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# Fetal head-to-trunk volume ratio in chromosomally abnormal fetuses at 11 + 0 to 13 + 6 weeks of gestation

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**KEYWORDS:** 3D ultrasound; chromosomal defects; fetal volume; first trimester; screening; VOCAL

## ABSTRACT

***Objective*** *To determine the pattern of early growth disturbance in chromosomally abnormal fetuses by comparing the volume of the fetal head to that of the trunk.*

***Methods*** *The fetal trunk and head volume was measured using three-dimensional (3D) ultrasound in 145 chromosomally abnormal fetuses at a median gestational age of 12 (range, 11 + 0 to 13 + 6) weeks. The head volume was measured separately and then subtracted from the total head and trunk volume to obtain the volume of the fetal trunk. The head-to-trunk ratios were then calculated and the Mann–Whitney* U*-test was used to determine the significance of differences from 500 chromosomally normal fetuses.*

***Results*** *The fetal head volume for crown–rump length (CRL) was significantly smaller than normal in trisomy 21, trisomy 13 and Turner syndrome (*$P < 0.001$*,* $P < 0.001$ *and* $P = 0.001$*, respectively), whereas no significant differences were found in trisomy 18 and triploidy (*$P = 0.139$ *and* $P = 0.070$*, respectively). The fetal trunk volume for CRL was significantly smaller in all chromosomal abnormalities (*$P < 0.001$*) except Turner syndrome (*$P = 0.134$*). The head-to-trunk ratio for CRL was significantly larger in trisomy 18, trisomy 13 and triploidy (*$P < 0.001$*), but normal in trisomy 21 (*$P = 0.221$*) and Turner syndrome (*$P = 0.768$*).*

***Conclusions*** *In trisomy 21 and Turner syndrome, the growth deficit was symmetrical with the head and trunk being equally affected, whereas in triploidy and trisomies 18 and 13 there was asymmetrical growth restriction with the trunk being more severely compromised than the head.*


## INTRODUCTION

Chromosomal abnormalities are associated with fetal growth restriction, which is evident from the first trimester of pregnancy[1–6]. Three-dimensional (3D) ultrasound has now made it possible to measure the fetal head and trunk volume, and in a study of chromosomally abnormal fetuses at 11 + 0 to 13 + 6 weeks of gestation we found that in trisomy 21 and Turner syndrome, the crown–rump length (CRL) for gestation was similar but the fetal trunk and head volume was about 10–15% lower, whereas in trisomy 18, trisomy 13 and triploidy the deficit in volume was about 45% and the deficit in CRL was less than 15%[7,8]. These findings suggested that chromosomally abnormal fetuses are 'thinner than shorter', presumably reflecting a generalized disturbance in growth in which the various organs are affected even more than the skeleton.

Traditionally, fetal growth restriction has been classified as asymmetrical or symmetrical, depending on whether the head-to-abdomen circumference ratio is increased or normal. It is generally thought that fetal growth restriction due to impaired placental perfusion is asymmetrical, whereas in fetal abnormalities the growth restriction is symmetrical[9]. The aim of this study was to investigate further the early growth disturbance in chromosomally abnormal fetuses by comparing the volume of the fetal head to that of the trunk.

## METHODS

In our center fetal trunk and head volume is measured using 3D ultrasound before fetal karyotyping by chorionic villus sampling at a median gestational age of 12 (range, 11 + 0 to 13 + 6) weeks. In all cases there is prior screening for chromosomal defects by a combination of maternal age and fetal nuchal translucency thickness[10]. We have previously reported the deficit in fetal trunk

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and head volume in 140 singleton pregnancies with chromosomally abnormal fetuses compared to 500 chromosomally normal fetuses[8]. In this study of 145 chromosomally abnormal and 500 normal fetuses, including all those studied previously[8], we measured the head volume separately and then subtracted this measurement from the total head and trunk volume to obtain the volume of the fetal trunk.

In each fetus the fetal head and fetal head and trunk volume was measured using the Virtual Organ Computer-aided AnaLysis (VOCAL) technique (Voluson 730 Expert Operation Manual, GE Healthcare, Milwaukee, WI, USA). A sequence of six longitudinal sections of the fetal head, and fetal head and trunk, around a fixed axis were obtained, each after a 30° rotation from the previous one. The contour of the fetal head, and fetal head and trunk, was drawn manually in each of the six different planes to obtain the 3D-volume measurement (Figure 1). Every measurement was carried out by the same operator, and without knowledge of the result of the karyotype.

