Ultrasound Obstet Gynecol 2006; **28**: 870–875
Published online 6 November 2006 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.3858

Brachycephaly and frontal lobe hypoplasia in fetuses with trisomy 21 at 11 + 0 to 13 + 6 weeks

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KEYWORDS: brachycephaly; first-trimester screening; frontothalamic distance; three-dimensional ultrasound; trisomy 21

ABSTRACT

Objective *To investigate the incidence of brachycephaly and frontal lobe hypoplasia in fetuses with trisomy 21 at 11 + 0 to 13 + 6 weeks of gestation.*

Methods *A three-dimensional (3D) volume of the fetal head was obtained before fetal karyotyping at 11 + 0 to 13 + 6 (median, 12 + 5) weeks of gestation in 100 fetuses that were subsequently found to have trisomy 21 and in 300 fetuses subsequently found to be chromosomally normal. The multiplanar mode was used to obtain a sequence of transverse views of the fetal head and to demonstrate the biparietal and suboccipitobregmatic views. We measured the biparietal diameter (BPD), the occipitofrontal diameter (OFD) and the frontothalamic distance (FTD) between the inner table of the frontal bone and the posterior thalami.*

Results *In the chromosomally normal group the BPD, OFD and FTD increased linearly with crown–rump length (CRL) from 16.7 mm, 19.0 mm and 12.1 mm at a CRL of 45 mm to 26.7 mm, 31.7 mm and 18.7 mm, respectively, at a CRL of 84 mm. In the trisomy 21 fetuses, compared to normal fetuses, there was shorter BPD (mean difference = −0.63 mm; 95% CI, −0.97 to −0.30 mm,* $P < 0.0001$*), OFD (mean difference = −1.41 mm; 95% CI, −1.75 to −1.07 mm,* $P < 0.0001$*) and FTD (mean difference = −0.77 mm; 95% CI, −1.02 to −0.54 mm;* $P < 0.0001$*) and higher BPD to OFD ratio (mean difference = 0.022; 95% CI, 0.012 to 0.032,* $P < 0.0001$*) but no significant difference in the FTD to OFD ratio (mean difference = 0.004; 95% CI, −0.006 to 0.013,* $P = 0.448$*).*

Conclusions *In fetuses with trisomy 21 at 11 + 0 to 13 + 6 weeks of gestation there is evidence of brachycephaIy but not of frontal lobe hypoplasia.* Copyright © 2006 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Postnatal and some prenatal studies have reported that trisomy 21 is associated with brachycephaly and frontal lobe hypoplasia (Table 1)[1–15]. An anthropometric study in 199 patients with trisomy 21 between 6 months and 61 years of age reported the finding of brachycephaly, because the head length was shorter than the head width[1]. In two postmortem studies with a combined total of 415 fetuses with trisomy 21 aborted at 15–40 weeks, the ratio of the biparietal diameter (BPD) to occipitofrontal diameter (OFD) or head circumference was significantly higher than in normal fetuses from as early as 15 weeks[2,3]. However, seven prenatal sonographic studies with a combined total of 136 fetuses with trisomy 21 at 9–23 weeks did not find a significant difference in the BPD to OFD ratio from chromosomally normal fetuses[4–10].

A postmortem study of 101 patients with trisomy 21 between the neonatal period and 5 years of age reported that the occipitofrontal length of their brain hemispheres was shorter than normal, owing to a reduction in frontal lobe growth[11]. Similarly, a magnetic resonance imaging (MRI) study reported that the volume of the frontal lobes in 16 patients with trisomy 21 was significantly lower than normal, but this difference was proportional to the overall reduction in brain volume[12]. Two prenatal sonographic studies of a combined total of 71 fetuses with trisomy 21 at 15–21 weeks reported that the frontothalamic distance (FTD) – defined as the distance between the inner table of the frontal bone and the posterior thalami – was significantly smaller than normal[14,15]. They suggested that this was an expression of frontal lobe hypoplasia and a useful sonographic marker for trisomy 21. In contrast, a study of seven fetuses with trisomy 21 at 16–21 weeks reported that the frontothalamic distance was not significantly different from normal[13].

