Postnatal development of fetuses with a single umbilical artery: differences between malformed and non-malformed infants

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Background: **The presence of a single umbilical artery (SUA) is a fetal soft marker of congenital abnormalities. Among the most common related malformations, there are cardiological, nephrourological and digestive anomalies, most of which are considered to have a vascular etiology. There is an association between increased incidence of intrauterine growth retardation and adverse perinatal indicators, but whether this association is due to related anomalies or isolated SUA (iSUA) is controvisal.**

Methods: **We reviewed 96 cases of iSUA and non-isolated SUA (niSUA), diagnosed in a period of two years in a referral hospital for high-risk pregnancies. Data on prenatal explorations, including fetal ultrasonography and karyotyping, were obtained. niSUA was diagnosed when no malformations were found prenatally or in postnatal evaluation.**

Results: **Sixty-six newborns (68.8%) had no other anomalies and 30 (31.3%) presented with a variety of malformations including heart diseases, urophaties, digestive, nervous and musculoskeletal disorders, genetic abnormalities and complex malformations. Cardiological and nephrourological abnormalities were found to be the most frequent association with a SUA (both in 23.8% of malformed SUA newborns). Intrauterine growth restriction was not higher in iSUA newborns than in a normal population. Ultrasound allowed optimal prenatal diagnosis in most cases.**

Conclusions: **The prognosis of the fetus with a SUA is determined by the presence of other malformations observed by an expert sonographer. If no other findings are made, only a routine physical examination should be performed in newborns, but no other complementary examinations are required.**

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Key words: **cardiovascular abnormalities; congenital abnormalities; fetal growth retardation; prenatal ultrasonography; single umbilical artery**

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Introduction

According to the Canadian Society of Obstetricians and Gynecologists, umbilical vessels should be assessed as part of the routine ultrasound examination from 16 to 20 weeks of gestation. The presence of a single umbilical cord is considered as a fetal soft marker of congenital abnormalities. If a single umbilical artery (SUA) is found, a detailed examination of fetal anatomy is recommended, including the kidneys and heart, and adequate monitoring of fetal growth. Since SUA is an isolated finding, invasive techniques that are used to rule out fetal chromosomal abnormalities are not recommended.[1]

The consensus document of the Spanish Society of Gynecology and Obstetrics (SEGO) reports, that more than 90% of cases of SUA represent an isolated anomaly.[2] Nevertheless, some studies have found a higher frequency of structural anomalies in newborns with a SUA, between 20% and 30%.[3,4] SUA is associated with congenital malformations of potential vascular etiology, such as renal aplasia, atresia of gastrointestinal organs or limb shortening defects, suggesting a similar underlying anomaly in the development of SUA and its associated findings.[5] A higher incidence of intrauterine growth retardation

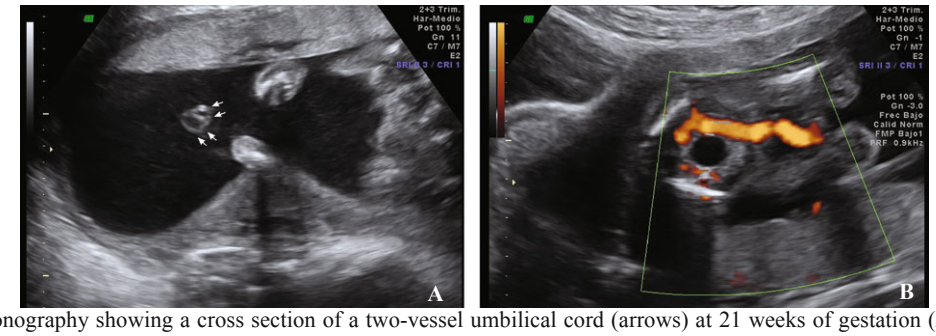

Fig. 1. Fetal ultrasonography showing a cross section of a two-vessel umbilical cord (arrows) at 21 weeks of gestation (**A**). Doppler ultrasound showing only one signal corresponding to one umbilical artery closed to the urinary bladder (**B**).

(IUGR), prematurity and adverse perinatal indicators has also been reported in gestations with a SUA. However, controversy exists over whether this effect is due to its associations or related to isolated SUA.

The aim of the present study was to review the evidence in the current literature regarding the management of newborns with a SUA and to determine its clinical significance in our population with an isolated SUA (iSUA) or a non-isolated SUA (niSUA).

