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Single Umbilical Artery: Does Side Matter?

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Abstract

Objective: We sought to determine if laterality of the absent umbilical artery (LAUA) is associated with specific ultrasonographic findings, Doppler abnormalities, chromosomal defects, or postpartum birth defects.

Study Design: In this retrospective cohort study, ultrasound reports and corresponding medical records of patients who received at least one obstetric ultrasound at the University of Iowa Hospitals and Clinics with an identified LAUA from 1989 to 2007 (n=405) were reviewed. Patients were classified by either a left or right absent umbilical artery as observed on ultrasound. Multivariate logistic regression was performed to refine the associations between LAUA and other clinical findings while adjusting for confounding.

Results: In a multivariate analysis, a sonographically right absent umbilical artery and sonographically identified fetal gastrointestinal abnormalities are significantly associated ($p<0.001$). No other ultrasonographic findings, Doppler abnormalities, chromosomal defects, or documented postpartum birth defects were significantly associated to a specific LAUA.

Conclusion: Contrary to previous literature, our study identified a significant association between a right absent umbilical artery and fetal GI abnormalities.

Keywords

congenital malformations; Doppler; side of absent umbilical artery; single umbilical artery

Introduction

A fetal single umbilical artery (SUA) is a common congenital malformation with an overall incidence reported between 0.2–2.0%^{1–4}. This ultrasonographic finding is associated with autopsy confirmed congenital malformations spanning all organ systems⁵ as well as chromosomal abnormalities^{6, 7}. The rate of SUA associated with other congenital abnormalities has been reported between 18–68%^{8, 9}. In addition, the risk of chromosomal defects has been shown to be higher in fetuses with a SUA with other congenital

malformations in comparison to those fetuses with an isolated SUA^{10, 11}. The presence of a SUA is also associated with increased perinatal mortality³, growth restriction³ and preterm labor¹.

While many studies have addressed the conditions and abnormalities most associated with a SUA, few have addressed the connection between these abnormalities and laterality of the absent umbilical artery (LAUA). Studies suggest that a determination of the LAUA can be predictive of fetal malformations. This claim has yet to be well substantiated. To date, there are only five studies that directly attempt to answer the question if LAUA has any clinical significance. Abuhamad and colleagues evaluated 77 fetuses with SUA. In the 11 cases with one anomaly and a SUA, 7 cases presented with a left absent umbilical artery. In the 9 complex cases with multiple malformations and SUA, all the cases had a left absent artery¹². This clinical importance of LAUA has been refuted in other small studies^{13–16}.

The objective of this retrospective cohort study is to compare the rates of abnormal ultrasound findings, chromosomal abnormalities, and Doppler abnormalities in fetuses with a left or right absent umbilical artery (AUA). Also, we aim to determine if there are any ultrasound findings associated with either a left or right AUA. Information from this study may help clinicians properly counsel their patients on the clinical significance of a SUA and the clinical value of the LAUA.

Materials and Methods

This retrospective cohort study was conducted at the University of Iowa Hospitals and Clinics (UIHC) to estimate the relationship between LAUA and other clinical findings. UIHC institutional review board approval was obtained prior to the study. Ultrasound reports identified from the UIHC Fetal Diagnosis and Therapy Unit Ultrasound Database were screened for the ultrasound diagnosis of single umbilical artery (SUA) for patients seen in the clinic from January 1989 to May 2007. An evaluation for a single umbilical artery was performed during each routine anatomy scan. Our cohort was composed of all the patients who had a clear designation of a left or right missing umbilical artery. Screening for a clear designation of left or right missing umbilical artery in all of the database identified SUA charts was performed by 3 of the authors (M.S., D.F., and D.S.). The ultrasound reports and the corresponding medical records of this cohort of patients were utilized to extract pertinent data including demographics, medical and obstetrical history data. Fetal ultrasound biometry data for upper extremities⁴, lower extremities (LE), biparietal diameter (BPD), abdominal circumference (AC), and presence of IUGR (EFW < 10th percentile) were extracted as dichotomous variables (0 = no abnormality, 1 = abnormality). Individual biometry data was considered abnormal if it fell less than the 10th percentile with the exception of upper and lower extremities for which less than the 5th percentile was considered abnormal. Placental appearance and amniotic fluid index were extracted in a similar way. Oligohydramnios was defined as an amniotic fluid index measuring less than the 3rd percentile. Body area specific anatomic abnormalities were noted and extracted as dichotomous variables as above for the following anatomic groups: head, neck, face, spine, cardiac, gastrointestinal, genitourinary, upper extremity, lower extremity, and other thoracic anatomy defined as thoracic anatomy excluding the heart. A detailed review of these body area specific anatomic abnormalities is

illustrated in Table 1. Chromosomal diagnoses and Doppler findings were also extracted as dichotomous variables. Rates of prenatally diagnosed congenital defects, Doppler abnormalities, and chromosomal abnormalities were also calculated.