A recent three-dimensional (3D) ultrasound study of 72 fetuses with trisomy 21 at 11 + 0 to 13 + 6 weeks

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Accepted: 22 August 2006

Table 1 Previous studies investigating brachycephaly (defined as increased biparietal diameter to occipitofrontal diameter ratio) and frontal lobe hypoplasia (defined as reduced frontothalamic distance) in trisomy 21

Reference	*Type of study*	*Trisomy 21* (n)	*Normal* (n)	*Age*	*Brachycephaly*	*Frontal lobe hypoplasia*
Allanson *et al.* 1993[1]	Anthropometry	199	1538	6 months–61 years	Yes	
Stempfle *et al.* 1999[2]	Postmortem	60	82	15–40 weeks	Yes	
Guihard-Costa *et al.* 2006[3]	Postmortem	355	922	15–38 weeks	Yes	
Perry *et al.* 1984[4]	Ultrasound	8	308	15–23 weeks	No	
Lockwood *et al.* 1987[5]	Ultrasound	16	180	16–21 weeks	No	
Brumfield *et al.* 1989[6]	Ultrasound	15	45	16 weeks	No	
Shah *et al.* 1990[7]	Ultrasound	17	17	15–23 weeks	No	
Borrell *et al.* 1997[8]	Ultrasound	14	555	13–18 weeks	No	
Rosati *et al.* 1999[9]	Ultrasound	36	1087	9–16 weeks	No	
Lim *et al.* 2004[10]	Ultrasound	30	551	14–18 weeks	No	
Schmidt-Sidor *et al.* 1990[11]	Postmortem	101	80	0–5 years		Yes
Pinter *et al.* 2001[12]	Anthropometry	16	15	5–23 years		Yes
Crade *et al.* 1991[13]	Ultrasound	7	37	16–21 weeks		No
Bahado-Singh *et al.* 1992[14]	Ultrasound	19	125	16–21 weeks		Yes
Winter *et al.* 2000[15]	Ultrasound	52	52	15–21 weeks		Yes

reported that the fetal head volume was smaller than in chromosomally normal fetuses[16].

The aim of this study was to investigate brachycephaly and frontal lobe hypoplasia in fetuses with trisomy 21 at 11 + 0 to 13 + 6 weeks' gestation by 3D ultrasound evaluation of the fetal head.

METHODS

A 3D volume of the fetal head was acquired before fetal karyotyping by chorionic villus sampling (CVS) at 11 + 0 to 13 + 6 weeks of gestation, in singleton pregnancies that had been evaluated for the risk of trisomy 21 by a combination of maternal age and fetal nuchal translucency (NT) thickness for crown–rump length (CRL)[17]. The 3D volume was obtained with the fetal head in the mid-sagittal plane and the transducer parallel to the nose. All 3D examinations were carried out transabdominally (RAB 4-8L probe, Voluson 730 Expert, GE Medical Systems, Milwaukee, WI, USA).

We searched our database to identify 3D volumes of the fetal head from 100 cases with trisomy 21 and 300 chromosomally normal fetuses. Two doctors with extensive experience in 3D ultrasonography subsequently examined the volumes without prior knowledge as to the fetal karyotype. The 3D volume of the fetal head was displayed in the three orthogonal planes that compose the multiplanar mode of the 3D image. The sagittal view showing the fetal profile in this mode was then selected and, as this plane was scrolled, the series of corresponding transverse and coronal images of the fetal head were simultaneously demonstrated. Measurements were obtained of the BPD, OFD and FTD (Figures 1 and 2). For the measurement of the FTD the plane was scrolled down to the level of the thalami as previously described[15].

