

Should fetal growth be a matter of concern in isolated single umbilical artery?

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SUMMARY

Objective: To examine birth weight in pregnancies with isolated single umbilical artery (ISUA).

Methods: Case control study with retrospective review of 131 singleton pregnancies with isolated single umbilical artery diagnosed before birth. Control group consisted of 730 singleton pregnancies recruited prospectively, that had histological confirmation of a 3 vessels cord. Pregnancies were classified as uncomplicated or high-risk according to the presence of diseases that increase the risk of placental insufficiency during pregnancy. Mean birth weight and frequency of low birth weight (< 2.500 g), very low birth weight (< 1.500 g) and fetal growth restriction below the 5th and 10th centiles were compared between groups.

Results: Mean birth weight difference between ISUA (n=131, 2840±701g) and control (n=730, 2.983 ± 671g) pregnancies was 143g (95% CI= 17-269; p=0.04) and birth weight below the 5th centile was significantly more common in ISUA group [28/131 (21.4%) *versus* 99/730 (13.6%), p=0.02]. When only uncomplicated pregnancies were considered in both groups, no birth weight differences were observed. Amongst high-risk subgroups, birth weight below the 5th centile remained significantly more common in ISUA compared to control pregnancies [10/35 (28.6%) *versus* 53/377 (14.1%), p=0.04].

Conclusion: Isolated single umbilical artery does not increase the risk of fetal growth restriction in uncomplicated singleton pregnancies.

Key words: single umbilical artery, fetal growth retardation, birth weight, ultrasonography.

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INTRODUCTION

Normally, the human umbilical cord contains two arteries that transport blood from the fetus to the placenta, and oxygenated blood returns to the fetus via a single umbilical vein. However, a single umbilical artery (SUA) can be diagnosed antenatally by ultrasound in up to 2% of pregnancies¹ and, when it is associated with other fetal structural defects, there is an increased risk of chromosomal abnormalities and adverse pregnancy outcome.²

Nevertheless, the clinical relevance of an isolated SUA remains controversial. Compensatory mechanisms allow increase in blood flow through the single artery in order to meet the demands of fetal growth and development throughout pregnancy.³ Although several studies have reported diminished fetal growth in these pregnancies,⁴⁻¹²

others have not shown differences.¹³⁻¹⁵ These contradictory findings may be attributed to diverse methodological differences in the published literature.

The present study examines birth weight in pregnancies with isolated single umbilical artery diagnosed antenatally in a tertiary care teaching hospital.

METHODS

This was a case-control study involving singleton pregnancies that attended the Department of Obstetrics and Gynecology at the São Paulo University Medical School Hospital, a tertiary care teaching medical facility. The study protocol was approved by the hospital's ethics committee (0685/10).

Isolated single umbilical artery study group

A computer database search was performed to retrospectively identify all singleton pregnancies in which an isolated single umbilical artery (ISUA) was diagnosed antenatally by ultrasound scan between 1998 and 2010. The diagnosis was based on the visualization of two vessels in a cross section view of a free loop of umbilical cord in a fetus without structural abnormalities. All cases were confirmed after birth by clinical and/or pathological examination of the cord. Live born infants with no phenotypic features of a chromosomal defect were assumed to be euploid.

Control group

It was based on a cohort of 759 unselected singleton pregnancies prospectively examined between 2007 and 2009 – that had already been included in a previous publication¹. In this group, a three vessels cord was confirmed by two ultrasound examinations (carried out at 11-13 weeks and 17-24 weeks) and placental examination after delivery. Seven hundred and thirty (96.2%) women delivered phenotypically normal live born infants.

Data collection

Hospital records were reviewed for pregnancy and outcome information. Women who delivered their babies in other hospitals were contacted by telephone.

Maternal characteristics including age, ethnic group and presence of clinical or obstetrical complications were recorded. Pregnancies were classified as uncomplicated or high-risk according to the presence of diseases that increase the risk of placental insufficiency during pregnancy: hypertension, cardiomyopathy, asthma, diabetes, hemoglobinopathy, thrombophilia, thromboembolism, cirrhosis, kidney failure or auto immune diseases.

Gestational age was calculated based on the first day of the last menstrual period when available and confirmed by early ultrasound examination. When menstrual dates were uncertain, or there was discrepancy greater than 7 days between clinical and ultrasound dates, gestational age was established according to the earliest ultrasound scan findings.

Birth weight was examined according to previously published reference values¹⁶ and primary outcomes were defined as birth weight below the 5th and 10th centiles.