Laterality of the absent umbilical artery was determined by a color Doppler examination of the umbilical arteries around the fetal bladder in the transverse plane. Laterality was assigned based on the position of the absent umbilical artery and other sided organs such as the stomach or heart. Postnatal birth defects or abnormalities were confirmed on either the delivery note description of the fetus or fetal autopsy.

To control for bias, only 3 members of the research team (MS, DS, and DF) performed the data extraction. As described above, guidelines defining each variable were followed in order to correctly classify if a finding was an abnormality. Each member of the data extraction team performed a preliminary data extraction of at least 10 charts that was reviewed with the primary author. Once the other members of the data extraction team were noted to be congruent with the guidelines, further charts were evaluated.

Our primary outcome was to detect a difference in sonographically identified malformation rates between fetuses with a sonographically identified left or right absent umbilical artery. We also studied if LAUA predicts and is associated with other ultrasonographic abnormalities. In order to detect a 10% difference in overall malformation rates between fetuses with a left or right absent umbilical artery at 80% power and significance level 0.05, at least 406 cases would need to be evaluated.

Descriptive statistics described and compared the baseline maternal characteristics of our two study groups: right absent umbilical artery (Right AUA) and left absent umbilical artery (Left AUA). For continuous variables, Student's t test was used and a Fisher exact test was utilized for categorical variables. A univariate analysis was performed to estimate the unadjusted relative risk of the following data: biometric data, body site specific ultrasound abnormalities, chromosomal abnormality, umbilical artery Doppler abnormality, clinically documented postpartum abnormalities, and the number of concomitant ultrasound abnormalities.

To identify potentially confounding factors, stratified analyses were performed. In order to provide a better estimate of the relationship between laterality of the absent umbilical artery and other clinical factors and to control for confound, we used multivariate logistic regression modeling. Significant variables from the univariate analysis and variables with biologic significance as determined by the literature were also included in the logistic regression analysis. Backward stepwise regression was also employed to identify significant variables which may be predicted by the main predictor variable: LAUA. All variables that were statistically significant was included in the final models. Statistical significance was designated at $\alpha=0.05$. All statistical analyses were performed with SigmaStat 11 software (Systat Software, Inc, California) and confirmed using SAS 9.1 software (SAS Institute Inc, Cary, NC).

Results

Of the patients who received at least one obstetric ultrasound at UIHC during the sampling timeframe, 1055 patients were identified who either were referred for or carried a fetal ultrasound diagnosis of SUA. Of the 554 fetuses with a sonographically identified SUA, 164 (29.6 %) had a right absent umbilical artery, 241 (43.5%) had a left absent umbilical artery, and 149 (26.9%) fetuses had a single umbilical artery but laterality was not indicated on the ultrasound report. A total of 405 (73.1%) fetuses had either a left or right absent umbilical artery for comparison. As seen in Table 2, mean age, gravidy, and gestational age at time of ultrasound were similar in the right and left AUA groups. In addition, the racial distributions were also similar with a majority of the patients self identified as White/Caucasian.

As seen in Table 3, all majority of abnormality variables confirmed higher unadjusted relative risks of abnormality in fetuses with a right AUA in comparison to left AUA except for the following: Other Thoracic and Genitourinary abnormalities. Of note, the rates chromosomal abnormality, umbilical artery Doppler abnormality, and clinically detected postpartum defects are similar between fetuses with an ultrasonographically identified right or left AUA.

The goal of this study was to determine if laterality of the absent umbilical artery is associated with other ultrasound findings and clinical variables. To screen for potentially significant variables, multivariate regression modeling was utilized while controlling for the presence of a documented chromosomal abnormality. In this analysis, gastrointestinal abnormalities (GI, $p=0.013$) and genitourinary abnormalities (GU, $p=0.033$) were initially statistically significant. To examine if either variable confounds the other, only GI and GU were included in the analysis, GI is the only variable that remains statistically significant ($p=0.001$). When controlling for chromosomal abnormalities, GI remains the only variable significantly associated to LAUA ($p<0.001$).

