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Gestational sac volume measured by three-dimensional ultrasound at 11 to 13 + 6 weeks of gestation: relation to chromosomal defects

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KEYWORDS: chromosomal defects; first trimester; gestational sac volume; screening; VOCAL; 3D ultrasound

ABSTRACT

Objective *To determine the potential value of measuring the gestational sac volume (GSV) at 11 to 13 + 6 weeks of gestation in screening for chromosomal defects.*

Methods *The GSV was measured using three-dimensional (3D) ultrasound in 500 consecutive singleton pregnancies immediately before chorionic villus sampling (CVS) for fetal karyotyping at 11 to 13 + 6 (median 12) weeks of gestation.*

Results *The fetal karyotype was normal in 417 pregnancies and abnormal in 83. In the chromosomally normal group, the mean GSV increased significantly with gestational age from a mean of 69 mL at 11 weeks to 144 mL at 13 + 6 weeks (the standard deviation was 27 mL). In the chromosomally abnormal group, the mean GSV for gestational age was not significantly different from normal in fetuses with trisomy 21, trisomy 18 and Turner syndrome, but it was smaller in those with triploidy and trisomy 13. However, the mean GSV for crown–rump length (CRL) was significantly larger in trisomy 18, smaller in triploidy and trisomy 13, and not different from normal in trisomy 21 and Turner syndrome. The mean CRL for gestational age was significantly smaller than normal in trisomy 18, triploidy and trisomy 13.*

Conclusions *The measurement of the GSV at 11 to 13 + 6 weeks of gestation is unlikely to provide useful prediction of the major chromosomal defects. In trisomy 13 and triploidy, the small GSV may be due to early onset fetal growth restriction and reduced amniotic fluid volume. In trisomy 18, the increase in GSV is probably due to the presence of associated fetal abnormalities that interfere with fetal swallowing. Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

In this study we investigated the potential value of the gestational sac volume (GSV), measured by three-dimensional (3D) ultrasonography at 11 to 13 + 6 weeks of gestation, in screening for chromosomal defects. Previous studies have reported that, in the majority of cases of miscarriage the underlying cause is a chromosomal defect[1–4]; that a small GSV is associated with an increased risk of miscarriage[5,6]; and that volume measurements obtained by 3D ultrasonography are more accurate than those obtained by conventional two-dimensional (2D) ultrasonography[7,8].

METHODS

The GSV was measured using 3D ultrasonography before fetal karyotyping by chorionic villus sampling (CVS) at 11 to 13 + 6 weeks of gestation in 500 consecutive singleton pregnancies with known last menstrual period date and regular menstrual cycles of 26–30 days' duration. The study was carried out in our center during the 10-month period from December 2003 to September 2004. In all cases there was prior screening for chromosomal defects by a combination of maternal age and fetal nuchal translucency thickness, and the patients included in the study had opted for invasive testing after counseling[9]. All the scans were carried out by sonographers with extensive experience in 3D ultrasonography.

A 3D volume of the uterus was obtained by transabdominal sonography in all cases (RAB 4–8L probe, Voluson 730 Expert, GE Medical Systems, Milwaukee, WI, USA) and the volume of the gestational sac, including the amniotic and the celomic cavities, was measured. Before the scan of the uterus, a sweep angle of 85° was selected in order to include the

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whole gestational sac. The Virtual Organ Computer-aided AnaLysis (VOCAL) technique was used to obtain a sequence of six sections of the gestational sac, each after a 30° rotation from the previous one (Voluson 730 Expert Operation Manual, GE Medical Systems, Milwaukee, WI, USA). The contour of the gestational sac was drawn manually in each of the six different planes to obtain the 3D volume measurement (Figure 1). Every measurement was done off-line after the scan by the same operator and before knowing the result of the karyotype.

In 40 randomly selected cases, the GSV was measured by the same sonographer twice and also by a second sonographer once in order to compare the measurements and calculate intra- and inter-observer agreement.

