

Retrospective Study

Ultrasound blood flow characteristics changes in fetal umbilical artery thrombosis: A retrospective analysis

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Grade E (Poor): 0**P-Reviewer:** Alsaidan A, Saudi Arabia**Received:** August 30, 2023**Peer-review started:** August 30, 2023**First decision:** December 7, 2023**Revised:** December 18, 2023**Accepted:** December 26, 2023**Article in press:** December 26, 2023**Published online:** January 16, 2024**Si-Jie Hong, Xiao-Qin He, Xiao-Hong Zhong**, Department of Ultrasound, Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen 361000, Fujian Province, China**Li-Wei Hong**, Ministry of Science and Education, Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen 361000, Fujian Province, China**Corresponding author:** Xiao-Hong Zhong, MS, Chief Physician, Department of Ultrasound, Women and Children's Hospital, School of Medicine, Xiamen University, No. 10 Zhenhai Road, Xiamen 361000, Fujian Province, China. 232738827@qq.com**Abstract****BACKGROUND**

Umbilical artery thrombosis (UAT) is extremely uncommon and leads to adverse perinatal outcomes. Hypercoagulation of blood in pregnant women is suspected to be an important risk for UAT. Ultrasound is an effective way to detect thrombosis. The mother can monitor her own fetal health using ultrasound, which enables her to take preventative action in case of emergency.

AIM

To investigate ultrasonic blood signal after UAT in the umbilical artery, and evaluate the relationship between hypercoagulability and UAT.

METHODS

We described a case of a newly formed UAT with markedly altered ultrasonic indices of umbilical artery blood flow, and retrospectively studied it with 18 UAT patients confirmed by histopathology from October 2019 and March 2023 in Xiamen Women and Children's Hospital. Patients' information was collected from medical archives, including maternal clinical data, neonatal outcomes, pathological findings and ultrasonic indices of umbilical artery blood flow, such as systolic-diastolic duration ratio (S/D), resistance index (RI), pulsatility index (PI) and peak systolic velocity (PSV). Ultrasound and coagulation indices were analyzed with matched samples *t*-test and Wilcoxon rank sum test using the statistical packages in R (version 4.2.1) including car (version 3.1-0) and stats (version 4.2.1), and visualized by ggplot2 package (version 3.3.6).

RESULTS

A patient with normal findings in second and third-trimester routine ultrasound scan developed UAT with severe changes in ultrasonic indices of umbilical artery

blood flow (within 2.5th of reference ranges) in a short period of time. Statistical analysis of umbilical artery blood flow ultrasound indices for 19 patients with UAT showed that the decrease in S/D, RI, and PI and increase of PSV during the disease process was greater than that of non-UAT. All 18 patients delivered in our hospital showed characteristic manifestations of UAT on histological examination after delivery, most of which (16/18) showed umbilical cord abnormalities, with 15 umbilical cord torsion and 1 pseudoknot. Coagulation parameters were not significantly changed in UAT patients compared with normal pregnancy women.

CONCLUSION

Significant changes in ultrasound indicators after UAT were demonstrated. PSV can play important roles in the diagnosis of UAT. Hypercoagulability alone is not sufficient for the occurrence of UAT.

Key Words: Umbilical artery thrombosis; Obstetric ultrasonography; Peak systolic velocity; Hypercoagulation; Umbilical cord abnormalities; Fetus

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Core Tip: A case of umbilical artery thrombosis (UAT) occurring within a short period of time was reported, resulting in significant changes in the ultrasound flow indices of the umbilical artery. Then, a retrospective study of 19 patients revealed a high prevalence of umbilical cord abnormalities among those with UAT, while the coagulation status did not significantly differ from that of normal pregnant women. Notably, the proportion of decrease in systolic-diastolic duration ratio, resistance index and pulsatility index, and increase in peak systolic velocity were considerably higher in UAT cases compared to normal pregnant women, which might help to detect UAT in advance using ultrasound.

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INTRODUCTION

Umbilical artery thrombosis (UAT) is a rare pregnancy and delivery problem, but it can threaten the life of a fetus. UAT is a risk factor for intrauterine asphyxia and fetal growth restriction during pregnancy or even stillbirth[1]. Early detection of UAT allows for rapid treatment to guarantee the optimum fetal development. The pathogenesis of UAT has not yet been fully understood.

