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Single umbilical artery and its siding in the second trimester of pregnancy: relation to chromosomal defects

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Objectives To determine the possible association between single umbilical artery (SUA) in the second trimester of pregnancy and the incidence of chromosomal abnormalities. To determine whether the presence of chromosomal defects in fetuses with SUA is related to the side of the missing artery.

Methods Color flow imaging of the fetal pelvis was used to determine the number of umbilical arteries in 2147 fetuses immediately before amniocentesis for karyotyping in the second trimester of pregnancy.

Results SUA was diagnosed in 102/2147 (4.8%) cases. The left umbilical artery was absent in 60/102 (58.8%) fetuses, compared with the 42/102 (41.2%) for the right artery. The rate of chromosome abnormalities was significantly higher among fetuses with SUA than among those with 2 umbilical arteries (19/102 or 18.6% *versus* 109/2045 or 5.3%; OR = 4.1, 95% CI 2.3–7.1, $p < 0.0001$). Among fetuses with SUA, there was no significant difference in the rate of chromosome abnormalities between those with absence of the left *versus* the right artery (11/60 or 18.3% *versus* 8/42 or 19.0%, $p = 0.93$). There was an SUA in 5/39 (12.8%) cases with trisomy 21, 8/16 (50%) with trisomy 18, 1/4 (25%) with trisomy 13 and 5/69 (7.2%) with other chromosomal defects. There were no chromosome abnormalities in fetuses where a single umbilical artery was an isolated sonographic finding. All fetuses with SUA and chromosomal defects had associated abnormalities detected by ultrasound.

Conclusion A single umbilical artery (SUA) in the second trimester of pregnancy has a high association with trisomy 18, 13, 21 and other chromosomal defects, but all chromosomally abnormal fetuses had associated malformations detected by ultrasound. The absence of the left artery is more frequent than the absence of the right artery. The association with chromosomal abnormalities seems to be equal on each side. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS: single-umbilical artery; chromosomal defect; second trimester; prenatal diagnosis; ultrasonography

INTRODUCTION

A single umbilical artery (SUA) is found in 0.2–2.0% of deliveries and occurs three or four times more frequently in twin births *versus* singletons (Heifetz, 1984; Leung and Robson, 1989; Lilja, 1991; Jones *et al*., 1993; Gornall *et al*., 2003; Prucka *et al*., 2004; Martinez-Payo *et al*., 2005). The condition is associated with malformations of all major organ systems and chromosomal defects (Heifetz, 1984; Persutte and Hobbins, 1995). Previous ultrasonographic studies reviewed by Rembouskos *et al*., in the second and third trimesters of pregnancy, reported chromosomal defects in about 10% of fetuses with SUA, most commonly trisomy 18, but in the vast majority of such cases there were other major defects (Rembouskos *et al*., 2003).

In this study, we examine the association between SUA and chromosomal abnormalities in the second trimester of pregnancy and whether it matters which artery is missing.

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METHODS

This was a prospective study in 2147 consecutively examined singleton pregnancies to determine the incidence of SUA in fetuses undergoing karyotyping by amniocentesis in the second trimester of pregnancy (at 16–22 weeks' gestation).

In all cases, there was a prior second-trimester screening for chromosomal defects by a combination of maternal age (age alone >35 years), biochemical screening (alfa fetoprotein + human chorionic gonadotrophin + unconjugated estriol; cut-off >1 : 250) and ultrasound (associated structural abnormalities and markers of chromosomal defects according to Table 1). The patients included in this study were those who after counseling elected to have invasive testing.