Statistical analysis

In the chromosomally normal group, linear regression analysis was used to determine the significance of the association between GSV and gestational age in days. Each measurement of the GSV was then expressed as a deviation from the expected mean for gestation (delta value). Because the number of cases in the chromosomally abnormal groups was too small to assume a normal distribution of their mean delta values, the Mann–Whitney U-test was used to determine the significance of differences in the delta values between the chromosomally normal and abnormal groups. The same analysis was performed to determine the association between GSV and crown–rump length (CRL), and the relation between CRL and gestation. The Bland–Altman analysis was used to compare the measurement agreement and bias for a single examiner and between different examiners[10]. The data were analyzed using the statistical software SPSS 11.5 (Chicago, Illinois, USA), and a *P*-value of less than 0.05 was considered to be statistically significant.

RESULTS

The median maternal age was 37 (range 19–47) years, the median fetal CRL was 67 (45–84) mm and the median gestational age was 12 (11 to 13 + 6) weeks. The GSV was successfully measured in all cases. The fetal karyotype was normal in 417 pregnancies and abnormal in 83 (Table 1). In the chromosomally normal group the GSV increased significantly with gestation, from a mean of 69 mL at 11 weeks to 144 mL at 13 + 6 weeks (GSV = 3.764 × gestational age in days −220.678, standard deviation (SD) = 27 mL, $r = 0.496$,