Statistical analysis

In the chromosomally normal group, regression analysis was used to determine the significance of the association between CRL and BPD, OFD and FTD as well as the ratios BPD/OFD and FTD/OFD. Linear regression analysis was also used to examine whether the outcome variables were associated with the NT measurements or the presence/absence of nasal bone in both the normal and trisomy 21 fetuses. Before applying linear regression analysis we confirmed the goodness of fit of the model by checking the assumptions of normal distribution of the errors and the pattern of scedasticity and by plotting the predicted vs. observed values for the outcome variable.

Each measurement in both the chromosomally normal and the trisomy 21 fetuses was then expressed as a difference from the expected normal mean for CRL (delta

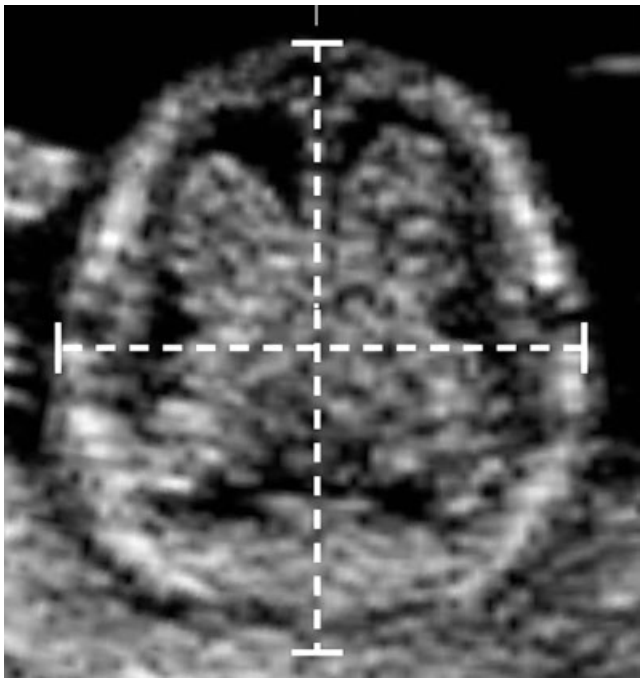

Figure 1 Measurement of the biparietal diameter and the occipitofrontal diameter.

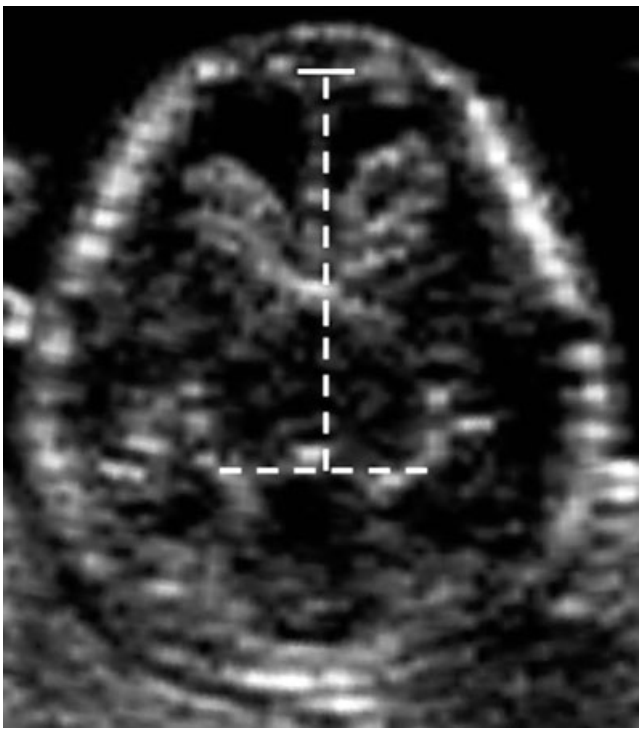

Figure 2 Measurement of the frontothalamic distance.

value). The Kolmogorov–Smirnov test confirmed that the delta values in both groups were normally distributed. Independent-samples *t*-test was used to determine the significance of difference in the delta values between the chromosomally normal and trisomy 21 fetuses.

