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MATERNAL-FETAL MEDICINE

Isolated single umbilical artery is an independent risk factor for perinatal mortality and adverse outcomes in term neonates

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Abstract
Objective To determine whether an isolated single umbilical artery (iSUA) is an independent risk factor for perinatal mortality in term neonates with normal estimated fetal weight (EFW) prior to delivery.
Method A population-based study was conducted, including all deliveries occurring between 1993 and 2013, in a tertiary medical center. Pregnancies with and without iSUA were compared. Multiple gestations, chromosomal, and structural abnormalities were excluded from the cohort. Only pregnancies delivered at term with normal EFW evaluated prior to delivery were included. Stratified analysis was performed using multiple logistic regression models to evaluate the risk of adverse outcomes and perinatal mortality for iSUA fetuses.
Results During the study period, 233,123 deliveries occurred at "Soroka" University Medical Center, out of which 786 (0.3 %) were diagnosed with iSUA. Different pregnancy complications were more common with iSUA fetuses including: placental abruption (OR = 3.4), true knot of cord (OR = 3.5) and cord prolapse (OR = 2.8). Induction of labor and cesarean delivery were also more common in these pregnancies (OR = 1.5 and OR = 1.9, respectively). iSUA neonates had lower Apgar scores at 1 and 5 min (OR = 1.8, OR = 1.9, respectively) compared to the control group and perinatal mortality rates were higher both antenatally (IUFD, OR = 8.1) and postnatally (PPD, OR = 6.1).
Conclusion iSUA appears to be an independent predictor of adverse perinatal outcomes in term neonates.

Keywords SUA · Term pregnancy · Pregnancy complications · Intra-uterine fetal death · Post-partum death

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Introduction

The umbilical cord typically contains three vessels: one vein that carries oxygenated blood from the placenta to the fetus, and two arteries that carry the blood from the fetus back to the placenta. Single Umbilical Artery (SUA) refers to a variation of the umbilical cord in which there is only one artery instead of the normal two. It is a common variation of the umbilical cord with a reported incidence of 0.2–2 % of pregnancies [1]. SUA was shown to be associated with several fetal structural and chromosomal abnormalities (including cardiac, gastrointestinal and renal anomalies) leading to fetal and neonatal complications [2]. Thus, the American Institute of Ultrasound in Medicine (AIUM) recommends imaging of the umbilical cord including the number of vessels in the cord during the routine prenatal ultrasound examinations [3]. If SUA is identified, a targeted ultrasound is warranted to rule out known associated anomalies.

The term isolated SUA (iSUA) refers to fetuses identified with SUA and no other apparent abnormality on ultrasound. iSUA is more common than non-isolated SUA [4–7], and the significance of this finding is controversial. Several studies evaluating the significance of iSUA revealed associations with fetal growth restriction, preterm delivery and low birth weight [1, 2, 8, 9], although others failed to establish such associations [10–13]. Recent

studies suggested increased rates of cesarean deliveries (mainly due to non-reassuring fetal heart rate patterns) and lower umbilical cord blood PH [14] in these pregnancies. iSUA was also shown to be an independent risk factor for perinatal mortality [15].

The present study was designed to evaluate perinatal outcomes of fetuses with iSUA and no other risk factors for perinatal complications. We excluded other well-established risk factors for perinatal mortality including growth-restricted fetuses and preterm deliveries in an effort to isolate any independent association of iSUA with adverse perinatal outcome.

Methods

This was a population-based retrospective study including all singleton deliveries, which occurred during a 20-year period (1993–2013) at the "Soroka" University Medical Center. This is a tertiary hospital and the largest in the Negev, the southern part of Israel. The hospital serves the entire obstetrical population in this region, thus, the study is based on non-selective data. The institutional review board approved the study that has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (# SOR-0236-13 approved on November 20, 2013).