An oblique transverse section of the lower fetal abdomen, including the umbilicus and the fetal bladder, was first obtained and color flow mapping was then used to visualize the umbilical arteries on either side of the bladder and in continuity with the umbilical cord insertion to the fetus (Figure 1). All the scans were performed transabdominally using 5-MHz transducers (Toshiba Powervision 6000, Toshiba, Tokyo, Japan; GE Voluson 730 Expert, GE Healthcare Technologies, Zipf,

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Table 1—Single umbilical artery in chromosomally abnormal fetuses with associated structural abnormalities and markers of chromosomal defects detected in the second-trimester scan ($n = 19$)

	Absent LUA (no. of cases)	Absent RUA (no. of cases)
Trisomy 21 ($n = 5$)	**3**	**2**
Ventriculomegaly	1	
Choroid plexus cysts		1
Enlarged cysterna magna		1
Cardiac anomalies	1	1
Mild hydronephrosis	2	2
Sandal gap	1	
Hydrops	1	
Total	6	5
Trisomy 18 ($n = 8$)	**5**	**3**
Strawberry-shaped head		1
Choroid plexus cysts	2	2
Absent corpus callosum	1	
Dandy–Walker malformation	1	1
Facial cleft	1	2
Cardiac anomalies	2	1
Diaphragmatic hernia		1
Exomphalos	1	1
Small for gestational age	1	
Radial aplasia	1	
Overlapping fingers	2	1
Total	12	10
Trisomy 13 ($n = 1$)		**1**
Holoprosencephaly		1
Facial cleft		1
Postaxial polydactyly		1
Total	0	3
Other chromosomal defects ($n = 5$)	**3**	**2**
Ventriculomegaly		1
Hygroma colli	1	1
Cardiac anomalies	1	
Mild hydronephrosis	1	
Generalized hydrops	1	1
Small for gestational age	1	
Syndactyly		1
Molar placenta	1	
Total	6	4

LUA, left umbilical artery; RUA, right umbilical artery.

Austria). The fetal biparietal diameter (BPD), head circumference (HC), abdomen circumference (AC) and femur length (FL) were also measured and a systematic search was made for the detection of any associated structural abnormalities or markers of chromosomal defects. Examination of the umbilical arteries was successfully achieved in all cases and its duration was about 1 min. In all cases of SUA fetal echocardiography was performed.

Statistical analysis was performed using the χ^2 test, or Fisher's exact test when appropriate.

RESULTS

The indications for amniocentesis were maternal age alone (>35 years)—38%, abnormal serum screen in the second trimester (cut-off >1 : 250)—47%, abnormal ultrasound examination alone—8%, others—7%. The median maternal age was 32 (range, 14–47) years, the median gestation was 18 (range, 16–22) weeks. SUA was diagnosed in 102/2147 (4.8%) cases. The left umbilical artery was absent in 60/102 (58.8%) fetuses, compared with the 42/102 (41.2%) for the right artery.

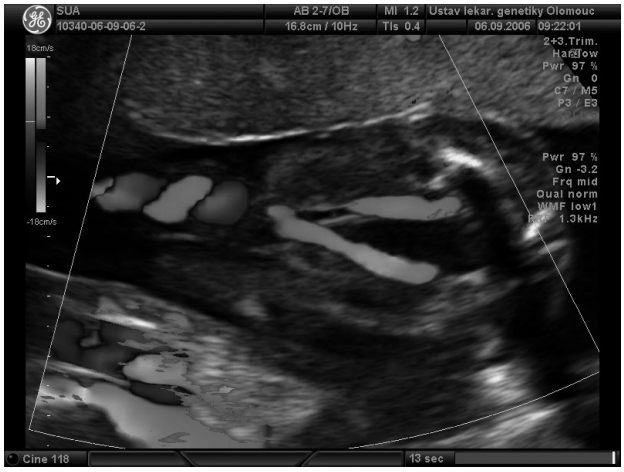

Figure 1—Transverse view of fetal pelvis, with color flow Doppler showing umbilical arteries as they course around the bladder

The associated structural abnormalities or markers of chromosomal defects were detected by ultrasound in 225 cases (10.4%). The rate of associated abnormalities was significantly higher among fetuses with SUA than among those with 2 umbilical arteries (25/102 or 24.5% *versus* 200/2045 or 9.8%; OR = 3.0, 95% CI 1.8–4.9, $p < 0.0001$). Among fetuses with SUA, there was no significant difference in the rate of associated abnormalities between those with absence of the left *versus* the right artery (14/60 or 23.3% *versus* 11/42 or 26.2%, $p = 0.74$). Among the fetuses with SUA and associated sonographic abnormalities, there were 24 fetuses with associated major structural anomalies and one fetus with trisomy 21, where there were only markers of aneuploidies and right umbilical artery was missing. Among the fetuses with 2 umbilical arteries and associated sonographic abnormalities, there were 83 fetuses with associated major structural anomalies and 117 fetuses where there were only markers of aneuploidies.