Previous studies have shown that blood hypercoagulation, abnormalities of the umbilical cord may lead to stagnant blood flow and the formation of blood clots[2-4]. The blood of pregnant women was reported to be hypercoagulable and that the risk of thrombosis during pregnancy increases over 4-fold compared to non-pregnant cohorts, suggesting that hypercoagulable mechanical injury may be an important trigger for UAT[5,6].

Ultrasound is one of the best techniques to evaluate the fetus vascular function in both laboratory investigations and clinical contexts due to its relative low cost, simplicity, non-invasiveness, and the capacity to spot minor abnormalities[7]. By detecting various frequencies of sound waves reflected off red blood cells, Doppler ultrasound is used to image blood flow[8]. Although some studies have shown the clinical value of cord blood flow changes in the assessment of fetal anomalies or distress, the association of ultrasound flow indices of the umbilical cord vessels with cord thrombosis has rarely been reported.

MATERIALS AND METHODS

Diagnose data of 19 UAT cases were obtained for this study from the accumulative database of 51969 patients who gave birth in Xiamen Women and Children's Hospital from October 2019 and March 2023. Patients were screened by serial routine ultrasound scans during the second and third trimesters, and the diagnosis was further confirmed by postnatally pathological examination except the first case who insisted on being discharged from hospital. Initial clinical information of patients in UAT and non-UAT groups was collected for baseline analysis, including age, body mass index at booking and ethnicity. Transabdominally ultrasonic examination was performed using 4-6 MHz transducers (Philips iU22 or GE Voluson E8). The diagnosis of UAT was confirmed by two experienced sinologists independently. Doppler measurements were obtained from both umbilical arteries following the International Society of Ultrasound in Obstetrics and Gynecology guidelines. Longitudinal and transverse scans of the umbilical cord are performed after locating the umbilical cord, and the number of blood flows in the umbilical arteries on both sides is examined at the bladder transverse section. When measuring the umbilical artery blood flow proximal to the fetal, sinologist should avoid measuring during fetal

respiratory-like movements and instruct the pregnant woman to temporarily hold her breath in order to facilitate obtaining a stable umbilical artery spectrum. Random umbilical artery is tested in normal pregnant women, while the remaining umbilical artery is tested in UAT patients. Ultrasound indices of umbilical artery blood flow were recorded. Reference ranges for umbilical artery Doppler indices was used for the evaluation of fetal hemodynamics in this research [9]. Observation of indicators such as fetal movement count, fetal heart monitoring, umbilical artery flow, amniotic fluid volume were taken after UAT was detected, and cesarean section was performed in the event of possible fetal distress. The study was reviewed and approved by the research ethics committee of Xiamen Women and Children's Hospital (Approval No. KY-2023-081-K01), and all work had been conducted in accordance with the World Medical Association Declaration of Helsinki.

Statistical analyses were performed using IBM SPSS version 24.0 software (IBM Corp., Armonk, NY, United States). We applied descriptive analyses to detect sample differences. To ensure that both samples actually differed in two groups compared, we calculated matched samples *t*-test or Mann-Whitney U test (Wilcoxon rank sum test).

RESULTS

One case with a newly formed umbilical artery thrombosis

A 33-year-old, gravida 2 para 0, pregnant woman had an unremarkable gestational course before 30 wk and 4 d. An ultrasound scan for fetal malformations at 24⁺¹ wk of the pregnancy showed normal findings. Two umbilical arteries were detected during an ultrasound examination (Figure 1A). The corresponding systolic-diastolic duration ratio (S/D), resistance index (RI), and pulsatility index (PI) locus in 50th to 75th percentile of reference ranges (Table 1). Peak systolic velocity (PSV) was also in normal range. Then at 30 wk and 4 d of gestation, a third-trimester routine ultrasound imaging also showed umbilical cord was still normal (Figure 1B), while S/D, RI and PI values were reduced into 10th-25th and 25th-50th percentile respectively (Table 1). Worse yet, just two days later, the pregnant woman returned to the hospital because of abdominal tightness. Only one side of the bladder is seen to be surrounded by umbilical artery blood flow, with no blood flow signal detected on the other side (Figure 1C). Ultrasound images of the fetus suggest a double umbilical artery, one of which is embolised. When UAT was diagnosed, the all S/D, RI and PI values of umbilical artery were less than the 2.5th percentile, and ultrasound examination also revealed a 1.53 times higher PSV than 2 d before, indicating a significant increase of blood flow rate after the occurrence of the UAT (Table 1). However, this patient insisted on not to keep the fetus and requested to be discharged and transferred to another hospital for treatment after informed consent.