Delivery was defined as one occurring at a gestational age of 22 weeks and above and resulting in a neonate weighing 500 g and above. The primary exposure was a diagnosis of iSUA during pregnancy. Gestational age was determined using menstrual history and first trimester ultrasound. A comparison was made between pregnancies with and without iSUA. Multiple gestations, chromosomal, and structural abnormalities were excluded from the cohort to fit the definition of iSUA. In our institution, all women admitted for delivery undergo a routine sonographic evaluation, which includes an estimation of fetal weight (EFW) by the admitting physician. Only pregnancies delivered at term (37 completed weeks of gestation and above) with a normal EFW (appropriate for gestational age—AGA) prior to delivery were included in the analysis. Following delivery, midwives routinely evaluate the placenta and umbilical cord, thus all cases of SUA are confirmed by a physical examination postnatally.

Data was collected from the hospital's computerized perinatal database, which consists of information recorded immediately following delivery by an obstetrician. Medical secretaries routinely review the information prior to entering it into the database to ensure its maximal completeness and accuracy. Coding is performed after assessing medical prenatal care records as well as routine hospital documents.

Statistical analysis was performed with the SPSS package 17 ed. (SPSS, Chicago, IL). Categorical data are shown in counts and percentages and the differences were assessed by Chi-square for general association. Student *t* test and one-way ANOVA were used for differences in continuous variables. A multivariable logistic regression model, with backward elimination, was constructed to isolate independent outcomes associated with SUA and specifically perinatal mortality while controlling for confounders. Stratified analysis, using the Mantel–Haenszel technique was used to assess the association between SUA and other variables with clinical significance while controlling for possible confounders. We controlled for diabetes mellitus (gestational and pre-gestational), polyhydramnios, oligohydramnios, placental abruption, placenta previa, cord prolapse, true knot of cord, non-reassuring fetal heart rate, vasa previa and induction of labor. Odds ratios (OR) and their 95 % confidence interval (CI) were computed. A P value of <0.05 was considered statistically significant.

Results

During the study period 233,123 deliveries met the inclusion criteria, of which 786 (0.3 %) were fetuses with confirmed iSUA. Table 1 presents maternal characteristics and pregnancy complications in women with and without iSUA. Women were slightly younger and smoking was more prevalent in the iSUA group. There were higher rates of recurrent abortions and infertility treatments in this group and diabetes (either pre-gestational or gestational) was more prevalent. There was no significant difference in hypertension (chronic, gestational or pre-eclampsia) between the groups. Pregnancies with iSUA had significantly more complications, including placenta previa, polyhydramnios and oligohydramnios. Table 2 compares various complications at birth in both groups. Women with iSUA underwent induction of labor more often compared with women without iSUA and tended to deliver at an earlier gestational age. During labor, women with iSUA presented more often with pathological presentations, and exhibited higher rates of non-reassuring fetal heart rate tracing, placental abruption and cord prolapse, as well as higher rates of cesarean deliveries. Table 3 highlights the perinatal outcomes of neonates with iSUA compared with neonates with normal umbilical cord. Poorer perinatal outcomes were noted with iSUA neonates, including lower Apgar scores at 1 and 5 min, lower birth weights and higher mortality rates, both ante-partum (intrauterine fetal death—IUFD) and post-partum (post-partum death—PPD). In the multivariable regression model presented in Table 4 the following variables and potential confounders were included: diabetes mellitus (gestational and pre-

Table 1 Maternal characteristics and pregnancy complications

	Isolated SUA	Normal UC	OR	95 % CI	*P* value
Maternal age (years)	28.6 ± 5.6	28.1 ± 5.7			0.017
Gestational age (weeks)	39.1 ± 1.3	39.4 ± 1.2			<0.001
Smoking (%)	2.7	1.0	2.7	1.7–4.2	<0.001
ART (%)	3.2	1.6	1.9	1.3–2.9	0.001
Habitual Abortions (%)	6.6	4.9	1.3	1.0–1.8	0.025
Diabetes Mellitus[a] (%)	9.4	4.9	2.0	1.5–2.5	<0.001
Hypertension[b] (%)	5.0	4.4	1.1	0.8–1.5	0.460
Placenta previa (%)	0.6	0.2	2.9	1.2–7.2	0.011
Vasa previa (%)	0.9	0.1	15.8	7.3–33	<0.001
Polyhydramnios (%)	7.5	3.3	2.3	1.8–3.1	<0.001
Oligohydramnios (%)	3.6	2.0	1.8	1.2–2.6	0.002

