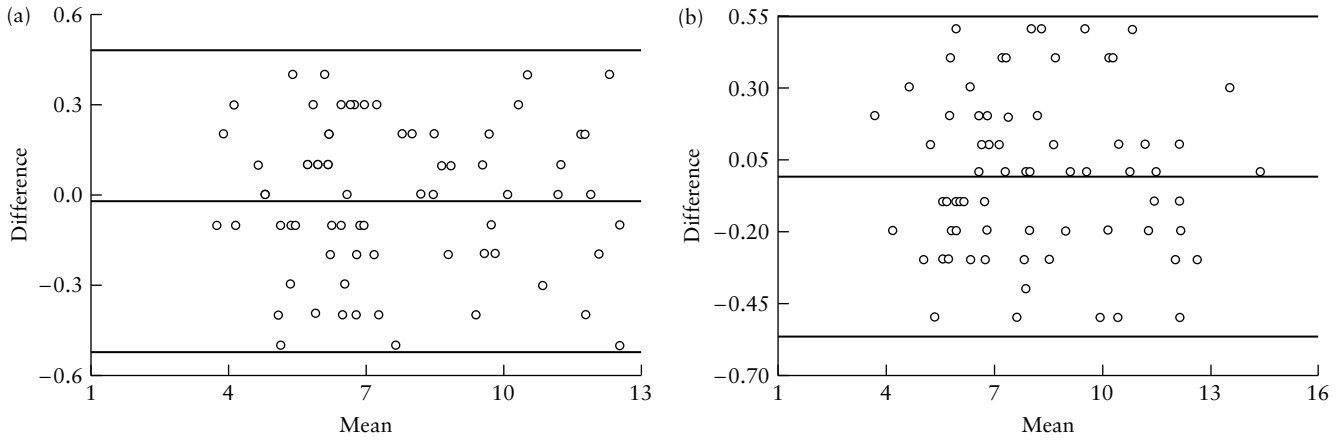

Figure 2 Bland–Altman plot of the difference against the mean of paired measurements in (a) femur and (b) humerus length.

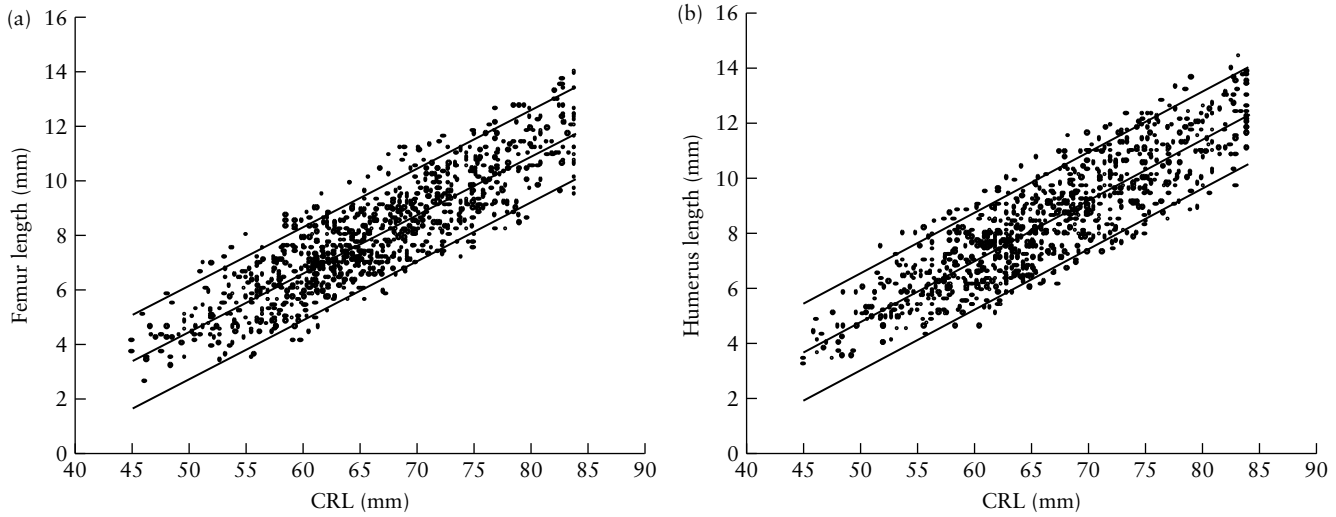

Figure 3 Reference range (mean, 95th and 5th centiles) with crown–rump length (CRL) in (a) femur and (b) humerus length in the chromosomally normal fetuses at 11–14 weeks of gestation.