Retrospective analysis of 19 patients with umbilical artery thrombosis

To further investigate the changes of ultrasonic blood signal after UAT, we retrospectively studied 19 patients with UAT from 51,969 pregnant women in last 3.5 years, and 19 patients without UAT were set as control group. Two groups of patients did not show statistically differences at the baseline (Supplementary Table 1). The incidence of cord artery thrombosis is about 1 in 2600 deliveries. In all cases, the routine second-trimester ultrasound scans exhibited normal findings with one umbilical vein and two umbilical arteries observed, and UAT occurred in gestational age of the third trimester. Maternal clinical data and neonatal information were listed in Table 2. 16 cases showed umbilical cord abnormalities, with 15 umbilical cord torsion and 1 pseudoknot, which represents a significantly higher proportion and severity of umbilical cord abnormalities compared to those in normal pregnancies (Supplementary Table 2). Finally, except for one patient who required automatic discharge, 18 patients were delivered by cesarean section, and all the maternal outcomes were good. Eight patients were full-term (8/18), 10 patients (10/18) were preterm. 9 fetal (9/18) were low birth weight, 2 fetal (2/18) was very low birth weight. All 18 patients showed characteristic manifestations of UAT on histological examination after delivery compared to normal umbilical artery (Figure 2).

Previous studies have reported that hypercoagulability is one of the main risks leading to thrombosis in pregnancy [10]. So we collected coagulation data from the patients with UAT (17/19, 2 patients with UAT did not undergo coagulation testing), and compared them with general population of women (*n* = 30) and pregnant women (*n* = 17), including international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT) and fibrinogen (Fbg). As previous studies reported, UAT and non-UAT pregnant women showed hypercoagulability, with higher Fbg and lower INR, PT, aPTT and TT. To our surprise, no significant differences were seen in the five coagulation parameters tested between UAT patients and non-UAT group (Figure 3).

Finally, the ultrasound indices of umbilical artery flow were analyzed (Supplementary Table 3). We found that the umbilical artery flow ultrasound indices S/D, RI and PI decreased significantly from second to third trimester, while PSV increased significantly in both normal pregnant women and UAT group (Figure 4A). However, the proportion of decrease in S/D, RI and PI and increase in PSV were greater in the UAT group than the control group (Figure 4B), suggesting an increase in blood flow in the UAT group.

DISCUSSION

Infants rarely suffer from UAT, which is a difficult-to-predict disorder [11]. Although previous research exhibits that certain factors like umbilical cord structural dysplasia, maternal coagulopathy, vascular endothelial damage, elevated blood glucose, and intrauterine transfusion increase the chances of UAT [12,13], it still happens without warning. Moreover, the possibilities of negative outcomes, like distress asphyxia, and even death, keep increasing as a result of this

Table 1 The umbilical artery blood flow ultrasonic indices of the described case

Diagnosis gestational weeks	S/D	RI	PI	PSV (cm/s)
24 ⁺¹	3.70 (50 th -75 th)	0.73 (50 th -75 th)	1.20 (50 th -75 th)	37.9
30 ⁺⁴	2.30 (10 th -25 th)	0.57 (10 th -25 th)	0.93 (25 th -50 th)	38.7
30 ⁺⁶	1.82 (2.5 th)	0.45 (2.5 th)	0.62 (2.5 th)	59.1

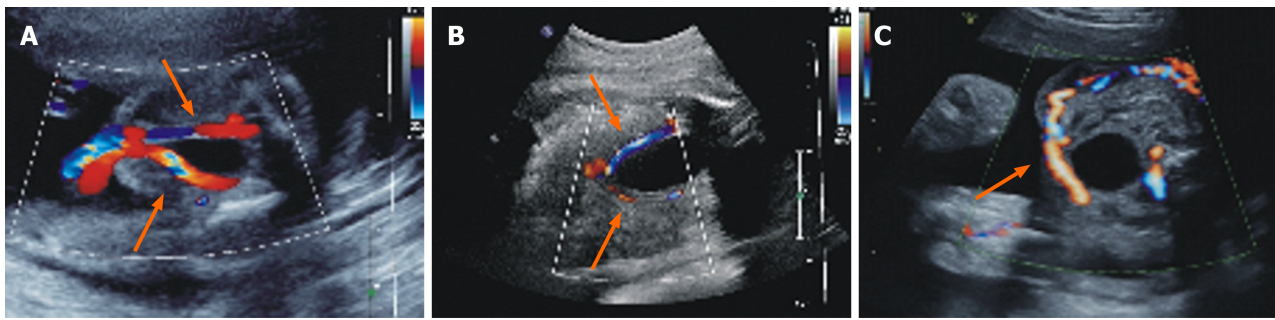
S/D: Systolic-diastolic duration ratio; RI: Resistance index; PI: Pulsatility index; PSV: Peak systolic velocity.