ART Assisted reproductive techniques

[a] Gestational and pre-gestational diabetes mellitus

[b] Chronic, gestational or pre-eclampsia

Table 2 Delivery complications

	Isolated SUA (%)	Normal UC (%)	OR	95 % CI	*P* value
Pathological presentation	6.0	4.4	1.3	1.0–1.8	0.028
True knot	3.6	1.0	3.5	2.4–5.2	<0.001
PROM	8.1	8.1	1.0	0.7–1.3	0.947
NRFHR	3.1	1.2	2.5	1.6–3.8	<0.001
Placental abruption	1.0	0.3	3.4	1.7–6.9	<0.001
Cord prolapse	0.9	0.3	2.8	1.3–5.9	0.004
Induction of labor	36.1	26.1	1.5	1.3–1.8	<0.001
Cesarean section	21.4	12.3	1.9	1.6–2.3	<0.001

PROM Premature rupture of membranes, *NRFHR* Non-reassuring fetal heart rate tracing

Table 3 Perinatal outcome

	Isolated SUA	Normal UC	OR	95 % CI	*P* value
Birth weight (grams)	3131.4 ± 467	3273 ± 438			<0.001
Perinatal mortality[a] (%)	2.5	0.4	7.3	4.6–11.5	<0.001
IUFD	1.7	0.2	8.1	4.7–14.2	<0.001
				0.7–39.6	
IPD	0.1	0	5.4		0.058
PPD[b]	0.8	0.1	6.1	2.7–13.7	<0.001
1 min Apgar score <7 (%)	8.3	4.7	1.8	1.4–2.3	<0.001
5 min Apgar score <7 (%)	3.7	2.0	1.9	1.3–2.7	0.001
Low birth weight (LBW) (%)	7.9	2.7	3.0	2.3–4.0	<0.001
Very LBW (%)	0.3	0	16.4	3.9–68.4	<0.001
SGA[c] (%)	7.4	4.0	1.8	1.4–2.4	<0.001

IUFD Intra-uterine fetal death, *IPD* Intra-partum death, *PPD* Post-partum death, *SGA* Small for gestational age

[a] Including: intra-uterine fetal death, intra-partum death, and post-partum death in the first week of life

[b] Defined as death in the first week of life

[c] Defined as birthweight smaller than the fifth percentile for gestational age

gestational), polyhydramnios, oligohydramnios, placental abruption, placenta previa, cord prolapse, true knot of cord, non-reassuring fetal heart rate, vasa previa and induction of labor. This model was adjusted for maternal age, birth weight and fertility treatments. Using this model we found diabetes mellitus, polyhydramnios, placental abruption,

Table 4 Multiple logistic regression with backward stepwise for association with SUA

Variable	OR	95 % CI	*P* value
Diabetes mellitus	1.74	1.35–2.24	<0.01
Polyhydramnios	2.32	1.76–3.05	<0.01
Oligohydramnios	1.42	0.97–2.08	0.07
Placental abruption	2.34	1.15–4.76	0.02
Placenta previa	2.40	0.98–5.86	0.05
Cord prolapse	2.19	1.03–4.67	0.04
True knot of cord	3.27	2.23–4.79	<0.01
NRFHR	1.96	1.29–2.96	<0.01
Vasa previa	11.06	5.09–24.05	<0.01
Induction of labor	1.55	1.33–1.80	<0.01

This model was adjusted for maternal age, birth weight and fertility treatment

NRFHR Non-reassuring fetal heart rate tracing

Table 5 Multiple logistic regression with backward stepwise for prediction of Perinatal Mortality