The fetal karyotype was normal in 2019 pregnancies and abnormal in 128 (6.0%). In the group of 128 chromosomally abnormal fetuses, there was an SUA in 19/128 (14.8%) fetuses and all of them had associated anomalies (Table 1). Two umbilical arteries were diagnosed in 109 (85.2%) cases (with associated anomalies 36/128 or 28.1%, without anomalies 73/128 or 57.1%). The rate of chromosome abnormalities was significantly higher among fetuses with SUA than among those with 2 umbilical arteries (19/102 or 18.6% *versus* 109/2045 or 5.3%; OR = 4.1, 95% CI 2.3–7.1, $p < 0.0001$). Among fetuses with SUA, there was no significant difference in the rate of chromosome abnormalities between those with absence of the left vs the right artery (11/60 or 18.3% *versus* 8/42 or 19.0%, $p = 0.93$). There were no chromosome abnormalities in fetuses where a SUA

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was an isolated sonographic finding. All fetuses with SUA and chromosomal defects had associated abnormalities detected by ultrasound 19/19 (100%); however, in one case with trisomy 21 there were only sonographic markers of aneuploidies (bilateral choroid plexus cysts, enlarged cysterna magna, bilateral mild hydronephrosis, and right umbilical artery was missing).

In the chromosomally normal group, the incidence of SUA was 4.1% (83/2019 cases). In the group of 83 fetuses with an SUA, there were six (7.2%) fetuses with associated structural abnormalities detected in the second-trimester scan (including one hypoplastic left ventricle, hydronephrosis, cleft lip and palate with missing left umbilical artery and one ventricular septal defect, renal agenesis, diaphragmatic hernia with missing right umbilical artery) and this was similar to the 1936 with two arteries, of which 164 fetuses had other defects (8.4%, $p = 0.69$).

In the chromosomally abnormal group, the incidence of SUA was 14.8% (19/128 cases). There was an SUA in 5/39 (12.8%) with trisomy 21, 8/16 (50%) with trisomy 18, 1/4 (25%) with trisomy 13 and 5/69 (7.2%) with other chromosomal defects (including two Turner's syndrome, two triploidies and one trisomy 16). In the group of 19 fetuses with SUA there were 19 (100%) fetuses with associated structural abnormalities detected in the second-trimester scan (Table 1) and this was significantly higher than in the 109 with two arteries, where there were 36 fetuses with other defects (33%, $p < 0.0001$).

SUA was diagnosed in 102/2147 (4.8%) cases. The rate of chromosome abnormalities was significantly higher among fetuses with SUA than among those with 2 umbilical arteries (19/102 or 18.6% *versus* 109/2045 or 5.3%; OR = 4.1, 95% CI 2.3–7.1, $p < 0.0001$).

Associated sonographic abnormalities were detected in 225 cases (10.4%). The rate of chromosome abnormalities was significantly higher among fetuses with associated sonographical abnormalities than among those without (55/225 or 24.4% *versus* 73/1922 or 3.8%; OR = 8.2, 95% CI 5.5–12.2, $p < 0.0001$).

Major defects were detected in 107 cases (5.0%). The rate of chromosome abnormalities was significantly higher among fetuses with associated major defects than among those without (44/107 or 41.1% *versus* 84/2040 or 4.1%; OR = 16.3, 95% CI 10.2–25.9, $p < 0.0001$).