Statistical analysis

All data was entered in an Excel spreadsheet (Microsoft Corporation, USA). Maternal demographics and frequency of birth weight below the 5th and 10th centiles were com-

pared between ISUA and control groups using unpaired Student *t* test and chi square tests or Fisher's exact test, when appropriate. Statistical calculations were performed using *Statsdirect* (StatsDirect Ltd, UK). Significance level was set as 0.05.

RESULTS

The database search identified 134 singleton pregnancies in which an isolated single umbilical artery was diagnosed prenatally by ultrasound. Mean gestational age at diagnosis was 25.1 ± 5.8 weeks and 18 (13.4%) cases were referred before 20 weeks. 131 (97.8%) pregnancies resulted in live births, and the diagnosis of ISUA was confirmed in all cases.

No differences were observed regarding maternal age, proportion of white women and gestational age at delivery between ISUA and control groups. Nevertheless, complications were observed significantly more often in control pregnancies (377/759, 49.7%) compared to the ISUA group (35/134, 26.1%, *p*<0.001, table 1).

TABLE 1 Characteristics and perinatal outcome in isolated single umbilical artery and control pregnancies.

	study group	control group	p*
n	134	759	
Maternal age, years (SD)	30.8 (6.7)	30.3 (6.6)	0.41
White, n (%)	78 (58.2)	400 (52.7)	0.28
Complications ^a , n (%)	35 (26.1)	377 (49.7)	<0.001
hypertension	16 (11.9)	260 (34.3)	
cardiomyopathy	9 (6.7)	32 (4.2)	
anemia	0	21 (2.8)	
diabetes	6 (4.5)	17 (2.2)	
autoimmune disease	1 (0.7)	39 (5.1)	
thrombophilia	3 (2.2)	26 (3.4)	
Outcome, n (%)			
stillbirth	3 (2.2)	29 (3.8)	0.46
live birth	131 (98.5)	730 (96.2)	
Gestational age at delivery, weeks (SD)	37.6 (2.3)	37.9 (2.3)	0.09
<34 weeks, n (%)	7 (5.3)	43 (5.9)	>0.99
<37 weeks, n (%)	31 (23.7)	144 (19.7)	0.29

GA: gestational age at delivery, n: number of cases, SD: standard deviation.

*Mann-Whitney U test or chi² test/Fisher's exact test.

^a defined in the present study as the occurrence of diseases that increase the risk of placental insufficiency during pregnancy.

Overall, significant differences were observed between ISUA and control pregnancies regarding mean birth weight (ISUA: 2.840 ± 701g, control: 2.983 ± 671g, mean difference=143g, 95% CI=17-269, *p*=0.04, figure 1) and birth weight below the 5th centile [ISUA: 28/131 (21.4%), control: 99/730 (13.6%),