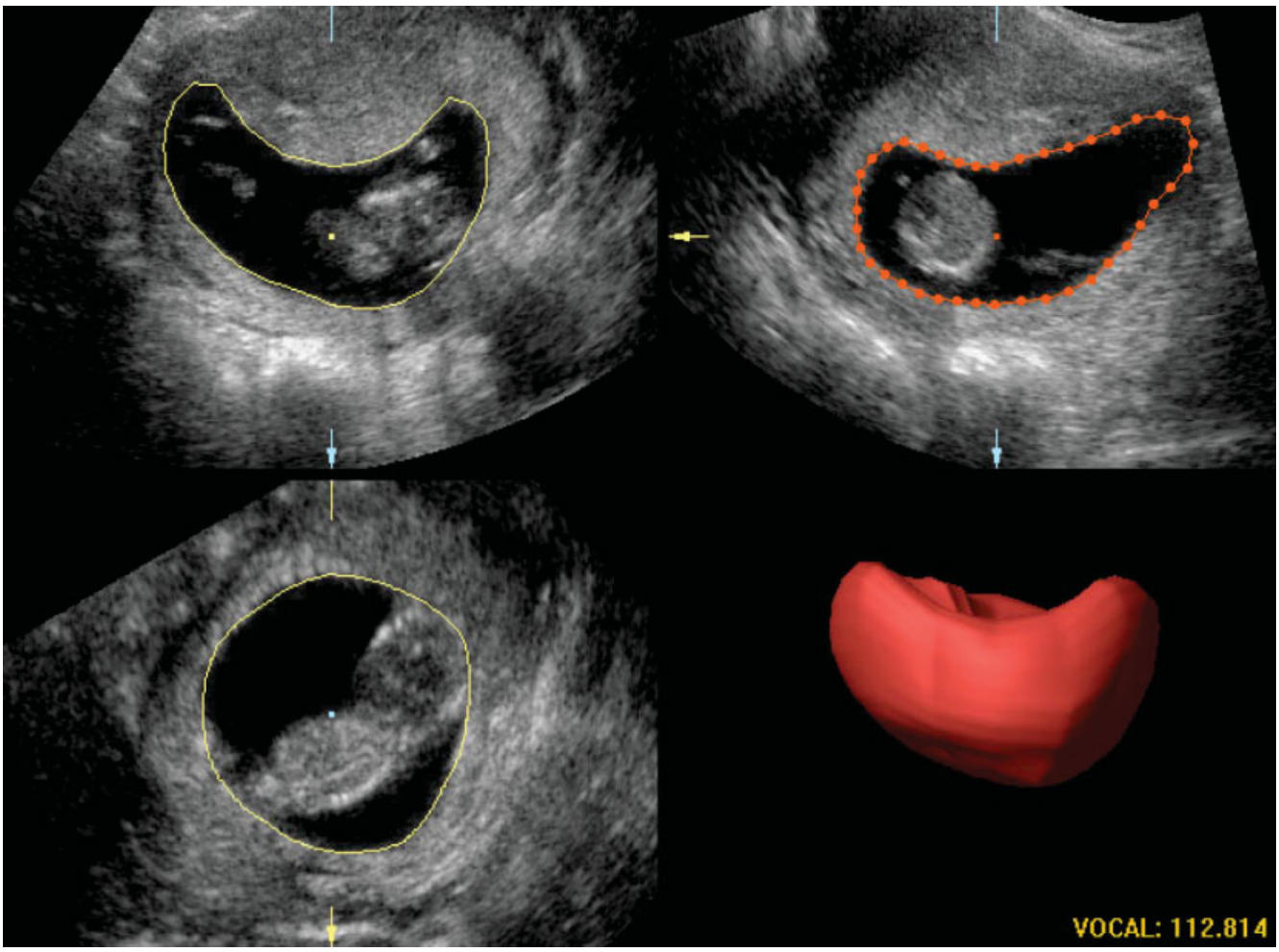

Figure 1 Three-dimensional volume of the gestational sac obtained using the Virtual Organ Computer-aided AnaLysis (VOCAL) technique.

Table 1 Mean differences in gestational sac volume (GSV) from the normal mean for gestational age (GA) in the chromosomally normal and abnormal pregnancies

Karyotype	n	*Mean difference in GSV for GA (95% CI for mean)*	*Mann–Whitney U-test*
Normal	417	0.02 (−2.61 to 2.65)	
Trisomy 21	45	0.08 (−8.64 to 8.79)	$P = 0.936$
Trisomy 18	17	−12.44 (−24.49 to −0.39)	$P = 0.053$
Turner syndrome	10	−11.17 (−26.61 to 4.27)	$P = 0.226$
Triploidy	5	−54.78 (−96.63 to −12.93)	$P = 0.003$
Trisomy 13	6	−44.68 (−59.24 to −30.11)	$P < 0.001$

$P < 0.001$; Figure 2) and with CRL, from a mean of 62 mL at a CRL of 45 mm to 160 mL at a CRL of 84 mm (GSV = 2.521 × CRL − 51.647, SD = 24 mL, $r = 0.642$, $P < 0.001$; Figure 3). The CRL increased with gestational age, from a mean of 48 mm at 11 weeks to 78 mm at 13 + 6 weeks (CRL = 1.480 × gestational age in days −65.876, SD = 5 mm, $r = 0.766$, $P < 0.001$; Figure 4).

The mean GSV for gestation in trisomy 21, trisomy 18 and Turner syndrome was not significantly different from normal, but in triploidy and trisomy 13 it was significantly smaller (Table 1 and Figure 5). The mean GSV for CRL was smaller in triploidy and trisomy 13 and larger in trisomy 18, but not significantly different in trisomy 21 and Turner syndrome (Table 2 and Figure 6). The CRL was significantly smaller for gestational age in trisomy 18, triploidy and trisomy 13 (Table 3 and Figure 7).

In the Bland–Altman plot, the mean difference between paired measurements by the same sonographer was −0.37 mL and the 95% limits of agreement were −7.24 mL (95% confidence interval (CI), −9.12 mL to −5.36 mL) to 6.50 mL (95% CI, 4.62 mL to 8.38 mL).

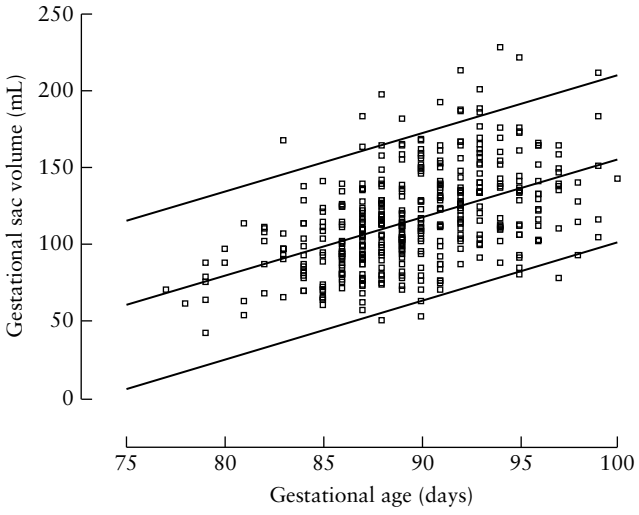

Figure 2 Reference range (mean, 95th and 5th centiles) of gestational sac volume with gestational age in the chromosomally normal pregnancies at 11–14 weeks of gestation.