Only markers of chromosomal defects were detected in 118 cases (5.5%). The rate of chromosome abnormalities was not significantly higher among fetuses with only markers of chromosomal defects than among those without (11/118 or 9.3% *versus* 117/2029 or 5.8%; OR = 1.7, 95% CI 0.83–3.3, $p = 0.11$).

In the group of 25 fetuses with SUA and associated sonographic abnormalities there were 19 (76%) fetuses with chromosome abnormalities (Table 1) and this was significantly higher than in the 1845 with two arteries and without associated sonographic abnormalities, where there were 73 fetuses with abnormal karyotype (4%, $p < 0.0001$).

DISCUSSION

In this study of fetuses in the second trimester of pregnancy (at 16–22 weeks' gestation), the incidence of SUA was 4.8%, which is lower than the reported incidence of 5.9% in the first trimester of pregnancy (at 11–14 weeks' gestation) (Rembouskos *et al*., 2003), but substantially higher than the reported birth incidence of 0.2–2.0% (Heifetz, 1984; Leung and Robson, 1989; Lilja, 1991; Jones *et al*., 1993; Gornall *et al*., 2003; Prucka *et al*., 2004; Martinez-Payo *et al*., 2005). Furthermore, the incidence of chromosomal defects in fetuses with SUA (19%) was considerably lower than 50% reported at 11–14 weeks' gestation (Rembouskos *et al*., 2003), but higher than 8% reported in second- and third-trimester ultrasonographic studies reviewed by Rembouskos *et al*. (2003). It is likely that both the observed incidence of SUA and the incidence of associated chromosomal defects are overestimated because our population was preselected for fetal karyotyping by a combination of maternal age, biochemical screening and ultrasound. In the first-trimester study (at 11–14 weeks' gestation) (Rembouskos *et al*., 2003) the population was preselected for fetal karyotyping by a combination of maternal age, being on average 37 years, and increased fetal NT, which was above the 95th centile for Crown-rump length (CRL) in 36% of cases (Snijders *et al*., 1998).

In our study, the incidence of SUA in the chromosomally abnormal group was almost four times higher than in the chromosomally normal group, but we have not found any chromosomal alteration in fetuses with isolated SUA and all chromosomally abnormal fetuses with SUA had associated malformations detected in the second-trimester scan.

As is known, the umbilical cord normally contains one vein and two arteries. The development of the vasculature of the cord begins at the end of the third week of gestation. Apart from the two arteries and the vein, the cord also contains the vitelline duct and its vessels (vitelline artery and vein), the latter normally regressing at the end of the third month.

There are three theories regarding the pathogenic mechanism resulting in SUA: (1) primary agenesis of one umbilical artery; (2) secondary atrophy or atresia of a previously normal umbilical artery; and (3) persistence of the original allantoic artery of the body stalk (Monie, 1970; Heifetz, 1984; Persutte and Hobbins, 1995). It is believed that atrophy is the most frequent mechanism. When both umbilical arteries close and the vitelline artery persists, it has been classified as an SUA type II and corresponds with approximately 1.4% of SUA cases. This type is normally associated with sirenomelia or caudal regression syndrome (Persutte and Hobbins, 1995). It is thought that the cause is insufficient irrigation of the terminal portion of the embryo, and depending on the stage of development at which this occurs, it will produce different clinical symptoms, so that if it occurs later, the result may be a fetus with no malformations (Gamzu *et al*., 2002). Hypoplasia of one of the two umbilical arteries is much less frequent, affecting 0.03% of pregnancies, and is associated

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with intrauterine growth retardation (IUGR), maternal diabetes, polyhydramnios, and congenital cardiopathy, described in a case of trisomy 18. This hypoplasia probably represents an incomplete form of SUA (Petrikovsky and Schneider, 1996).