Variable	OR	95 % CI	*P* value
iSUA	5.13	3.18–8.26	<0.01
Polyhydramnios	3.14	2.49–3.94	<0.01
Oligohydramnios	4.02	3.07–5.26	<0.01
Placental abruption	32.56	25.22–42.04	<0.01
Cord prolapse	6.43	4.11–10.06	<0.01
True knot of cord	3.46	2.41–4.98	<0.01
NRFHR	2.67	1.95–3.65	<0.01
Vasa previa	6.33	2.48–16.12	<0.01

This model was adjusted for Placenta previa

NRFHR Non-reassuring fetal heart rate tracing

cord prolapse, true knot of cord, non-reassuring fetal heart rate, vasa previa and induction of labor to be independently associated with the presence of iSUA. In the multivariable regression model presented in Table 5 we included the following risk factors: iSUA, polyhydramnios, oligohydramnios, placental abruption, cord prolapse, true knot of cord, non-reassuring fetal heart rate and vasa previa. This latter model was adjusted for placenta previa. Among the other risk factors evaluated, iSUA was found to be an independent risk factor for perinatal mortality.

Discussion

After reviewing the literature, our cohort seems to be the largest published cohort focusing on perinatal outcomes of iSUA. We included 786 cases of iSUA, all of which reached 37 completed weeks of gestation. We have shown that iSUA at term carry a significant risk for adverse perinatal outcome and increased perinatal mortality.

Overall, published data on iSUA demonstrated inconsistent and inconclusive results. While some studies found increased rates of preterm deliveries in iSUA [1, 2, 9, 16], others failed to demonstrate such outcome [10, 13]. Much of the research conducted on iSUA focused on fetal growth. Many studies [1, 2, 8, 9, 14–19] have shown that iSUA is associated with fetal growth restriction and SGA infants although other studies [11, 20–22] and a recent meta-analysis on this topic refuted this claim [12].

With regards to perinatal mortality, data is again inconclusive. The same meta-analysis mentioned above [12] concluded that there was a trend towards higher rates of perinatal mortality in iSUA pregnancies but this did not reach statistical significance.

These contradictory results may be explained by the fact that studies in which increased perinatal mortality [2, 9, 15] was demonstrated included in their analysis fetuses with growth restriction or premature deliveries (before 37 weeks), while studies which found no increased risk of perinatal mortality [1, 10, 14] had smaller sample sizes or were conducted only for live-born infants [23].

However, and unlike the results of this recent meta-analysis, our multivariable regression model suggests that even in the absence of any other demonstrable abnormality of the fetus or complication of pregnancy, presence of iSUA is an important and independent risk factor for immediate adverse perinatal outcomes.

We believe that the most important finding of our study is the higher rate of perinatal mortality demonstrated even after exclusion of other well-established risk factors (multiple gestations, structural and chromosomal abnormalities, prematurity and growth restricted fetuses) and controlling for possible confounders (placental abruption, birth weight, gestational age, etc.) in the iSUA group.

It is still unclear why iSUA may lead to perinatal adverse outcomes. One possible explanation of the increased rates of perinatal mortality in an otherwise healthy term fetus relates to some structural deviations noted by others, which may hypothetically elevate the risk of cord accident. Lacro et al. found an increased incidence of absent umbilical cord twist in SUA cords, as well as a reduction of Wharton's jelly surrounding the cord found by Raio et al., both of which were associated with an increased incidence of stillbirth [24, 25].

Currently, iSUA is not considered an indication for labor induction according to commonly used formal guidelines. However, since our study suggests that term, adequately grown, healthy iSUA fetuses, may be at a significantly higher risk for adverse outcomes including perinatal

mortality, we suggest consideration of labor induction at 40 weeks of gestation for iSUA fetuses.

Compliance with ethical standards

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Conflict of interest All Authors (Gutvirtz G, Walfisch A, Beharier O, Sheiner E) declare no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors. The institutional review board approved the study that has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (# SOR-0236-13 approved on November 20, 2013).

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