In 40 randomly selected cases, the fetal head volume was measured by the same sonographer twice, and also by a second sonographer once, in order to compare the measurements and calculate intra- and interobserver agreement. We have previously reported on these values for the measurement of the head and trunk volume[7].

### Statistical analysis

In each chromosomally abnormal fetus the observed fetal head volume was subtracted from the expected mean (delta value) for the same CRL of the chromosomally normal fetuses, and this difference was expressed as a percentage of the appropriate normal mean. The same analysis was performed to determine the association between fetal trunk volume and CRL and head-to-trunk ratio to CRL. The Shapiro–Wilk test demonstrated that not all of the study groups had a normal distribution of their delta values, and therefore the Mann–Whitney *U*-test was used to determine the significance of differences between the chromosomally normal and abnormal groups.

The Bland–Altman analysis was used to compare the measurement agreement and bias for a single examiner and between different examiners[11].

The data were analyzed using the statistical software SPSS 13.0 (SPSS, Chicago, IL, USA), and $P < 0.05$ was considered statistically significant.

## RESULTS

The median maternal age was 37 (range, 18–47) years and the median fetal CRL was 66 (range, 45–84) mm. In

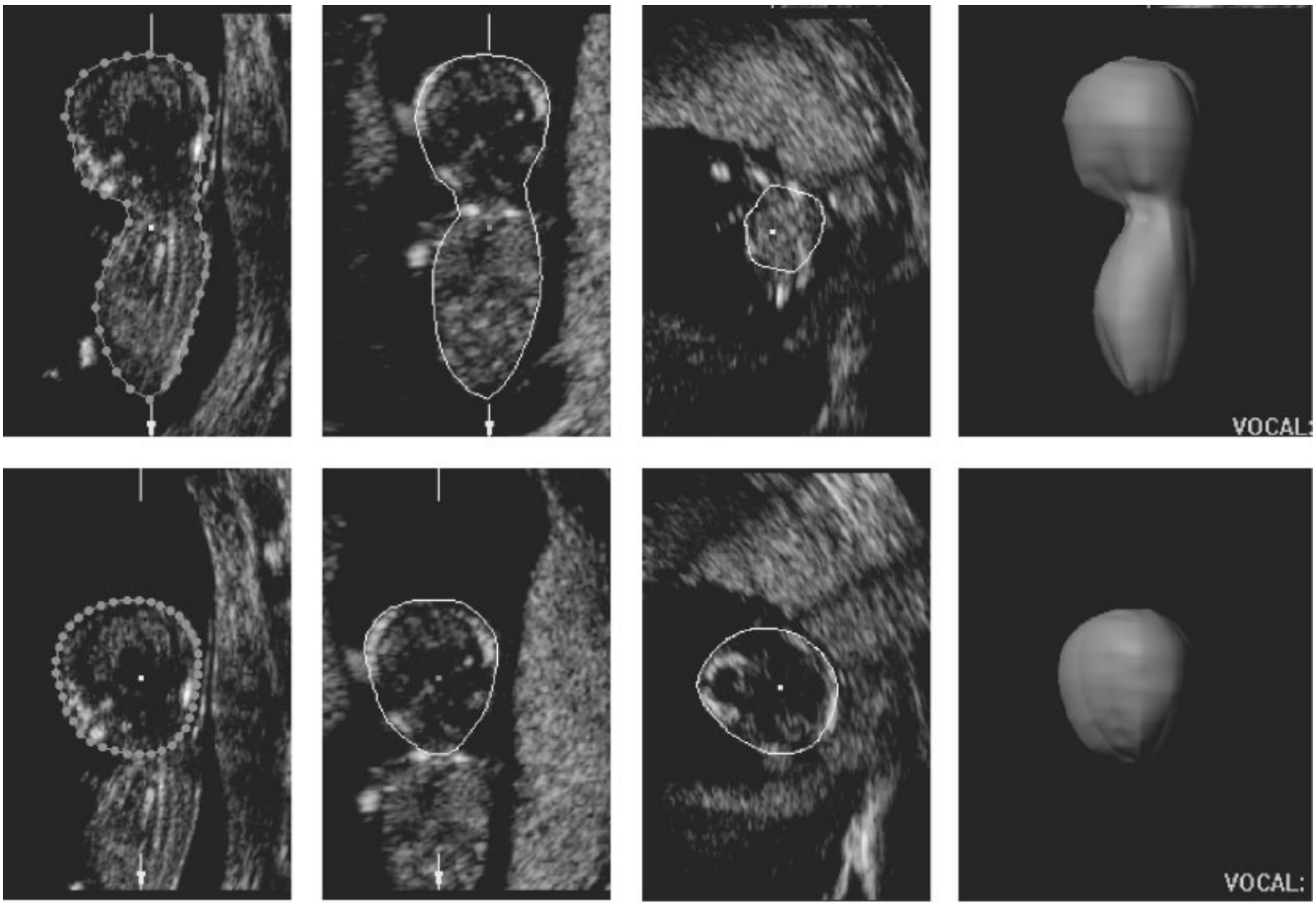


**Figure 1** Three-dimensional measurements of fetal head and trunk volume (top) and fetal head volume (bottom) obtained using the Virtual Organ Computer-aided AnaLysis (VOCAL) technique.

 