It is not clear why SUA is linked to other fetal anomalies, and although there is no unique malformative pattern, the most frequent anomalies are genitourinary, followed by cardiovascular malformations, whilst gastrointestinal malformations are the least frequent (Gornall *et al*., 2003). We have found these same data in our cases. In the study of Gornall *et al*. (Gornall *et al*., 2003), the diagnosis of congenital anomaly was almost seven times greater in the case group than in the control group. In this study, 20% of the fetuses with SUA had an added congenital anomaly. In our study, 25% of fetuses with SUA had associated structural abnormalities detected by ultrasound, which was more than 2.5 times greater than in the group of fetuses with two umbilical arteries (10%).

Similar to the results of Abuhamad *et al*. (Abuhamad *et al*., 1995) ($n = 77$ cases) and Geipel *et al*. (Geipel *et al*., 2000) ($n = 102$ cases), but in contrast to the studies with smaller numbers of cases by Blazer *et al*. (1997) ($n = 46$ cases) and Fukada *et al*. (Fukada *et al*., 1998) ($n = 10$ cases), which observed no differences in the distribution of the missing side, we found the absence of the left side (58.8%) was more frequent than the right (41.2%). Absent left umbilical artery was more common in fetuses of both groups: chromosomally normal (59%) and chromosomally abnormal (58%). Our results suggest that the left umbilical artery is more commonly absent than the right artery in fetuses with SUA. We could not find an explanation for this difference. It is interesting to note that the right umbilical artery is usually larger than the left (Lacro *et al*., 1987). This asymmetry in size between the two umbilical arteries may play a role in the pathogenesis of single umbilical artery by favoring one side over the other.

Because SUA may be associated with other fetal malformations, karyotype anomalies, IUGR, preterm birth, and low birth weight, the routine study of the umbilical cord is interesting. The diagnostic attitude on finding an SUA may be controversial. All authors agree that if an SUA is found, a detailed ultrasound must be carried out by an ultrasound specialist, in order to detect other associated fetal anomalies (Persutte and Hobbins, 1995; Chow *et al*., 1998; Rembouskos *et al*., 2003). Some authors recommend adding a fetal echocardiography to the ultrasound exploration if an SUA is found as an isolated finding (Abuhamad *et al*., 1995; Persutte and Hobbins, 1995; Parilla *et al*., 1995; Budorick *et al*., 2001; Prucka *et al*., 2004). If subsequent explorations are normal, prenatal fetal growth and wellbeing controls should be carried out, considering it as a pregnancy at risk until birth (Martinez-Payo *et al*., 2005).

The presence of an SUA as an isolated finding, in studies on the general population, is linked to a poor perinatal result, when compared with fetuses with two arteries. They tend to be of low weight, premature and twice as often below the 10th percentile in weight; likewise, a cesarean section is more frequent. Perinatal mortality is greater, six times greater for fetuses with SUA and without associated malformations (Gornall *et al*., 2003).

It is not clear why fetuses with SUA achieve poorer perinatal results, even without associated malformations. It has been demonstrated that these cords have a lower number of spirals (Lacro *et al*., 1987) and a lesser quantity of Wharton jelly, which make them less resistant in situations of stress, such as birth or compression of the umbilical cord, and may act in synergy with other unfavorable circumstances (Raio *et al*., 1999).

In our study, all chromosomally abnormal fetuses with an SUA had other abnormalities that were detectable by ultrasound. The aneuploidies most frequently found were trisomy 18, 13 and 21, although it was found in others such as triploidy, 45,X0 and trisomy 16. We have not found any chromosomal alteration in fetuses with isolated SUA and all chromosomally abnormal fetuses with SUA had associated malformations detected in the second-trimester scan.

Our results show that the systematic scanning with Doppler for the number of umbilical arteries in the 20th week of pregnancy is probably a good diagnostic method. The finding of an SUA should alert the ultrasonographer to search for associated malformations and markers of chromosomal defects, such as overlapping fingers, facial cleft, cardiac anomalies, spina bifida and many other abnormalities that are detectable at the 16–22 week scan. In cases of apparently isolated SUA, there is no indication for fetal karyotyping because in this group there is no evidence of increased risk of chromosomal defects and which artery is missing is not significant.

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