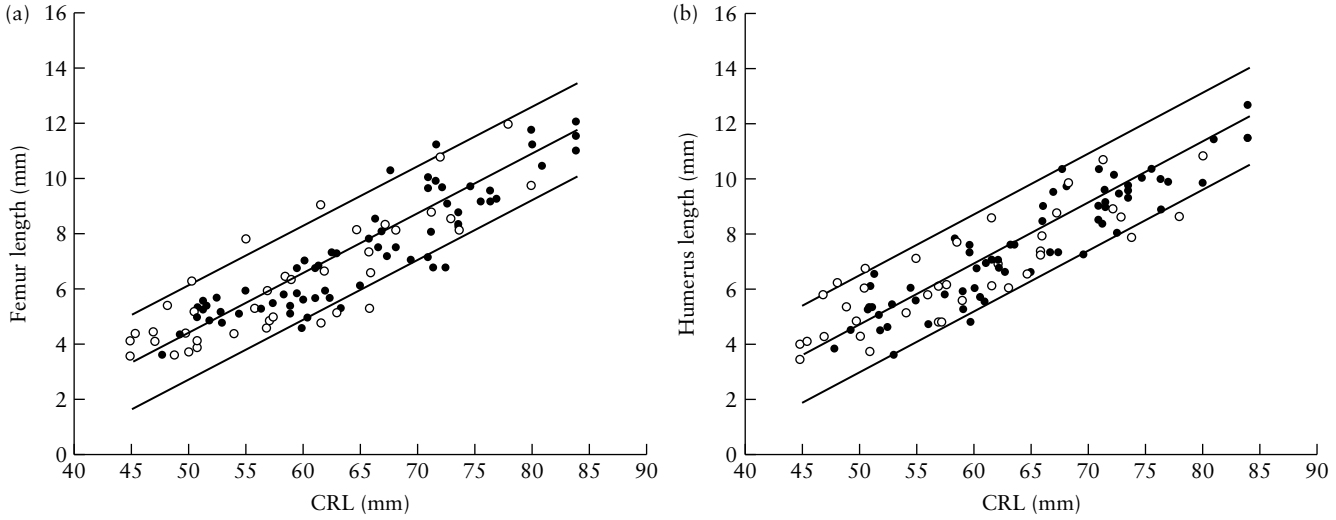

Figure 4 Fetal (a) femur and (b) humerus length in trisomy 21 (●) and other chromosomal defects (○) plotted on the reference range (mean, 95th and 5th centiles) with crown–rump length (CRL) of the chromosomally normal fetuses.

Table 1 Femur and humerus length at crown–rump lengths of 45 and 85 mm in the present study and previous reports on long bones in the first trimester

		Femur length (mm)		*Humerus length (mm)*	
Study	*Scan route*	*CRL = 45 mm*	*CRL = 85 mm*	*CRL = 45 mm*	*CRL = 85 mm*
Kustermann *et al.* (1992)[10]	Vaginal	6.9	13.5		
Zorzoli *et al.* (1994)[11]	Vaginal	6.3	13.1	5.3	13.1
Rosati and Guariglia (1997)[12]	Vaginal	6.0	15.6	5.6	15.0
Gabrielli *et al.* (1999)[13]	Vaginal	5.1	12.4		
von Kaisenberg *et al.* (2002)[14]	Abdominal	4.8	12.6		
Present study	Abdominal	3.3	11.9	3.7	12.5

*For the majority of the previous studies approximate values were extracted from the information provided. CRL, crown–rump length.

for femur length; $r = -0.022$, $P = 0.507$ for humerus length) or the trisomy 21 fetuses ($r = 0.017$, $P = 0.891$ for femur length; $r = -0.096$, $P = 0.445$ for humerus length).

DISCUSSION

This study has demonstrated the feasibility of measuring the fetal femur and humerus length at 11–14 weeks of gestation. These bones were successfully visualized and measured in all fetuses and the length of both bones increased linearly with gestation. The mean values of our measurements were shorter than those in all previous reports (Table 1)[10–14]. The most striking difference is observed in the long bone measurements at CRL of 45 mm with our measurements being about half of those reported in studies from the early 1990s. The most obvious explanations are that, first, the resolution and magnification of the image have improved during the last 10 years, allowing better visualization of the bones and more accurate placement of the calipers, and second, we ensured that the artifactual echogenicity beyond each end of the bones was minimized by maintaining a 45° angle between the ultrasound transducer and the bone examined. An additional problem with some of the previous studies is the gestational assessment of the fetuses examined. For example, in one study the mean CRL at 15 weeks is reported to be 85.5 mm, which is a substantial underestimate of the true measurement[12].

The finding that in trisomy 21 fetuses at 11–14 weeks of gestation the femur and humerus lengths were significantly reduced is compatible with the well-described association of trisomy 21 and shortening of the long bones in both postnatal studies and prenatal sonographic data from the second trimester of pregnancy[1–7]. Furthermore, there was no significant association between the degree of femur or humerus shortening and increase in NT.

The relative shortening of the femur and humerus of trisomy 21 fetuses may increase with gestation. For example, a study examining the biparietal diameter to femur length ratio reported that the ratio was above the 95th centile of the normal range in 24% of trisomy 21 fetuses at 18–20 weeks but in only 11% of cases at 15–17 weeks[15]. In the present study at 11–14 weeks the femur length was below the 5th centile of the normal range in only 9% of trisomy 21 fetuses. An additional problem with early gestation is the poor reproducibility of the measurements. Thus, at 11–14 weeks the mean difference between paired measurements was 0.21 mm for femur length and 0.23 for humerus length and the mean difference in femur and humerus length between trisomy 21 and normal fetuses was only 0.4 mm and 0.3 mm, respectively. Consequently, measurement of femur and humerus length at 11–14 weeks is unlikely to be useful in screening for trisomy 21.

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