the chromosomally normal group, the fetal head volume increased significantly with CRL, from a mean of 2.6 mL at a CRL of 45 mm to 18.7 mL at a CRL of 84 mm (head volume in mL = 0.412 × CRL − 15.909, SD = 1.6 mL, $r = 0.902$, $P < 0.0001$; Figure 2a). Also, the fetal trunk volume increased significantly with CRL from a mean of 2.9 mL at a CRL of 45 mm to 18.0 mL at a CRL of 84 mm (trunk volume in mL = 0.387 × CRL − 14.529, SD = 1.7 mL, $r = 0.885$, $P < 0.0001$; Figure 2b). The head-to-trunk ratio increased with CRL from a mean of 0.97 at a CRL of 45 mm to 1.07 at a CRL of 84 mm (head-to-trunk ratio = 0.003 × CRL + 0.821, SD = 0.19, $r = 0.140$, $P = 0.002$; Figure 2c).

The fetal head volume for CRL was significantly smaller than normal in trisomy 21, trisomy 13 and Turner syndrome, whereas no significant differences were found in trisomy 18 and triploidy (Table 1). The mean delta value increased with CRL for trisomy 18 ($r = 0.665$, $P < 0.0001$) and trisomy 13 ($r = 0.594$, $P = 0.012$), but did not change significantly for trisomy 21 ($r = 0.093$, $P = 0.435$), Turner syndrome ($r = 0.373$, $P = 0.189$) or triploidy ($r = 0.219$, $P = 0.518$).

The fetal trunk volume for CRL was significantly smaller in all chromosomal abnormalities except Turner syndrome (Table 2). The mean delta value increased with CRL for trisomy 18 ($r = 0.894$, $P < 0.0001$), trisomy 13 ($r = 0.615$, $P = 0.009$), Turner syndrome ($r = 0.550$, $P = 0.042$) and triploidy ($r = 0.880$, $P < 0.0001$), but did not change significantly for trisomy 21 ($r = 0.070$, $P = 0.560$).

The head-to-trunk ratio for CRL was significantly larger in trisomy 18, trisomy 13 and triploidy, but normal in trisomy 21 and Turner syndrome (Table 3, Figure 3). The mean delta value did not change significantly with CRL for any of the chromosomal defects: trisomy 18 ($r = 0.231$, $P = 0.211$), trisomy 13 ($r = 0.214$, $P = 0.409$), trisomy 21 ($r = 0.120$, $P = 0.315$), Turner syndrome ($r = 0.351$, $P = 0.219$), triploidy ($r = 0.077$, $P = 0.821$).