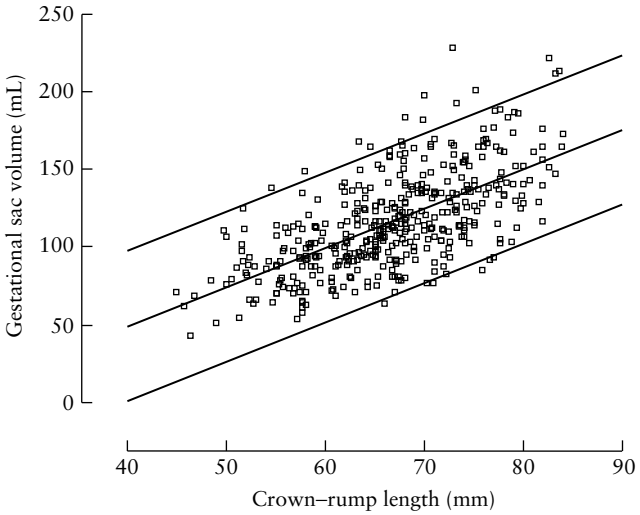

Figure 3 Reference range (mean, 95th and 5th centiles) of gestational sac volume with crown–rump length in the chromosomally normal pregnancies at 11–14 weeks of gestation.

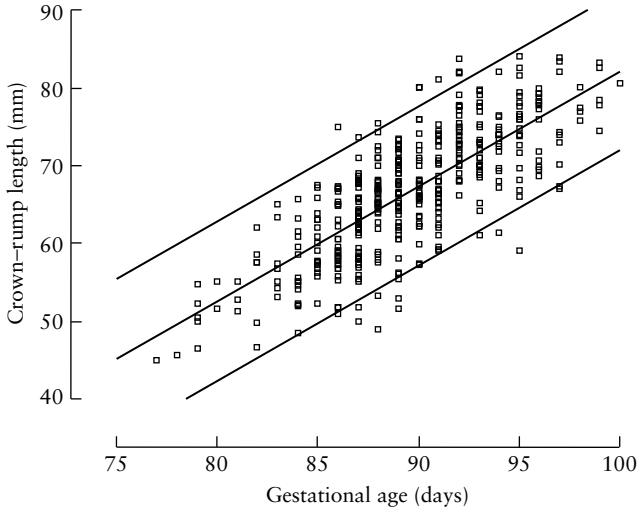

Figure 4 Reference range (mean, 95th and 5th centiles) of crown–rump length with gestational age in the chromosomally normal pregnancies at 11–14 weeks of gestation.

The mean difference between paired measurements by two sonographers was −2.17 mL and the 95% limits of agreement were −13.46 mL (95% CI, −16.55 mL to −10.37 mL) to 9.12 mL (95% CI, 6.03 mL to 12.22 mL).

DISCUSSION

This study has demonstrated that 3D ultrasonography can provide a highly reproducible measurement of the GSV; that in normal pregnancies the GSV increases with gestation, and that in fetuses with some chromosomal defects the GSV is altered. The observed doubling in GSV between 11 and 13 + 6 weeks can be partly attributed to the simultaneous doubling in fetal size and an increase in amniotic fluid volume. In the first