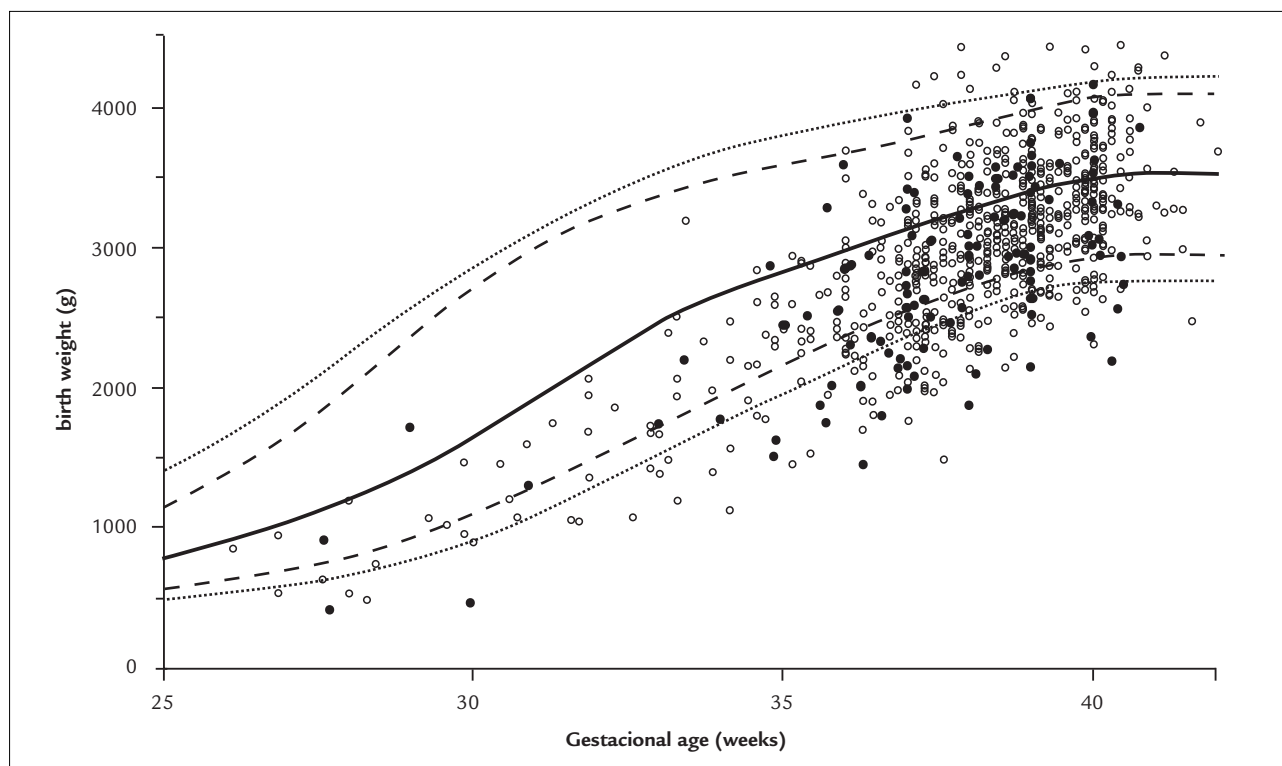


FIGURE 1 Scatter plot of birth weight according to gestational age at delivery. Open circles: control group (n=730), full circles: isolated single umbilical artery (n=131), continuous line: 50th percentile, dashed lines: 10th and 90th percentiles, dotted lines: 5th and 95th percentiles.¹⁶

p=0.02, table 2]. However, when only uncomplicated pregnancies were considered in both groups, no birth weight differences were observed. Amongst high-risk subgroups, birth weight below the 5th centile remained significantly more common in ISUA compared to control pregnancies [10/35 (28.6%) versus 53/377 (14.1%), p=0.04].

DISCUSSION

Several studies have previously shown the association between single umbilical artery and less fetal growth. Based on these findings, some authors have recommended that fetal growth should be monitored throughout pregnancy after prenatal diagnosis of a single umbilical artery.^{7-9,11,12} As a matter of fact, throughout the study period, our management protocol for pregnancies diagnosed with ISUA included serial follow up fetal growth scans. And when fetal growth restriction was diagnosed additional fetal well being tests were performed. Our current findings suggest that close fetal growth follow up is only necessary when ISUA is associated with the occurrence of maternal disease or pregnancy complication.

Moreover, gestational age at delivery and the rates of preterm delivery (before 34 and 37 weeks) were not statistically different between ISUA and control pregnan-

TABLE 2 Birth weight in isolated single umbilical artery and control pregnancies

	Study group	Control group	p*
n	131	730	
Birth weight, grams (SD)	2840 (701)	2983 (671)	0.04
< 1500 g, n (%)	5 (3.8)	28 (3.8)	0.99
< 2500 g, n (%)	34 (26.0)	148 (20.3)	0.18
Birth weight < 5 th centile, n (%)	28/131 (21.4)	99/730 (13.6)	0.02
GA < 34 weeks	2/28 (7.1)	12/99 (12.1)	0.73
GA < 37 weeks	13/28 (46.4)	34/99 (34.3)	0.24
Birth weight < 10 th centile, n (%)	40/131 (30.5)	169/730 (23.2)	0.07
GA < 34 weeks	3/40 (7.5)	19/169 (11.2)	0.77
GA < 37 weeks	18/40 (45)	56/169 (33.1)	0.16
Uncomplicated pregnancies			
Birth weight, grams (SD)	2927 (704)	3058 (642)	0.13
Birth weight < 5 th centile, n (%)	18/96 (18.8)	46/353 (13.0)	0.21
Birth weight < 10 th centile, n (%)	26/96 (27.1)	72/353 (20.4)	0.21
High-risk pregnancies ^a			
Birth weight, grams (SD)	2601 (647)	2912 (690)	0.01
Birth weight < 5 th centile, n (%)	10/35 (28.6)	53/377 (14.1)	0.04
Birth weight < 10 th centile, n (%)	14/35 (40.0)	97/377 (25.7)	0.11

GA: gestational age at delivery, n: number of cases, SD: standard deviation.

*Mann-Whitney U test or chi² test/Fisher's exact test.