**Table 1** Mean percentage differences in fetal head volume from the normal mean for crown–rump length in the chromosomally abnormal fetuses

| *Karyotype* | n | *Mean percentage difference (95% CI for mean)* | *Mann–Whitney U-test* P |
|---|---|---|---|
| Trisomy 21 | 72 | −10.2 (−14.0 to −6.3) | < 0.001 |
| Trisomy 18 | 31 | −3.1 (−9.5 to 3.2) | 0.139 |
| Trisomy 13 | 17 | −15.6 (−22.9 to −8.4) | < 0.001 |
| Turner syndrome | 14 | −12.8 (−18.6 to −6.9) | 0.001 |
| Triploidy | 11 | 19.3 (−5.0 to 43.7) | 0.070 |

**Table 2** Mean percentage differences in fetal trunk volume from the normal mean for crown–rump length in the chromosomally abnormal fetuses

| *Karyotype* | n | *Mean percentage difference (95% CI for mean)* | *Mann–Whitney U-test* P |
|---|---|---|---|
| Trisomy 21 | 72 | −6.2 (−11.0 to −1.47) | < 0.001 |
| Trisomy 18 | 31 | −33.7 (−39.3 to −28.0) | < 0.001 |
| Trisomy 13 | 17 | −36.6 (−43.9 to −29.2) | < 0.001 |
| Turner syndrome | 14 | −9.9 (−21.1 to 1.3) | 0.134 |
| Triploidy | 11 | −43.7 (−54.6 to −32.8) | < 0.001 |

In the Bland–Altman plot, the mean difference between paired measurements of the fetal head volume by the same sonographer was 0.20 mL and the 95% limits of agreement were −1.13 mL (95% CI, −1.50 mL to −0.77 mL) to 1.54 mL (95% CI, 1.17 mL to 1.90 mL). The mean difference between paired measurements by two sonographers was 0.11 mL and the 95% limits

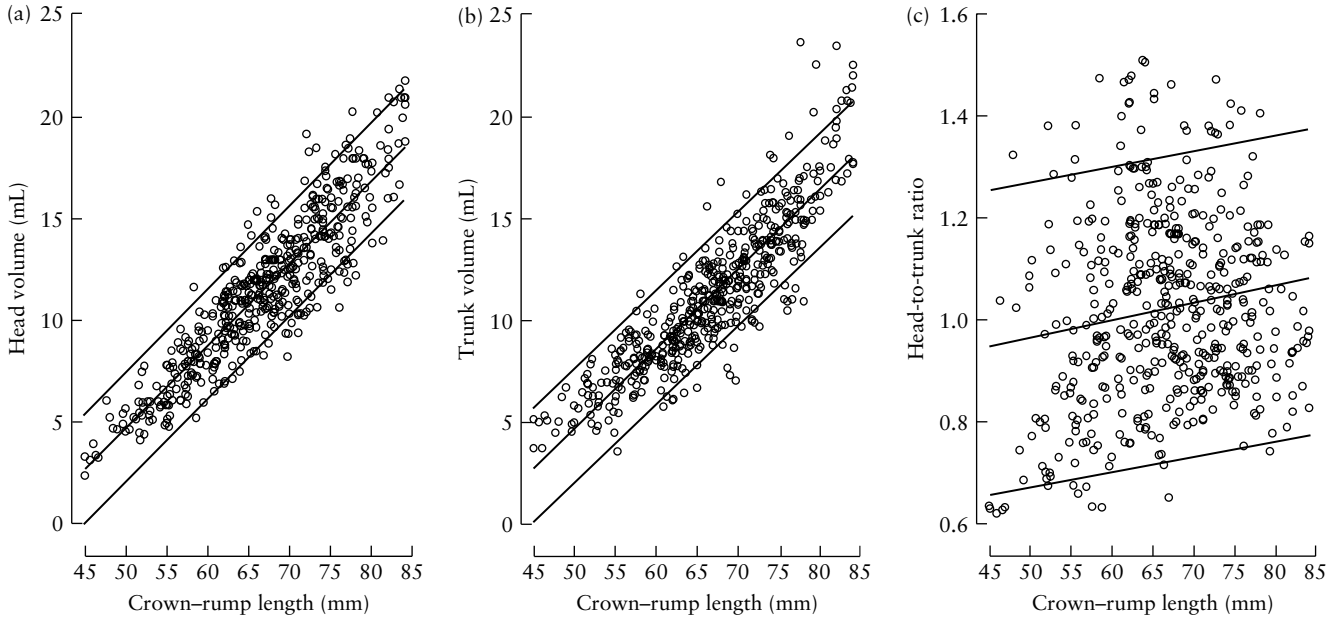


**Figure 2** Reference range (mean, 95th and 5th centiles) of (a) fetal head volume, (b) fetal trunk volume and (c) head-to-trunk ratio with crown–rump length in chromosomally normal pregnancies at 11 + 0 to 13 + 6 weeks of gestation.