Table 2 Maternal clinical data and neonatal outcomes of patients with umbilical artery thrombosis

No.	Age (yr)	Gravidity (times)	Parity (times)	Diagnosis gestational weeks	Delivery gestational weeks	Apgar score	Umbilical cord abnormalities	Birth weight (g)
1	32	2	0	30 ⁺⁶	-	-	-	-
2	28	3	2	30 ⁺⁶	31 ⁺²	6-8-8	Torsion for 48 cycles	1380
3	28	1	1	36 ⁺³	37 ⁺¹	10-10-10	Torsion for 44 cycles	2330
4	27	1	1	33 ⁺⁶	33 ⁺⁶	9-9-9	Torsion for 30 cycles	2315
5	28	2	1	31 ⁺⁵	32	8-9-9	Torsion for 45 cycles	1300
6	35	2	2	34 ⁺⁴	34 ⁺⁴	9-9-9	Torsion for 45 cycles	2442
7	24	1	1	35 ⁺²	35 ⁺³	10-10-10	Torsion for 40 cycles	2220
8	25	1	1	32	36 ⁺³	10-10-10	Torsion for 38 cycles	2475
9	31	2	2	37 ⁺²	37 ⁺²	1-7-7	Torsion for 41 cycles	3480
10	31	1	1	29 ⁺³	32 ⁺³	8-9-9	Torsion for 38 cycles	1690
11	31	2	1	36 ⁺⁶	37 ⁺¹	9-10-10	Torsion for 35 cycles	2915
12	30	2	1	36	36	10-10-10	Torsion for 30 cycles	3023
13	27	1	1	39 ⁺¹	39 ⁺¹	9-9-10	Pseudoknot	3000
14	35	4	2	37 ⁺⁴	37 ⁺⁴	10-10-10	-	2477
15	35	3	2	39 ⁺⁵	39 ⁺⁵	10-10-10	-	3468
16	25	1	1	34 ⁺³	34 ⁺³	9-9-9	Torsion for 45 cycles	1830
17	35	3	2	31	31	9-9-9	Torsion for 41 cycles	1715
18	32	1	1	28 ⁺⁴	37	10-10-10	Torsion for 55 cycles	2590
19	36	3	2	37 ⁺²	37 ⁺³	8-10-10	Narrow, torsion for 30 cycles with tight spirals	3055