Methods

We conducted a retrospective and descriptive study of all cases with a SUA diagnosed prenatally between March 2009 and February 2012. In the study, all pregnant women (both low and high-risk patients) were referred for the 2nd trimester scan to the Obstetrics Department of our center (University & Polytechnic Hospital La Fe, Valencia, Spain), being attended by a group of obstetricians highly specialized in prenatal ultrasound diagnosis as part of the normal pregnancy control and/or as specialized follow-up given that our hospital is a referral center for monitoring high-risk pregnancies. Ultrasound scans were carried out in all cases with a Voluson 730 Expert equipment using the color Doppler examination to find the two umbilical arteries, which surround separately both sides of the vesical wall of the fetus and later leave the fetal abdominal wall joint. The diagnosis of a single umbilical artery can also be made by scanning the number of vessels in a cross section of a free loop of the umbilical cord, but the color Doppler method is thought to be more reliable than the last one (Fig. 1).[2]

All cases underwent fetal somatometry, ultrasound study of the brain, reno-vesical apparatus and heart, including the four chambers and outflow tracts. In case of SUA, if the ultrasound scan did not present any other morphological alteration or markers of chromosomopathy, and there was a low-risk pregnancy, the patient was given a new appointment to repeat ultrasound according to the current protocols of normal pregnancy follow-up, intensifying the assessment of fetal growth. If one of the mentioned premises was not met, a study of fetal karyotype was performed.

Among 14 930 gestations, we found 96 cases of SUA. Only two cases were not included because of lack of data. Data on postnatal mortality, pathology or demographic features were obtained by the pediatric and maternal electronic medical reports. iSUA was diagnosed when no other malformations were found by prenatal ultrasound and postnatal examination following the decision-making guidline (Fig. 2).

Statistical analysis was made with SPSS 19.0 (IBM, Chicago, USA). For qualitative variables, data were summarized using frequencies, and quantitative variables are shown using mean±standard deviation. In order to compare quantitative variables, Student's *t* test or nonparametric tests was used in case they were not normally distributed (the Mann-Whitney *U* test). The Chi-square test was used to evaluate the association between qualitative variables and Fisher's exact test was also used when necessary. $P<0.05$ was considered statistically significant.

In literature search, recent articles concerning this issue were retrieved from Medline, Embase and Tripdatabase using the Medical Subject Heading (MeSH) "Single Umbilical Artery".

Results

Ninety-six cases of SUA were diagnosed between March 2009 and February 2012. A total of 14 930 gestations were controlled at the 2nd trimester, thus representing a prevalence of 0.64% [95% confidence interval (CI): 0.53%-0.78%]. Thirty cases (31.3%; 95% CI: 22.8%-41.1%) were related to other malformations or pathological conditions, and the other 66 (68.8%; 95% CI: 58.9%-77.1%) were iSUA. Twenty-two cases of niSUA had unique associations and 8 a complex malformation involving more than one system. Genetic

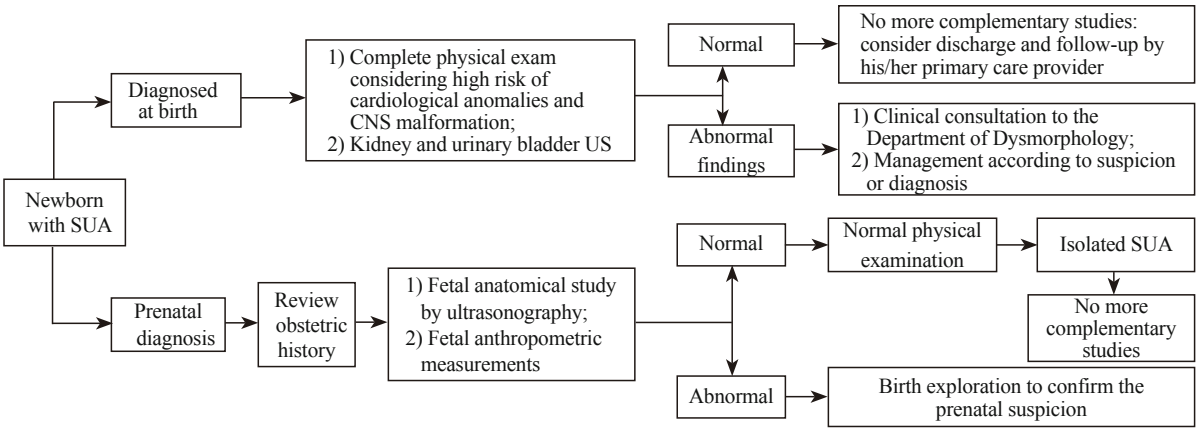

Fig. 2. Single umbilical artery (SUA) management flowchart. CNS: central nervous system; US: ultrasound.