In 30 cases, the Bland–Altman analysis was used to compare the measurement agreement and bias for each of two examiners and between the two examiners[18]. The data were analyzed using the statistical software SPSS 13.0 (Chicago, IL, USA) and Excel for Windows 2000 (Microsoft Corp., Redmond, WA, USA). A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

The median maternal age was 37 (range, 18–47) years, the median fetal CRL was 67 (range, 45–84) mm and the median gestation was 12 + 5 (range, 11 + 0 to 13 + 6) weeks. In the chromosomally normal group the BPD, OFD and FTD increased whilst the BPD/OFD ratio and FTD/OFD ratio decreased linearly with CRL (Table 2; Figures 3–6).

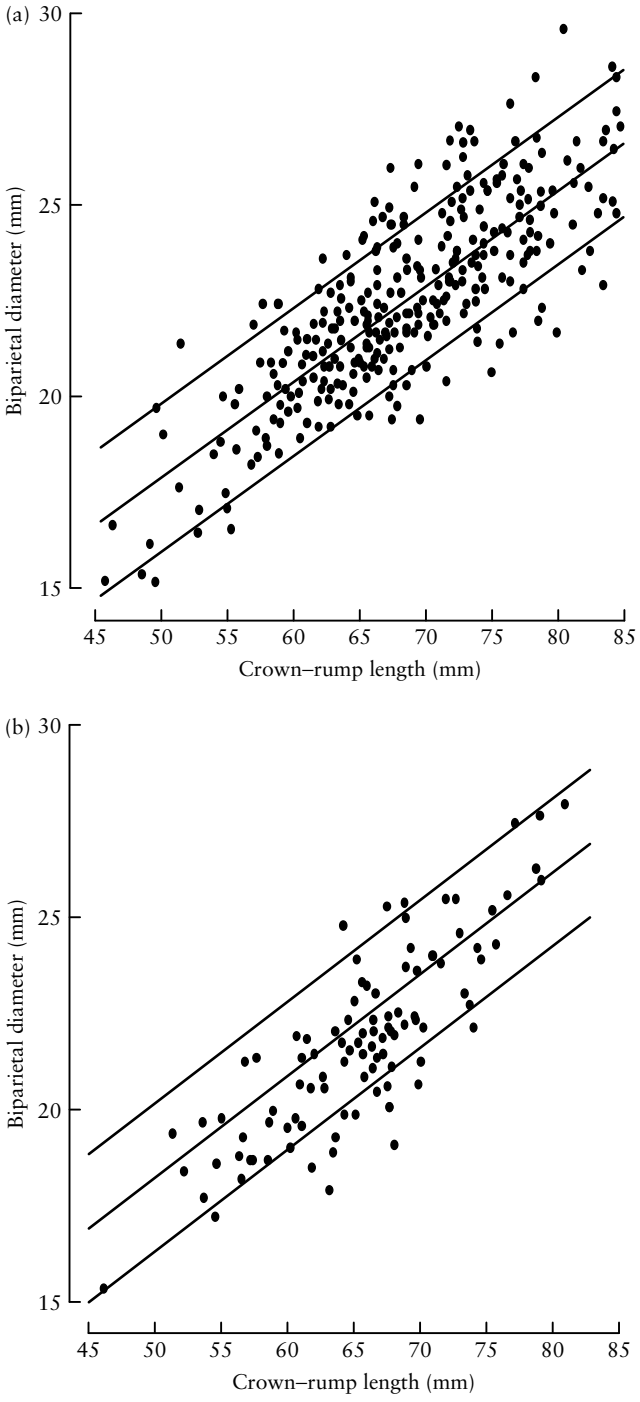

Figure 3 (a) Reference range (mean, 95th and 5th centiles) of biparietal diameter with crown–rump length in the chromosomally normal fetuses at 11 + 0 to 13 + 6 weeks of gestation. (b) Biparietal diameter in trisomy 21 fetuses plotted on the reference range with crown–rump length of the chromosomally normal fetuses.