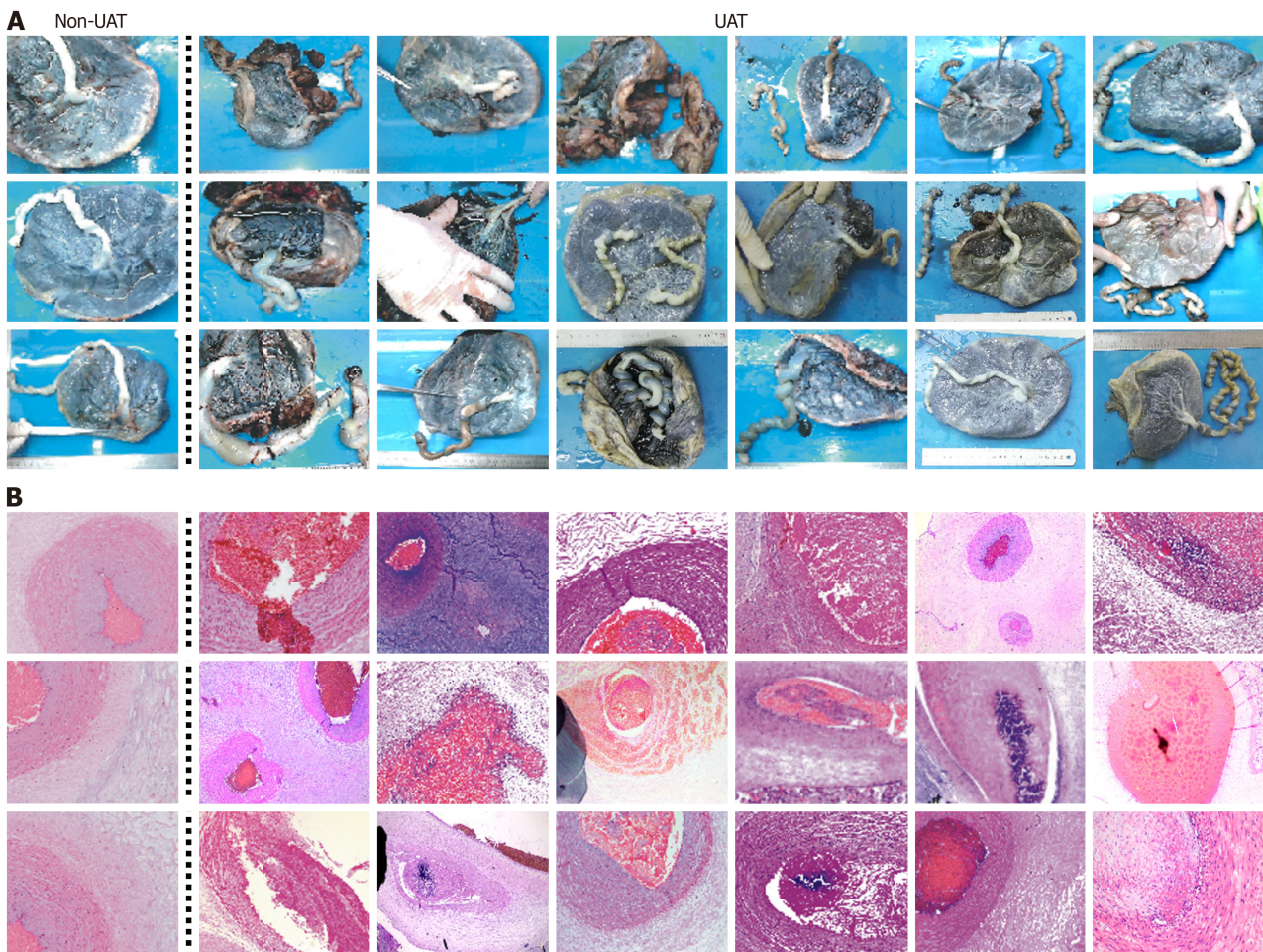
unpredictable nature. In view of the uncontrollable nature of UAT, it is challenging to understand the exact course in the process. Ultrasound is an important method of examining the blood flow and physiological changes in the umbilical cord. However, changes in ultrasound flow indicators after the onset of UAT were overlooked.

In the routine practice, we encountered a patient who seemed to be normal during second-trimester. The umbilical artery ultrasound flow indicators ranged from 50th to 75th. Later, at 30⁺⁴ wk of late pregnancy, the routine ultrasound images showed no significant abnormalities in the flow of either umbilical artery, but the ultrasound flow indicators changed (within the 10th-25th reference range). It probably meant that the UAT was progressing but not causing physiological changes. Nevertheless, just two days later, the woman was back with abdominal tightness, and ultrasound findings showed that only one of the two umbilical artery flows that should have been surrounding the bladder was left, indicating that the patient suffered from an UAT. Ultrasonic results revealed significantly abnormal S/D, RI and PI of the umbilical artery flow (lower than the 2.5th reference range) and a 1.53-fold increase in PSV of the remaining umbilical artery after UAT, indicating a significantly increased flow rate of the remaining umbilical artery. This might be due to the dilation of remaining artery in compensation to maintain the blood flow from the fetus to the placenta as previously reported[14]. This case suggests that umbilical artery flow ultrasound indices change gradually during the course of thrombosis, and alter dramatically when thrombosis eventually leads to physiological structural changes, which may be used as a predictor of the occurrence of UAT. This hypothesis needs to be validated by more cases that real-time ultrasound tracking was performed to observe the UAT forming.



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Figure 1 Ultrasonic imaging of the described case. A: Ultrasound image of the fetus at 24⁺¹ wk; B: Ultrasound image of the fetus at 30⁺⁴ wk; C: Ultrasound image of the fetus at 30⁺⁶ wk. The orange arrows indicate umbilical artery blood flow.