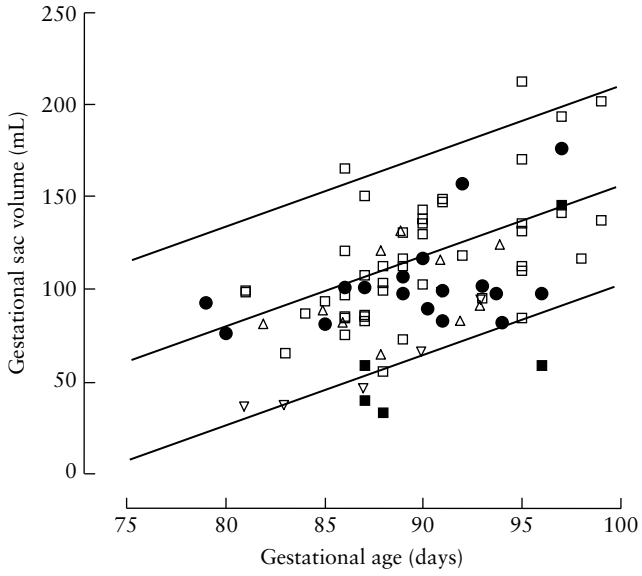

Figure 5 Gestational sac volume in fetuses with chromosomal defects plotted on the reference range (mean, 95th and 5th centiles) for gestational age of the chromosomally normal pregnancies. Trisomy 21 (□), trisomy 18 (●), Turner syndrome (△), triploidy (■), trisomy 13 (▽).

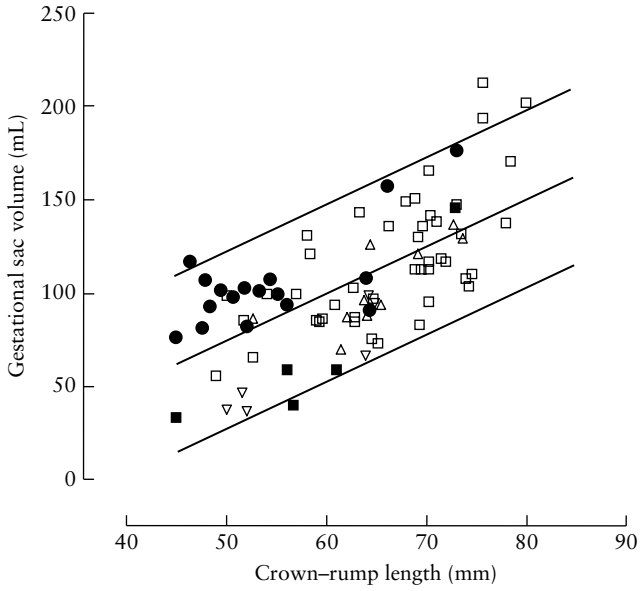

Figure 6 Gestational sac volume in fetuses with chromosomal defects plotted on the reference range (mean, 95th and 5th centiles) for crown–rump length of the chromosomally normal pregnancies. Trisomy 21 (□), trisomy 18 (●), Turner syndrome (△), triploidy (■), trisomy 13 (▽).

Table 2 Mean differences in gestational sac volume (GSV) from the normal mean for crown–rump length (CRL) in the chromosomally normal and abnormal pregnancies

Karyotype	n	*Mean difference in GSV for CRL (95% CI for mean)*	*Mann–Whitney U-test*
Normal	417	−0.02 (−2.34 to 2.31)	
Trisomy 21	45	1.99 (−5.98 to 9.95)	$P = 0.814$
Trisomy 18	17	18.55 (8.98 to 28.12)	$P = 0.001$
Turner syndrome	10	−9.62 (−20.43 to 1.18)	$P = 0.209$
Triploidy	5	−28.31 (−59.21 to 2.59)	$P = 0.017$
Trisomy 13	6	−29.99 (−43.88 to −16.09)	$P = 0.002$

Table 3 Mean differences in crown–rump length (CRL) from the normal mean for gestational age (GA) in the chromosomally normal and abnormal pregnancies

Karyotype	n	*Mean difference in CRL for GA (95% CI for mean)*	*Mann–Whitney U-test*
Normal	417	0.01 (−0.49 to 0.51)	
Trisomy 21	45	−0.76 (−2.44 to 0.93)	$P = 0.358$
Trisomy 18	17	−12.30 (−15.81 to −8.78)	$P < 0.001$
Turner syndrome	10	−0.63 (−3.94 to 2.69)	$P = 0.599$
Triploidy	5	−10.48 (−18.46 to −2.51)	$P = 0.001$
Trisomy 13	6	−5.86 (−9.38 to −2.33)	$P = 0.004$

trimester of pregnancy the electrolyte composition and osmolality of amniotic fluid are essentially the same as those of maternal blood, and the most likely mechanism for the formation of amniotic fluid is an active transport of solute by the amnion into the amniotic space, with water moving passively down the chemical potential gradient[11]. Subsequently, with the onset of fetal urination and swallowing, these are the two major pathways for the formation and clearance of amniotic fluid. Sonographic studies have demonstrated the presence of the fetal bladder and stomach from as early as 8 weeks and in nearly all fetuses by 11 weeks[12,13].