Table 2 Linear regression of head measurements to crown–rump length (CRL) in the chromosomally normal fetuses

Fetal head measurement	*Regression equation*	*SD*	r	P
Biparietal diameter (BPD)	5.367 + 0.254 × CRL	1.501	0.805	< 0.0001
Occipitofrontal diameter (OFD)	4.456 + 0.324 × CRL	1.511	0.865	< 0.0001
Frontothalamic distance (FTD)	4.489 + 0.169 × CRL	1.172	0.757	< 0.0001
FTD/OFD	0.677 − 0.001 × CRL	0.041	0.201	< 0.0001
BPD/OFD	0.915 − 0.001 × CRL	0.026	0.160	0.006

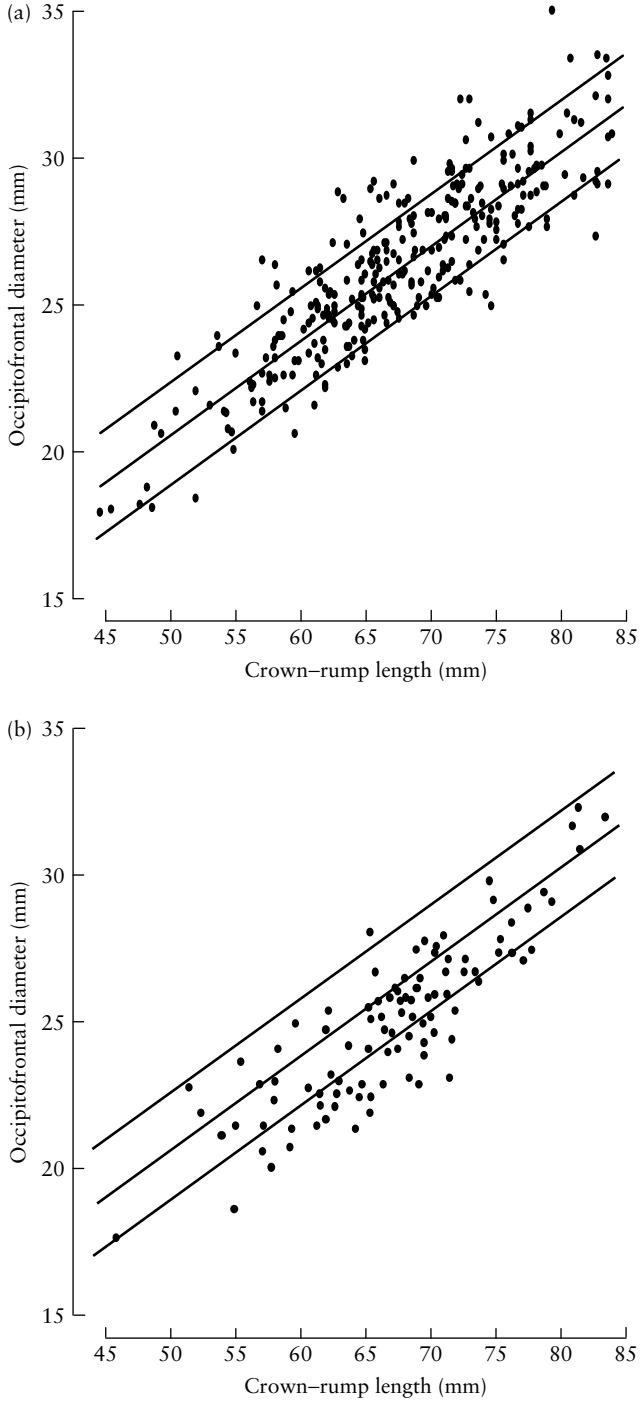

Figure 4 (a) Reference range (mean, 95th and 5th centiles) of occipitofrontal diameter with crown–rump length in the chromosomally normal fetuses at 11 + 0 to 13 + 6 weeks of gestation. (b) Occipitofrontal diameter in trisomy 21 fetuses plotted on the reference range with crown–rump length of the chromosomally normal fetuses.