After controlling for multiple ultrasonographic abnormalities and chromosomal abnormalities, laterality of the AUA is strongly associated with GI abnormalities. More specifically, the probability of having a GI abnormality with a right AUA is 13.6%. The probability of having a GI abnormality with a left AUA is 4.1%. Therefore, there is a significant three-fold increase in the probability of observing an ultrasonographic GI abnormality with a concomitant right AUA ($p<0.001$).

As seen in Table 4, the probability of a GI abnormality is increased in the presence of a right sided AUA with or without a concomitant GU abnormality. Given a right AUA and a concomitant GU abnormality, the probability of a GI abnormality is 39.8%. However in the case of a right AUA without a concomitant GU abnormality, the probability of a GI abnormality is 9.4%. This increase in probability, by a factor of 4.2, is statistically significant ($p<0.001$). In the absence of a GU abnormality, the probability of observing a GI abnormality with a concomitant left AUA is 2.6%. In the face of a concomitant GU abnormality and left AUA, the probability of having a GI abnormality is 14.7%. Even in the absence of a GU abnormality, there is a statistically significant ($p=0.001$) 3.6-fold increase in the risk of having an ultrasonographic GI abnormality if there is a detected right AUA.

The GI variable was further subdivided into specific GI abnormality groups including omphalocele, gastroschisis, echogenic bowel, and other GI abnormality. The other GI abnormality subgroup included stomach abnormalities and dilated or atretic appearing bowel. None of these subgroups were significantly associated to laterality of the AUA (See Table 5).

Comment

Our data demonstrate that a sonographically identified right AUA is significantly associated with higher rates of ultrasound abnormalities in comparison to a left AUA. When controlling for chromosomal abnormality and other multiple sonographic anomalies, GI abnormalities, as a group, were significantly associated with a right AUA. Although not significant in the multivariate analysis, a concomitant sonographically identified GU abnormality does increase the probability of a GI abnormality irrespective of the LAUA. In addition, our study is the first study (MEDLINE search terms: single umbilical artery and side, single umbilical artery and laterality, single umbilical artery; year: 1950 to present) to compare potential Doppler differences in the present umbilical artery. There were no significant differences in Doppler abnormalities and chromosomal abnormalities when comparing right versus left AUA.

In concordance with the current literature, we observe that there are significantly more left AUA than right AUA. In contrast to a majority of the literature, we demonstrate that laterality of the absent umbilical artery does have a significant association with ultrasonographic abnormalities. The left AUA group has a significantly higher proportion of isolated AUA cases. Whereas the right AUA group has a significantly higher proportion of cases with 2 abnormalities in addition the AUA. These findings differ from the report from Abuhamad *et al.* which purport that more abnormalities are associated with a left AUA (12).

These data may provide the clinician some guidance on the management of a single umbilical artery. Although there is a statistically significant higher proportion of isolated single umbilical arteries on the left side, the difference in proportions would likely not preclude the further ultrasonographic evaluation of the rest of the body systems (33.5% vs. 43.6%, $p=0.049$). Yet, the identification of a right absent umbilical artery may prompt a higher scrutiny of the ultrasound images because it is associated with an approximately 20% higher risk of finding 2 anomalies (50.6% vs. 33.2%, $p=0.00064$). In cases when the GI tract has some questionable findings, the presence of a right single umbilical artery can prompt the clinician to further scrutinize these GI findings in a future ultrasound. Given the high rate of associated malformations with an absent umbilical artery of any laterality, any single umbilical artery found on a general screening ultrasound should be considered for referral for a detailed ultrasound.

Embryologically, this association between a single umbilical artery and GI abnormality is plausible. Abuhamad *et al.* cites three potential mechanisms of the formation of a single umbilical artery: 1. primary agenesis of one of the umbilical arteries 2. secondary atrophy of one of the umbilical arteries and 3. persistence of a single allantoic artery¹². Malignant signaling mechanisms involved in the return of the physiologic umbilical hernia into the

body cavity may potentially affect the development of the umbilical arteries. The increase in the probability of a GI abnormality in the face of a concomitant GU abnormality may provide further evidence that these 2 body systems are involved in the pathogenesis of a single umbilical artery. Currently, there are little data to prove a definitive etiology of a single umbilical artery.