^a defined in the present study as the occurrence of diseases that increase the risk of placental insufficiency during pregnancy.

cies. This finding suggests that prenatal diagnosis of single umbilical artery does not prompt anticipation of delivery, nor adds additional clinically relevant morbidity besides fetal growth deviation.

As a matter of fact, Wiegand *et al.*¹⁷ evaluated fetal growth by repeated ultrasound examinations in 138 pregnancies following the diagnosis of ISUA. Intrauterine growth restriction was observed in 3% of the cases and the authors concluded that the risk of growth impairment is not different from the rest of their population.

Additional clinical relevance of ISUA was also evaluated after birth in a prospective cohort by Chetty-John *et al.*¹⁰ No significant differences in physical growth and neurological development were observed. There was also no evidence of increased need for admission to neonatal intensive care units (Bombrys *et al.*).¹⁴

In fetuses with two vessels cord, compensatory mechanisms are in place to allow the single artery to meet the demands for fetal development during late pregnancy. One of these mechanisms is an increase of the arterial diameter. Sepulveda *et al.* have described that in fetuses with ISUA, the diameter of the umbilical artery was greater than 50% of the umbilical vein, resulting in an umbilical vein to umbilical artery ratio ≤ 2 .³

Additional adaptive mechanism was suggested by the observation that birth weight centile correlates with both umbilical vein to artery perimeter ratio and impedance to flow in the uterine arteries.¹⁸ The authors hypothesized that fetal growth restriction associated with ISUA is not based on deficient trophoblast invasion but could be due to changes in the maternal uterine circulation and morphological characteristics of the vessels in the umbilical cord.

Moreover, a recent publication showed that birth weight was lower in left side absent umbilical artery singleton pregnancies compared to controls, but not in right side absent artery cases.¹⁹ The authors suggest that differences between left and right side vascular anatomy possibly also play a role in single umbilical artery fetal adaptive mechanisms.

Table 3 summarizes the studies that have evaluated the association between ISUA and low birth weight. Eleven series are based on cases diagnosed prenatally and significant differences in birth weight were demonstrated in four out of six studies that included control groups.^{6,7,11,13-15,18,20-23}

On the other hand, all post-natal studies have shown that birth weight is significantly lower in ISUA pregnancies compared to control pregnancies.^{5,9,10,12} This is possibly related to the fact that these are the studies with greater sample size. Moreover, since ISUA was not diagnosed

before birth, these pregnancies were more likely to have reached full term despite the presence of growth deviation.

Overall, twelve of these studies have made statements regarding the need for fetal growth follow up scans in pregnancies with ISUA: nine recommended routine scans and three considered them unnecessary (table 3).

The present study demonstrates that the likelihood of giving birth to a growth restricted neonate is not increased in uncomplicated pregnancies with an isolated single umbilical artery. However, in complicated pregnancies, this likelihood seems increased. Nevertheless, due to the limited sample size, and possible additional confounding factors that have not been addressed, this finding needs to be further evaluated.

Due to the tertiary nature of our hospital, our data presents an opportunity to examine the effect of ISUA on fetal growth in uncomplicated pregnancies, and a considerable number of cases with preexisting maternal medical and/or pregnancy complications. In the latter subgroup, the odds for fetal growth restriction seem enhanced and specific antenatal follow up and surveillance is advisable after the diagnosis of an ISUA. To the best of our knowledge, this is the first paper that presents specific data on the impact of ISUA on birth weight in high-risk pregnancies.

Nevertheless, due to the lack of robust prospective antenatal series, the true magnitude and long term impact of an ISUA on perinatal results and posterior childhood development are still not clear in these pregnancies, especially in otherwise uncomplicated ones. Prospective collaborative collection of data may help determine the best antenatal management protocols in these cases.

CONCLUSION

Isolated single umbilical artery does not increase the risk of fetal growth restriction in uncomplicated singleton pregnancies.

RESUMO

Artéria umbilical única isolada e restrição do crescimento fetal

Objetivo: Examinar a frequência de peso ao nascer abaixo dos percentis 5 e 10, em gestações únicas com artéria umbilical única isolada (AUUI), de acordo com a presença de complicações maternas.