 

**Table 3** Mean percentage differences in head-to-trunk ratio from the normal mean for crown–rump length in the chromosomally abnormal fetuses

| *Karyotype* | n | *Mean percentage difference (95% CI for mean)* | *Mann–Whitney* U-*test* P |
|---|---|---|---|
| Trisomy 21 | 72 | −1.3 (−6.2 to 3.7) | 0.221 |
| Trisomy 18 | 31 | 52.9 (38.3 to 67.4) | < 0.001 |
| Trisomy 13 | 17 | 39.1 (22.4 to 55.8) | < 0.001 |
| Turner syndrome | 14 | 2.2 (−13.4 to 17.8) | 0.768 |
| Triploidy | 11 | 120.4 (78.5 to 162.3) | < 0.001 |

of agreement were −2.50 mL (95% CI, −3.21 mL to −1.78 mL) to 2.71 mL (95% CI, 2.00 mL to 3.43 mL).

## DISCUSSION

The findings of this study confirm that chromosomal abnormalities are often associated with early onset fetal growth restriction. In addition, the data demonstrate that in trisomy 21 and Turner syndrome the growth deficit is symmetrical, with the head and trunk being equally affected, whereas in triploidy and trisomies 18 and 13 there is asymmetrical growth restriction, with the trunk being more severely compromised than the head. These findings contradict the traditional classification of growth restriction into symmetrical and asymmetrical types with the first being attributed to fetal abnormalities and genetic syndromes and the second being considered to be the consequence of impaired placental perfusion[9].

All major congenital malformations are associated with increased frequency of growth restriction and the symmetrical nature of growth deficit has been attributed to the timing of the insult that caused the malformation, which was early in the embryonic period[12,13]. Insults in early pregnancy, such as infection, exposure to certain teratogens, congenital malformations and chromosomal abnormalities, are thought to affect cell division and therefore the size of all organ systems[9]. In contrast, in the case of impaired placental perfusion, the ability of the placenta to meet the demands of the growing fetus is usually exceeded only during the end of the second trimester or in the third trimester of pregnancy. At this stage the fetus responds to varying degrees of hypoxemia by redistributing its own circulation in favor of the brain and at the expense of the abdominal viscera, with consequent asymmetry in growth restriction[14–16].

A possible explanation for our findings in triploidy and trisomies 18 and 13, is that, in these abnormalities, in addition to the early insult to the embryo associated with the chromosomal abnormality itself, there is an additional element of severe early onset placental insufficiency and redistribution in the fetal circulation.

In normal fetuses, placental insufficiency is thought to be the consequence of impaired maternal perfusion of the placenta due to inadequate trophoblastic invasion of the spiral arteries and their conversion into low resistance channels[17–20]. A first-trimester Doppler study of the maternal uterine arteries in pregnancies with fetal trisomies 21, 18 or 13, Turner syndrome or triploidy, has demonstrated that in these abnormalities impedance to flow is not significantly different from normal[21]. Consequently, unlike the situation in chromosomally normal fetuses where impaired placental function is the consequence of inadequate perfusion, in some chromosomal abnormalities the impaired function may be due to an inherent placental maldevelopment. Supportive evidence for impaired placentation in chromosomal abnormalities