One of the strengths of the study is that it is the largest study evaluating the clinical implications of the LAUA. In our series, we evaluated 405 cases of single umbilical artery with a known LAUA. The current literature *in toto* accounts for 337 cases (See Table 6). Our study was powered to detect a 10% difference in overall fetal abnormalities. Our population was one participant less than the required sample size based on our power calculations. In addition, each variable was not individually powered to determine if the sample size was appropriate. Despite a higher number of left AUA, we are confident that the data report true differences as maternal age, mean gestational age at time of ultrasound, demographic data, and rates of chromosomal abnormalities are the same for both the left and right AUA groups. Our multivariate analysis demonstrates a strength of this study. This analysis, not utilized in the previous literature, allowed us to control for many abnormalities and chromosomal anomalies which could further confound the results.

Bias secondary to the retrospective nature of the study is one potential weaknesses of the study. The ultrasound reports reflecting the laterality of the AUA may represent a source of reader bias as there were multiple physicians and sonographers at different levels of training assigning laterality. All of the extracted data were evaluated by a single author² and data extraction was performed by three different authors (MS, DS, DF). This may be another source of reader bias despite the evaluation period of data extraction interpretation. While regressing against multiple different ultrasound and clinical variables may have controlled for the major sources of confounding bias, it is possible that there are other conditions that were not identified in our data extraction that could confound the conclusions. Although there is this potential for confounding, we are confident that most of this effect is mitigated by our multivariate analysis. Finally, the patient population at the University of Iowa is fairly homogenous. Although our conclusions are internally valid, our study may not represent a more diverse population. A study of such a population could help validate our conclusions.

We conclude that an absent right umbilical artery is associated with increased ultrasonographic abnormalities. These data demonstrate an association between an absent right umbilical artery and GI abnormalities as a group. Our data may assign more importance to the identification to the laterality of the AUA. LAUA can be identified early in gestation via ultrasound and color Doppler techniques. An absent right umbilical artery may prove to be a marker for future GI abnormalities. These data may suggest that the early identification of LAUA on a screening ultrasound may necessitate a more detailed ultrasound to look for GI abnormalities. This early marker could potentially increase detection of these abnormalities. This association may also provide a basis in embryological research leading to newer hypotheses regarding the pathogenesis of a single umbilical artery. To verify our findings, a similar retrospective study should be performed in a larger database with a more diverse population. Prospective studies would need to be conducted to determine if early identification of the laterality of the absent umbilical artery is predictive

of other congenital malformations. Overall, these data emphasize the importance of a detailed ultrasound when an absent umbilical artery of any laterality is identified.

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Table 1:**Body Area Specific Abnormality Variables**

Body Area	Specific Abnormality
Head	Choroid Plexus Cysts
	Ventriculomegaly
	Neural Tube Defect Related Findings: Lemon sign, Banana Sign with a correlated open neural tube defect
	Holoprocencephaly
	Cerebellar abnormality: agenesis of splaying of the cerebellar vermis
Neck	Enlarged nuchal translucency including enlarged measurement to the cystic hygroma
	Enlarged thyroid
Face	Cleft lip
	Cleft palate
	Cyclops, proboscis
Spine	Open neural tube defect
	Scoliosis / Kyphosis
Cardiac	Echogenic focus
	Isolated ASD or VSD
	AV Canal Defect
	Hypoplastic left ventricle
	Isolated coarctation of the aorta
	Transposition of the great vessels
	Other multilesion cardiac abnormality
Other Thoracic	Diaphragmatic hernia
	Pleural effusion
	Congenital cystic adenomatoid malformation
	Pulmonary sequestration
GI	Omphalocele
	Gastroschisis
	Duodenal atresia
	Dilated bowel
	Echogenic Bowel
GU	Pyelectasis
	Hydronephrosis
	Cystic dysplastic kidney
	Pelvic kidney
	Renal agenesis
	Ambiguous genitalia
Upper extremity	Postured Hands
	Phocomelia
	Polydactyly

Body Area	Specific Abnormality
Lower Extremity	Isolated clubfoot
	Clubfoot with other abnormalities
	Rocker bottom feet
	Polydactyly

Table 2:

Maternal Characteristics of Patients with a Right Absent Umbilical Artery in Pregnancy Compared with Patients with a Left Absent Umbilical Artery.

	Right AUA N=164	Left AUA N=241	P Value
Mean Maternal Age	27.8	29	0.074
Mean GA at Scan	27.0	26.4	0.257
Race: White	158 (96.3%)	229 (95.0%)	0.628
Race: Black	1 (0.610%)	8 (3.32%)	0.090
Race: Hispanic	2 (1.22%)	3 (1.24%)	1.00
Race: Asian	3 (1.87%)	1 (0.440%)	0.308
Mean Gravidy	2.58	2.67	0.294
Mean Parity	1.60	1.65	0.755

Data are mean or %.