Métodos: Estudo caso-controle. De acordo com a presença de doenças maternas prévias à gestação, ou ocorrência de complicações obstétricas, as gestações foram classificadas em “não complicadas” ou de “alto risco”. As

TABLE 3 Studies evaluating the association between isolated single umbilical artery and low birth weight

Study	Design	Number of cases	Diagnosis	LBW criteria	Frequency (%)	Recommendation for fetal growth monitoring
Bryan & Kohler 1974 ²⁴	prospective	113	PN examination	<10 th centile	22.1	NS
Heifetz 1984 ⁴	Retrospective case-control	69	Autopsy	SGA	43.5 versus 23.8 (p<0.01)	NS
Lilja 1991 ⁵	Retrospective case-control	1674	PN examination	<2500g	11.4 versus 3.6 (p <0.0001)	NS
Jones <i>et al.</i> 1993 ⁶	Retrospective case-control	37	US + PN confirmation	Birth weight	2750 g versus 3170 g (p<0.01)	NS
Catanzarite <i>et al.</i> 1995 ²⁰	Retrospective	38	US + PN confirmation	<10 th centile	18.0	Yes
Parilla <i>et al.</i> 1995 ²¹	Retrospective	50	US + PN confirmation	<2500g	12.0	No
Geipel <i>et al.</i> 2000 ²²	Retrospective	59	US + PN confirmation	<10 th centile	10.2	NS
Rinehart <i>et al.</i> 2000 ²³	Retrospective	6	US	NS	50.0	Yes
Gornall <i>et al.</i> 2003 ⁷	Retrospective case-control	83	US + PN confirmation	<10 th centile	22.0 versus 12.0 (p <0.007)	Yes
Predanic <i>et al.</i> 2005 ¹³	Retrospective case-control	84	US + PN confirmation	<10 th centile	7.1 versus 4.8 (p= 0.75)	No
Mu <i>et al.</i> 2008 ⁸	Retrospective case-control	14	PN	<10 th centile	35.7 versus 3.6 (p= 0.01)	Yes
Bombrys <i>et al.</i> 2008 ¹⁴	Retrospective case-control	255	US + PN confirmation	<10 th centile	13.7 versus 13.1 (p= 0.84)	No
Burshtein <i>et al.</i> 2009 ⁹	Retrospective population based	243	PN	NS	9.5 versus 1.9 (p <0.001) OR 5.4 (95% CI 3.5-8.4)	Yes
Bugatto <i>et al.</i> 2010 ¹⁸	NS	60	US + PN confirmation	<10 th centile	30.0	Yes
Chetty-John <i>et al.</i> 2010 ¹⁰	Prospective cohort	263	PN	birth weight	3.1 kg versus 3.2 kg (p <0.0001)	NS
Horton <i>et al.</i> 2010 ¹⁵	Retrospective case-control	68	US + PN confirmation	<10 th centile	17.6 versus 8.8 (p= 0.06)	Yes
Hua <i>et al.</i> 2010 ¹¹	Retrospective cohort	281	US + PN confirmation	<10 th centile	OR 1.9 (95% CI: 1.4 - 2.5)	Yes
Murphy-Kaulbeck <i>et al.</i> 2010 ¹²	Retrospective population based-cohort	725	PN	<3 rd centile <10 th centile	11.1 versus 3.7 OR 2.5 (95% CI 1.9-3.2) 25.0 versus 10.9 OR 2.2 (95% CI 1.8-2.7)	Yes
Present study	Retrospective cases and prospective controls	131	US + PN confirmation	<5 th centile <10 th centile	21.4 versus 13.6 (p=0.03) 30.5 versus 23.2 (p=0.06)	Yes (high-risk pregnancies only)

CI: confidence interval, EFW: estimated fetal weight, LBW: low birth weight, NS: not stated, OR: odds ratio, PN: post natal, SGA: small for gestation age US: ultrasound.

frequências de peso ao nascer abaixo dos percentis 5 e 10 foram comparadas entre os subgrupos.

Resultados: O peso ao nascer foi significativamente menor em gestações com AUUI (n=134, 2840 ± 701 g) quando comparado com o grupo controle (n= 730, 2983 ± 671 g, p= 0,04; média da diferença=143 g, IC 95% = 17-269). Em gestações de alto risco, peso ao nascer abaixo do 5º percentil foi significativamente mais frequente no subgrupo com AUUI [10/35 (28,6%) *versus* 53/377 (14,1%), p= 0,04; razão de chances= 2.45 (IC 95% = 1,11-5,38)]; não foi observada diferença em relação ao peso abaixo do 10º percentil (p= 0,11). Em gestações não complicadas, não foram observadas diferenças na frequência de peso ao nascer abaixo do 5º e 10º percentis entre os subgrupos com AUUI e cordão com 3 vasos (p= 0,21).

Conclusão: Em gestações de alto risco, a frequência de peso ao nascer abaixo do percentil 5 é significativamente aumentada.

Unitermos: artéria umbilical única, retardo do crescimento intrauterino, peso ao nascer, ultrassonografia.

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