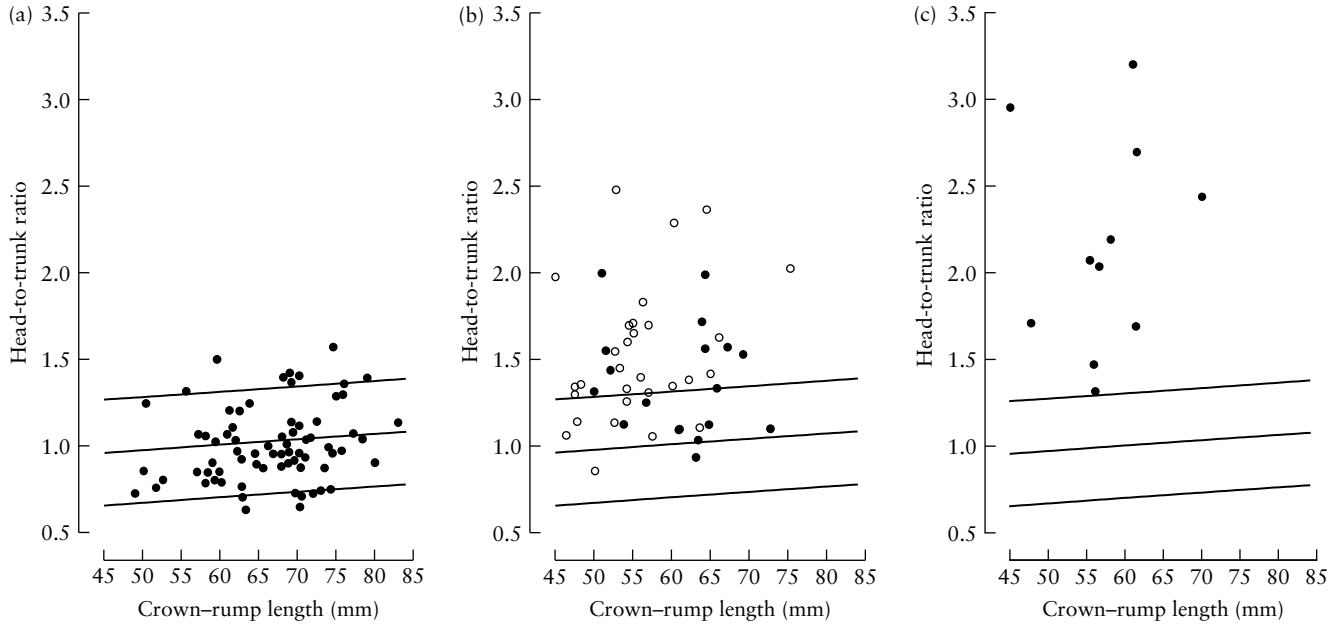


**Figure 3** Fetal head-to-trunk ratio in chromosomally abnormal fetuses plotted on the reference range (mean, 95th and 5th centiles) with crown–rump length of the chromosomally normal fetuses. The cases of (a) trisomy 21, (b) trisomy 18 (○) and trisomy 13 (●), and (c) triploidy.

is provided by firstly, the findings of 3D study of placental volume at 11 to 13 + 6 weeks of gestation, which demonstrated that the volume was reduced in trisomies 13 and 18 and digynic triploidy but not in trisomy 21 and Turner syndrome[22], secondly, prenatal Doppler studies documenting increased impedance to flow in the umbilical arteries in triploidy and trisomy 18, but not in trisomy 21[23–26], and thirdly, histological studies of the placenta at 11–14 weeks in trisomies, which showed undervascularization of the villi and increased basophilic stippling of the basement membrane that was particularly prominent in trisomies 18 and 13[27]. Further evidence of early-onset placental insufficiency in association with chromosomal abnormalities is provided by the placental hormone profile in maternal blood. Thus, the maternal serum concentration of both pregnancy-associated plasma protein-A (PAPP-A) and free ß-human chorionic gonadotropin (hCG) in trisomies 13 and 18 is about one-third of the normal and in triploidy it is one tenth[28–31]. In trisomy 21, PAPP-A is about half and free ß-hCG is double the normal, and in Turner syndrome PAPP-A is about half of the normal and free ß-hCG is not different from normal[32,33].

The ability to measure the volume of the fetal head and trunk has made it possible to document that triploidy and trisomies 18 and 13, all of which are associated with a high rate of intrauterine lethality, present with early-onset severe asymmetrical growth restriction. In contrast, in trisomy 21 and Turner syndrome, which are less lethal, growth restriction is milder and symmetrical. These differences in growth pattern may be explained by varying contributions of the impaired development of both the fetus and the placenta.

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