In trisomy 21, the GSV both for gestational age and fetal CRL is not significantly different from normal and, therefore, the measurement of the GSV does not provide useful prediction of this chromosomal defect. The same is also true for Turner syndrome. In contrast, trisomy 13 and triploidy are associated with a significantly smaller GSV than normal. In both of these chromosomal defects there was early onset fetal growth restriction, but the GSV for CRL was significantly reduced, suggesting that the decrease in GSV is not the mere consequence of small fetal size but also of a decrease in amniotic fluid volume. Such a decrease in amniotic fluid volume may reflect impaired placental function, acting either directly in the production of the ultrafiltrate and/or through a decrease in fetal urination.

In trisomy 18, as in trisomy 13 and triploidy, there was early onset fetal growth restriction. However, contrary to the findings in trisomy 13 and triploidy, where the GSV was decreased, in trisomy 18 the GSV was normal for gestational age but increased for CRL. These findings suggest that in fetuses with this chromosomal defect the amniotic fluid volume is actually increased. This increase is unlikely to be a consequence of improved placental function, because a common finding in all three of these chromosomal defects is an impaired production of free ß-human chorionic

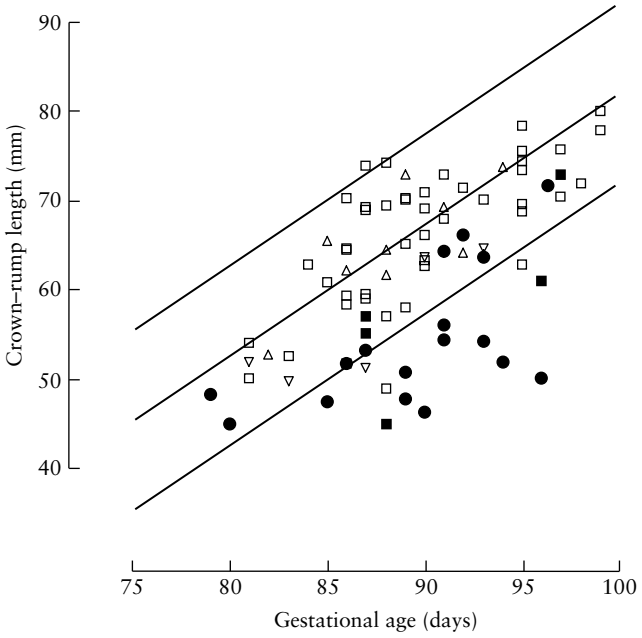

Figure 7 Crown–rump length in chromosomal defects plotted on the reference range (mean, 95th and 5th centiles) for gestational age of the chromosomally normal pregnancies. Trisomy 21 (□), trisomy 18 (●), Turner syndrome (△), triploidy (■), trisomy 13 (▽).

gonadotropin (ß-hCG) and pregnancy-associated plasma protein-A (PAPP-A)[14]. Consequently, the increase in GSV in trisomy 18 pregnancies is probably due to the presence of associated fetal defects that interfere with fetal swallowing, such as diaphragmatic hernia, esophageal atresia, or central nervous system abnormalities.

Measurement of the GSV at 11 to 13 + 6 weeks of gestation is unlikely to provide useful prediction of the major chromosomal defects. Although there are alterations in the GSV in trisomy 18, trisomy 13 and triploidy, in the vast majority of cases the values are within the normal ranges (Figures 5 and 6). Furthermore, effective screening for these defects is provided by a combination of fetal nuchal translucency thickness and maternal serum free ß-hCG and PAPP-A[14].

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