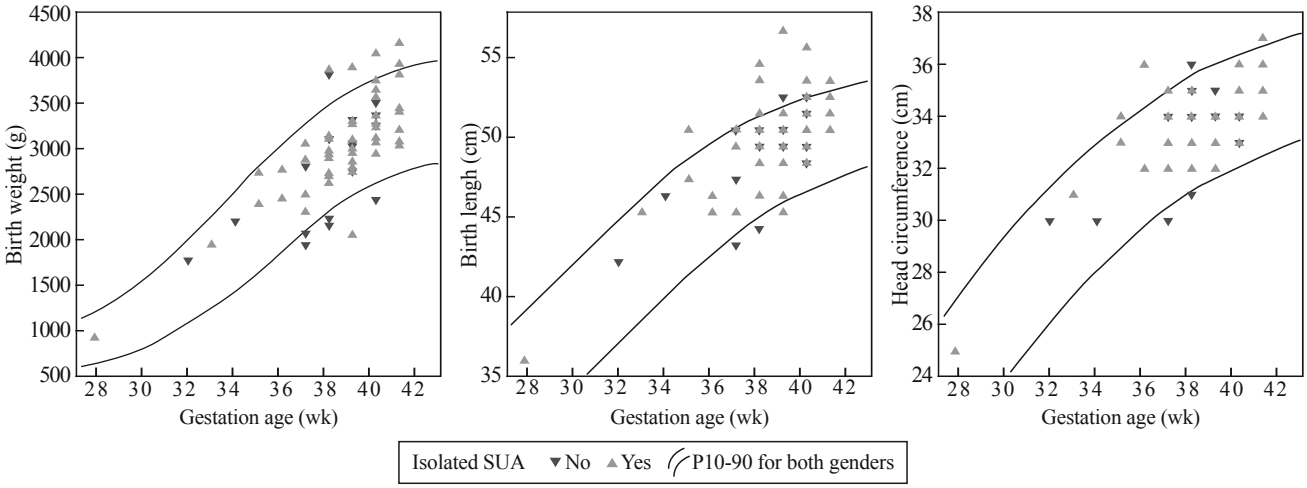

Fig. 3. Fetal somatometry: birth weight, height and head circumference of the 96 cases of single umbilical artery (SUA), differentiating between isolated and non-isolated SUA (Due to overlapping, one triangle may represent several cases).

anomalies were included in the unique-association niSUA. The only two cases of SUA diagnosed before the 15th week were of niSUA, one complex malformation and one with two septal defects. Table 1 shows the distribution of the associations by the system involved. Table 2 shows the individual anomalies in both babies with multiple anomalies and those with unique SUA-association.

The mean age of mothers at diagnosis of SUA was 31.6 years in the niSUA group and 31.5 in the iSUA group (P=0.903). About 5.2% of SUA cases were diagnosed in twin pregnancies, but none of them was in the niSUA group (P=0.321). There were no differences in the history of assisted reproductive technology, 92.3% of cases of niSUA were spontaneously conceived and 96.4% in the iSUA group (P=0.69). Total 54.5% of deliveries were vaginal among cases of niSUA and 65.7% among cases of iSUA. The rate of cesarean deliveries was non-significantly higher in cases of iSUA (25.7% and 18.2%), but there were more instrumented deliveries in the cases of niSUA (10% *vs.* 4.5%). Differences in the way of pregnancy end were also not significant (P=0.219). Apgar scores at 1 and 5 minutes were slightly better in the iSUA group with no statistical significance. Maternal and pregnancy characteristics of patients with iSUA compared with niSUA are shown in Table 3.