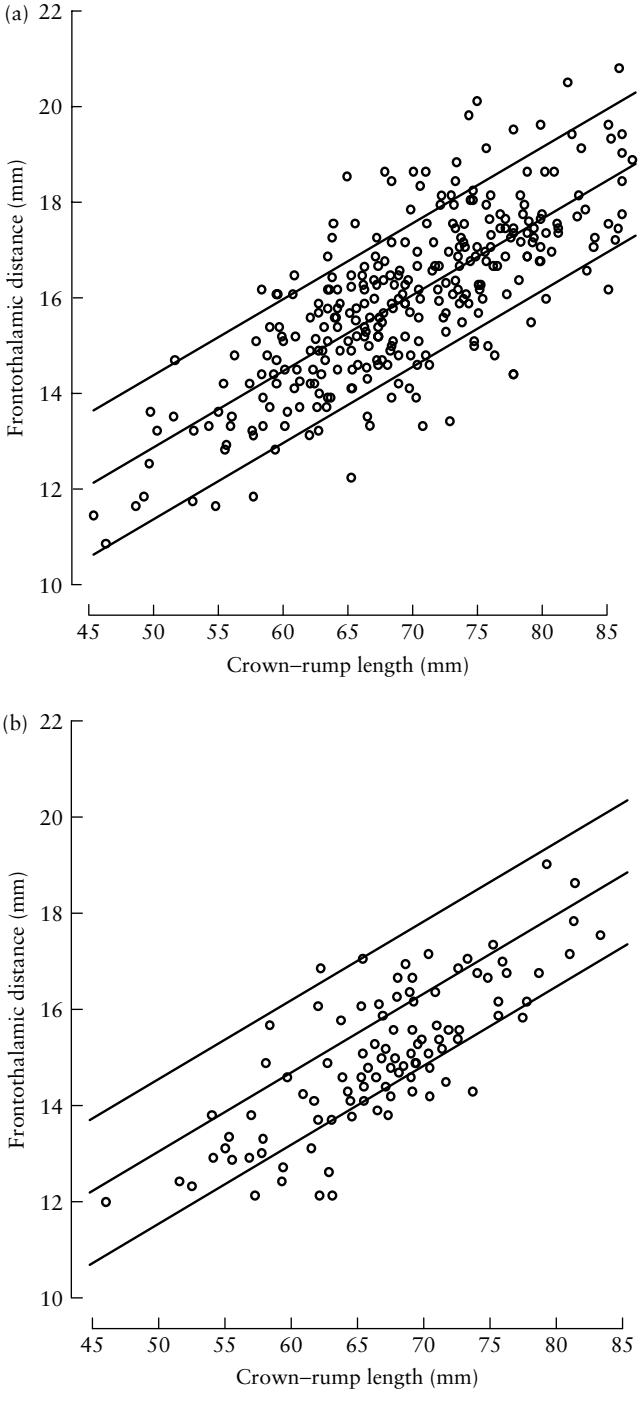

Figure 5 (a) Reference range (mean, 95th and 5th centiles) of frontothalamic distance with crown–rump length in the chromosomally normal fetuses at 11 + 0 to 13 + 6 weeks of gestation. (b) Frontothalamic distance in trisomy 21 fetuses plotted on the reference range with crown–rump length of the chromosomally normal fetuses.