Table 3:

Univariate Analysis: Unadjusted Relative Risks for Abnormalities in Pregnancies with a Right Absent Umbilical Artery Compared with those with a Left Absent Umbilical Artery.

Abnormality	Cohort (n=405)	Right AUA (n=164)	Left AUA (n=241)	Unadjusted RR (95% CI)	P Value
IUGR	67(15.5%)	45(27.4%)	22(9.13%)	3.006(1.879–4.808)	< 0.001
Head	62(15.3%)	35(21.3%)	27(11.2%)	1.905(1.201–3.021)	0.008
Neck	24(5.9%)	16(9.76%)	8(3.32%)	2.939(1.288–6.708)	0.013
Face	31(7.7%)	27(16.5%)	4(1.66%)	9.919(3.537–27.816)	< 0.001
Spine	25(6.2%)	20(12.2%)	5(2.07%)	5.878(2.251–15.347)	< 0.001
Cardiac	53(13.1%)	30(18.3%)	23(9.54%)	1.917(1.156–3.178)	0.016
Other Thoracic	17(4.2%)	11(6.71%)	6(2.49%)	2.694(1.016–7.141)	0.068
Gastrointestinal	34(8.4%)	24(14.6%)	10(4.15%)	3.527(1.733–7.177)	< 0.001
Genitourinary	45(11.1%)	22(13.4%)	23(9.54%)	1.406(0.811–2.436)	0.291
Upper Extremity	27(6.7%)	23(14.0%)	4(1.66%)	8.450(2.977–23.980)	< 0.001
Lower Extremity	38(9.4%)	30(18.3%)	8(3.32%)	5.412(2.545–11.508)	< 0.001
Abnormal Chromosomes	22(16.2%)	10(17.0%)	12(15.6%)	1.088(0.505–2.343)	0.983
Abnl Umbilical Artery Doppler	16(7.0%)	4(2.44%)	12(4.98%)	0.446(0.148–1.340)	0.219
Abnl PP Defects	42(21.9%)	23(28.0%)	19(17.2%)	1.624(0.950–2.776)	0.107
2 abnormalities	163(40.2%)	83(50.6%)	80(33.2%)	1.525(1.206–1.927)	< 0.001
Isolated SUA	232(57.3%)	80 (48.9%)	152 (63.1%)	0.773(0.643–0.930)	0.006

Table 4:

Probability of a GI abnormality

	Right AUA	Left AUA
GU Abnormality Positive	39.8%	14.7%
GU Abnormality Negative	9.4%	2.6%

Table 5:

Bivariate Logistic Regression: Predicting Specific GI Abnormalities with Laterality of the Absent Umbilical Artery

GI Variable	P Value
Omphalocele	0.648
Gastroschisis	0.996
Echogenic Bowel	0.903
Other GI Abnormality	0.216

Table 6:

Laterality of the absent umbilical artery: Review of the Literature. Adapted from Geipel, et al (16)

Authors	All cases	Isolated SUA	SUA with malformation	SUA with aneuploidy
Abuhamad <i>et al</i>	77	57 (54%)	14 (18.2%)	6 (7.8%)
Absent RUA	21 (27%)	17	4	--
Absent LUA	56 (73%)	40	10	6
Blazer <i>et al</i>	46	40 (87%)	6 (13%)	--
Absent RUA	21 (45.7%)	17	4	--
Absent LUA	25 (54.3%)	23	2	--
Fukada <i>et al</i>	10	4 (40%)	5 (50%)	1 (10%)
Absent RUA	6 (60%)	3	2	1
Absent LUA	4 (40%)	1	3	--
Geipel <i>et al</i>	102	59 (57.8%)	33 (32.4%)	10 (9.8%)
Absent RUA	31 (30.4%)	18	12	1
Absent LUA	71 (69.6%)	41	21	9
Lubusky <i>et al</i>	102	77 (75.5%)	25 (24.5%)	19 (18.6%)
Absent RUA	41 (41.2%)	31	11	8
Absent LUA	60 (58.8%)	46	14	11
Total	337	237 (70.3%)	83 (24.6%)	36 (5.1%)
Absent RUA	120 (35.6%)	86	33	10
Absent LUA	217 (64.4%)	151	50	26