Table 1. Single umbilical artery (SUA) and its association with other congenital malformations in newborn infants

SUA and its associations	Percentage (%)
Isolated finding: 72.4%	
Cardiological	23.8
Nephrourological	23.8
Chromosomopathy	14.3
Neurological	14.3
Gastrointestinal	4.8
Musculoeskeletal	4.8
Others	14.3*
Multiple malformations: 27.6%	

*: Column do not add up to 100% due to adjustments.

Table 2. Frequency of anomalies related to single umbilical artery in newborns with multiple malformations and with a single-association

Anomalies	No.
Cardiac anomalies	
Ventricular septal defect	5
Double superior vena cava	3
Pulmonary stenosis	2
Atrial septal defect	1
Common atrioventricular canal	1
Infundibular pulmonary stenosis	1
Aortic atresia	1
Hypoplastic left heart	1
Aortic coarctation	1
Double mitral valve	1
Nephrourologic anomalies	
Renal agenesis	3
Pelvicalyceal ectasia	3
Hypospadias	2
Ectopic kidney	1
Polycystic kidney	1
Musculoskeletal anomalies	
Diaphragmatic hernia	2
Facial dysmorphia	2
Thumb agenesis	2
Hip dislocation	1
Neurological anomalies	
Myelomeningocele	2
Absence of cerebellar vermis	1
Dandy-Walker malformation	1
Genetic anomalies	
XYY karyotype	1
Trisomy 21	1
Trisomy 16 in mosaicism	1
Gastrointestinal anomalies	
Jejunal atresia	1
Others	
Congenital tooth	2
Preauricular pit	2
Microphthalmia and lens luxation	2

We found 7 voluntary terminations of pregnancy in our sample, all in fetuses with SUA and related malformations. Two natural abortions occurred in iSUA cases. The mortality rate of live births was 21.7% in SUA cases with related conditions (2 cases of chromosomopathies: 21 and 16 trisomy, 2 cardiopathies and a sepsis in a newborn with bone dysplasia). There were no deaths in the iSUA group. Approximately 40.6% of newborns with niSUA were admitted to our hospital, in contrast to 16.7% in the iSUA group (P<0.001).

Anthropometric measurements showed 16.7% (95% CI: 7.3%-33.6%) cases of niSUA with a birth weight below the 10th percentile for their gestational age, showing a tendency to be higher than the expected 10%. In this group, 10% (95% CI: 3.4%-25.6%) cases had a birth length below the 10th percentile and 6.7% (95% CI: 1.8%-21.3%) had a head circumference <P10.

Table 3. Maternal and pregnancy characteristics of patients with isolated single umbilical artery (iSUA) compared with patients with non-isolated single umbilical artery (niSUA)

Chracteristics	iSUA	niSUA
Mean maternal age, y	31.5±5.2	31.6±6.3
Mean Apgar score at 1st minute	8.5±1.6	7.8±2.3
Mean Apgar score at 5th minute	9.6±1.0	9.0±1.7
Prematurity, %	12.3	30.4
Infant male sex, %	50.0	46.7
Assisted reproductive technology, %	3.6	7.7
Vaginal delivery, %	65.7	54.5
Instrumented delivery, %	4.5	10.0
Cesarean delivery, %	25.7	18.2
Pregestational diabetes mellitus, %	1.5	3.3
Gestational diabetes, %	13.6	13.3
Chronic hypertension, %	9.1	6.7
Preeclampsia/eclampsia, %	6.7	4.5
Tobacco exposure during pregnancy, %	12.1	13.3

Differences were insignificant (P>0.05).

In the iSUA cases alone, only 1.5% (95% CI: 0.3%-8.1%) was small for the gestational age (SGA) (Fig. 3).

Malformations associated with SUA were not diagnosed prenatally in three cases: one hypospadias in combination with an already observed thumb agenesis, one case of bilateral microphthalmia with lens luxation, and a double mitral valve which was disregarded in the context of a suspected multiple malformation involving unilateral kidney agenesis and ureteral ectasia. Double mitral valve was an isolated cardiac finding and presented with normal heart function.