In the fetuses with trisomy 21, compared to the normal group, the median BPD, OFD and FTD were lower, the median BPD/OFD ratio was higher and the median FTD/OFD ratio was not significantly different (Table 3; Figures 3–6). In the trisomy 21 fetuses the BPD, OFD and FTD were below the 5th centile of normal in 14%, 34% and 18% of cases, respectively, and the BPD to OFD ratio was above the 95th centile in 19% of cases.

There was no significant association between BPD/OFD and FTD/OFD with the presence or absence of the nasal bone or NT thickness in either the trisomy 21 ($r = 0.019$, $r = 0.122$) or the chromosomally normal fetuses ($r = 0.025$, $r = 0.051$).

The mean percentage difference and the 95% limits of agreement between paired measurements of the BPD, OFD and FTD by the same sonographer and between

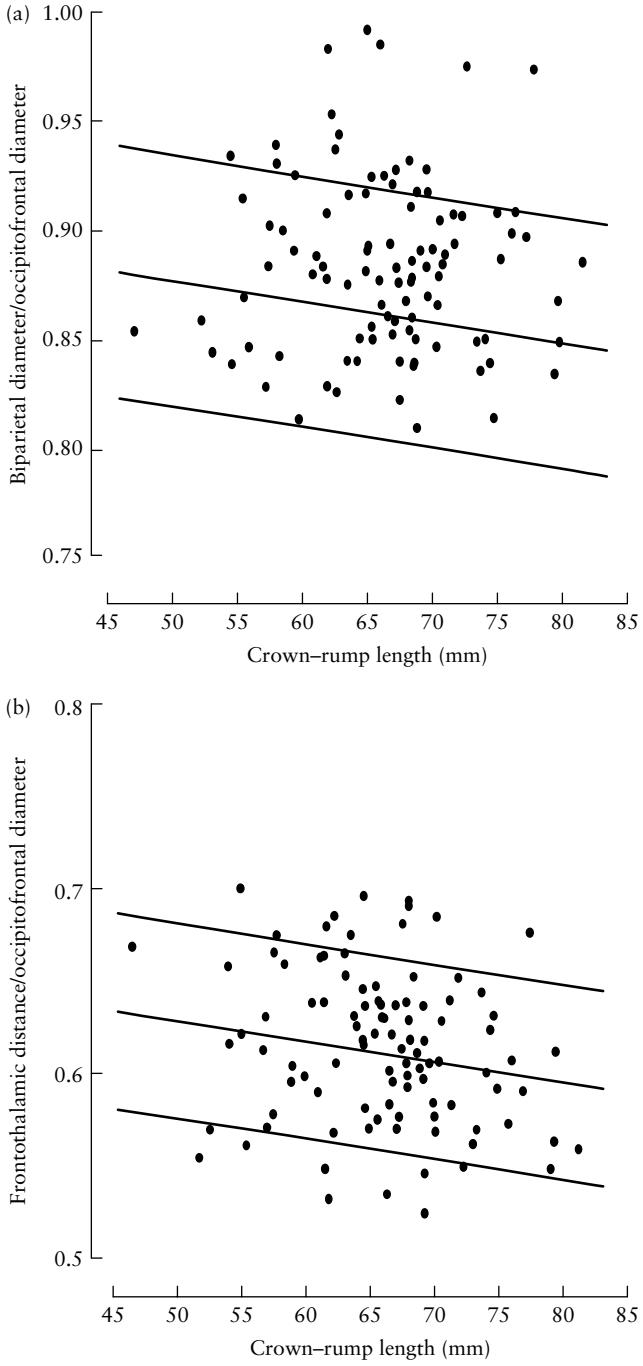

Figure 6 (a) Biparietal diameter to occipitofrontal diameter ratio in trisomy 21 fetuses plotted on the reference range with crown–rump length of the chromosomally normal fetuses. (b) Frontothalamic distance to occipitofrontal diameter ratio in trisomy 21 fetuses plotted on the reference range with crown–rump length of the chromosomally normal fetuses.

paired measurements by the two different observers are shown in Table 4.

DISCUSSION

This study has demonstrated that in fetuses with trisomy 21 at 11 + 0 to 13 + 6 weeks' gestation BPD, OFD and FTD are reduced. This is compatible with our previously reported finding that in trisomy 21 fetuses at this gestation the fetal head volume is smaller than that in chromosomally normal fetuses by about 10%[16]. In addition, we observed that the impairment in growth of the OFD is more marked than that of the BPD and consequently the BPD to OFD ratio is increased. This finding of brachycephaly in trisomy 21 fetuses is consistent with the results of anthropometric studies in postnatal life and postmortem studies in aborted fetuses. Nevertheless, the difference between trisomic and normal fetuses was small and the ratio was above the 95th centile in only 19% of affected fetuses. The failure of previous prenatal sonographic studies to demonstrate that the difference in BPD/OFD between normal and abnormal fetuses is significant is likely to be the consequence of the small number of cases examined in each study.

The finding that FTD in trisomy 21 fetuses is reduced is also consistent with the results of previous anthropometric and MRI studies in postnatal life and sonographic studies in prenatal life. However, the FTD to OFD ratio was not significantly different from normal, and consequently there is no evidence of hypoplasia confined to the frontal lobes. This is compatible with a postnatal MRI study which reported that in patients with trisomy 21 the reduction in volume of the frontal lobes is proportional to the overall reduction in brain volume[12]. Unfortunately previous prenatal sonographic studies that demonstrated a decrease in FTD in fetuses with trisomy

Table 3 Comparison of head measurements and ratios between the trisomy 21 fetuses and the chromosomally normal group

Fetal head measurement	*Mean difference (95% CI)*	P
Biparietal diameter (BPD), mm	−0.63 (−0.97 to −0.30)	< 0.0001
Occipitofrontal diameter (OFD), mm	−1.41 (−1.75 to −1.07)	< 0.0001
Frontothalamic distance (FTD), mm	−0.77 (−1.02 to −0.54)	< 0.0001
FTD/OFD ratio	0.004 (−0.006 to 0.013)	0.448
BPD/OFD ratio	0.022 (0.012 to 0.032)	< 0.0001

Table 4 Mean difference in *z* scores and the 95% limits of agreement between 30 paired measurements by the same sonographer and between 30 paired measurements by two different sonographers

Paired measurements	*Fetal head measurement*	*Mean difference (95% CI)*
Observer 1	Biparietal diameter	0 (−1.37 to 1.37)
	Occipitofrontal diameter	−1.47 (−5.9 to 2.9)
	Frontothalamic distance	0.013 (−1.16 to 1.19)
Observer 2	Biparietal diameter	−0.15 (−1.5 to 1.2)
	Occipitofrontal diameter	0 (−1.41 to 1.41)
	Frontothalamic distance	0.18 (−0.064 to 1.00)
Interobserver	Biparietal diameter	−0.01 (−1.04 to 1.02)
	Occipitofrontal diameter	−0.27 (−1.46 to 0.92)
	Frontothalamic distance	−0.005 (−1.1 to 1.00)

21 at 15–21 weeks' gestation, did not provide data on the measurement of OFD or head circumference to substantiate their claim that the decrease in FTD constitutes an expression of frontal lobe hypoplasia, rather than an overall reduction in the size of the brain[14,15].

In fetuses with trisomy 21 at 11 + 0 to 13 + 6 weeks of gestation there is no evidence of frontal lobe hypoplasia. Although such fetuses demonstrate brachycephaly, with an increase in the BPD to OFD ratio, the deviation from normal fetuses is very small and it is therefore unlikely that this ratio will prove to be a useful marker in screening for trisomy 21.

ACKNOWLEDGMENT

This study was supported by a grant from The Fetal Medicine Foundation (Charity No: 1037116).

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