Discussion

The presence of SUA affects around 0.5%-1% of the general population and it is one of the most common fetal malformations. We have found a prevalence of 0.64% (95% CI: 0.53%-0.78%), similar with that reported in recent works.[6-8] SUA is more frequent in twin pregnancies and aneuploid fetuses, in which it is diagnosed by ultrasonography in 10% of cases (as opposed to euploid fetuses: 0.2-1.6%).[9] In a collaborative study published in 2006, a total of 18 540 newborn infants with congenital malformations and 17 861 controls with no malformations were studied. In this study, SUA was found in 2.3% of the newborns with congenital defects and in 1% of those without abnormalities at birth.[10]

Since the SUA's first description in 1955,[11] its occurrence has been correlated to several factors, such as thalidomide administration during pregnancy, vitamin A overdose in pregnant women and otorhinolaryngologic or dental infections. A higher prevalence has also been proposed in Caucasians and

in infants born to diabetic mothers, epileptic mothers, or mothers with a history of infertility treatment,[12] in association with maternal smoking[13] and in infants born to older and primiparous mothers.[14] In most cases, it is an isolated defect but considered as a soft marker of fetal abnormalities.

For addressing this issue, it was essential to differentiate between niSUA and iSUA. In our study, 68.8% of cases were iSUA. This percentage is lower than that reported by the SEGO,[2] probably because our hospital is a referral center for high-risk pregnancies. Among both groups, there is a trend towards a higher percentage of SGA newborns and a higher percentage of hospital admission in children with niSUA, which were probably related to comorbidity. Malformations most frequently associated with niSUA are cardiologic and nephrourologic, with a similar frequency as a unique association. Hence, several reports have underlined that congenital heart disease is the most frequent association,[15-17] although this is still controversial. The most frequent cardiac malformations concurring in our cases were ventricular septal defects and duplication of the superior vena cava. Kidney malformations are estimated to be 16%, of which 54% are minor malformations.[8] In our study, the rate of major malformations was over 40%, the most common malformation was renal agenesis.

The incidence of fetuses with multiple malformations varies from 7.4% to 72%.[18,19] We reported in our series an incidence of 27.6%. Fetuses with chromosomal abnormalities could be added to this group, representing 14.3% of cases. Granese et al[20] reported an incidence of 42% of chromosomal abnormalities in fetuses with SUA. However, in our series, not every infant had karyotyping performed at the time of data collection, which could explain the differences. The incidence and type of brain malformations (myelomeningocele, absence of cerebellar vermis, and Dandy Walker malformation) were consistent with that reported elsewhere.[21]

Gastrointestinal defects are found to be linked to vascular insults during organogenesis. Atresia of the small intestine has been widely described in relation to SUA.[22] Similarly, neuromuscular disorders are probably due to disruptive causes such as agenesis of fingers, long bones, syndactyly, diaphragmatic or inguinal hernias.[7] In our series, musculoskeletal abnormalities accounted for 4.8%: two cases of agenesis of the thumb, two of diaphragmatic hernia, two facial dysmorphism, and congenital hip dislocation. Other malformations were congenital teeth, preauricular pits and microphthalmia and lens luxation.

What level of monitoring should pregnancies undergo when SUA is diagnosed? It has been agreed that a systematic morphological study of all organs should be conducted. According to the International Society of Ultrasound in Obstetrics and Gynecology, an evaluation of the four cameras is sufficient to rule out heart disease. Only cases of doubts about possible congenital heart disease would require ex utero confirmation.[23-25] Of note is that most authors do not recommend systematic amniocentesis.[23,26,27] In our series, prenatal diagnosis agreed with ex utero diagnosis in 97% of cases. With these results, we also support that when a pregnancy is diagnosed of SUA, a morphological ultrasound study is necessary, but no additional examinations are required if there are not additional risk factors.

In conclusion, when diagnosing SUA in a pregnant woman, it is mandatory to do a thorough survey of pregnancy to rule out intrauterine growth retardation (IUGR) and other malformations. The prognosis of the fetus will be determined by the presence of other malformations observed by an expert ultrasound examiner. The relevance of the findings will be what determines the evolution of the newborn. The performance of other prenatally diagnostic tests depends on other risk factors associated with pregnancy and not just the diagnosis of SUA. If SUA is detected during a pregnancy together with another malformation or IUGR, it is recommended to offer the parents an invasive technique to study the fetus, including karyotyping. If a newborn has an isolated single umbilical artery, a routine physical examination is necessary, and other complementary examinations are not required.

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Competing interest: We declare no conflict of interest.
Contributors: Vento M proposed the study. Arcos-Machancoses JV and Marín-Reina P contributed to the study equally. Pérez-Aytés A and Vento M are the guarantors. All authors contributed to further drafts.

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