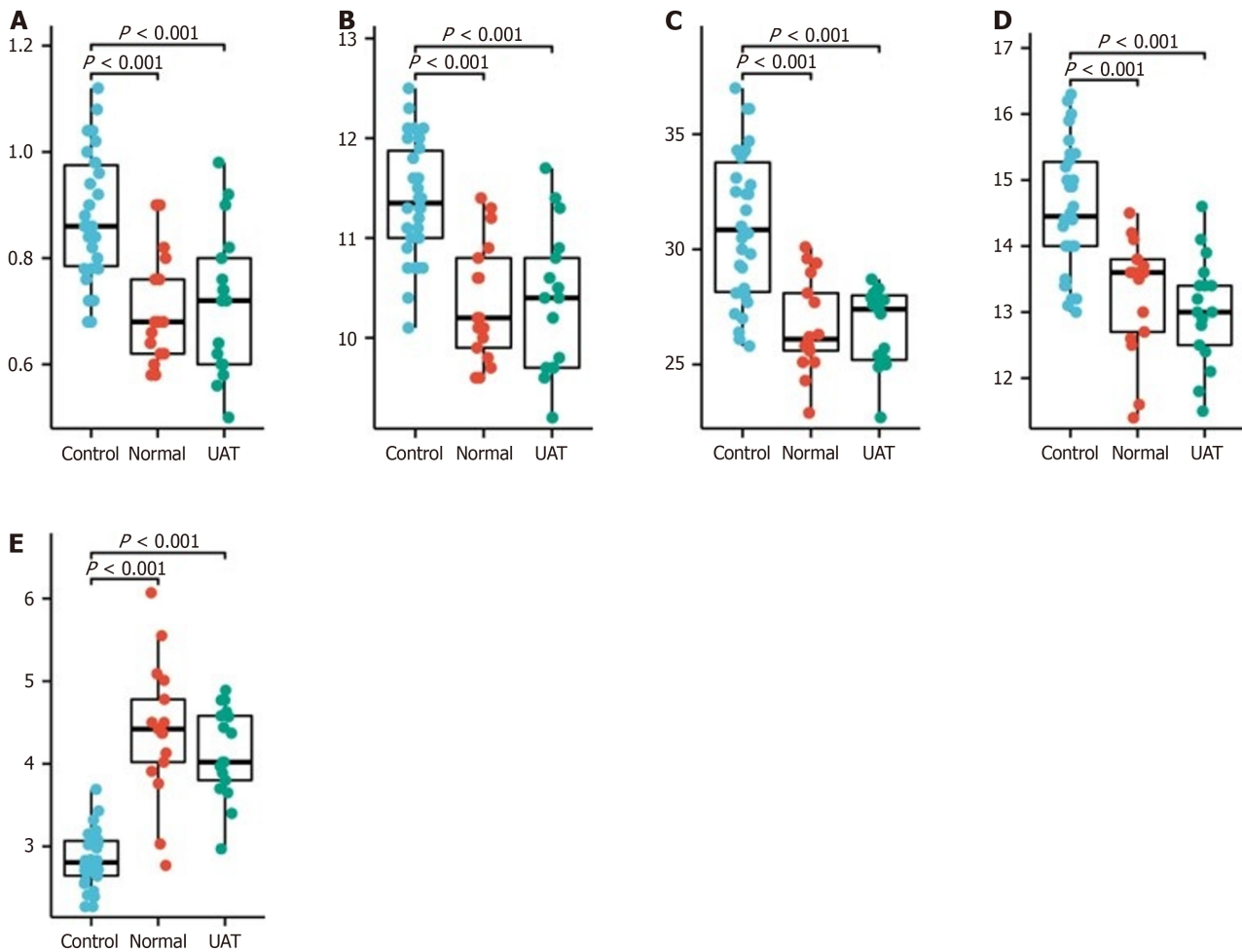


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Figure 2 Pathological findings of umbilical artery thrombosis compared with normal umbilical artery. A: Gross appearance of the umbilical cord; B: Pathological examination of the umbilical cord stained by hematoxylin and eosin.

For second best, we retrospectively analyzed 19 cases of UAT diagnosed in our department from October 2019 to March 2023, and further obtained some useful clues to understand UAT. All 19 patients with UAT we reported occurred during late pregnancy, and most patients associated with cord abnormalities, likely because the umbilical cord is more prone to robbery, entanglement, and torsion in later pregnancy.

It was reported that the risk of thrombosis during pregnancy is over 4 times higher than that in the non-pregnant women, indicating that hypercoagulability may indeed be a potential cause of UAT. Compared to normal women, both non-UAT and UAT pregnant women showed a phenomenon of hypercoagulability, while there was no significant difference between these two groups of pregnant women, suggesting that hypercoagulability alone is not sufficient for the occurrence of UAT, and other key factors need further investigation.



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Figure 3 Coagulation data in control normal women ($n = 30$), pregnant women ($n = 17$) and pregnant women with umbilical artery thrombosis ($n = 17$). A: Comparison of International Normalized Ratio among normal women (control), pregnant women (normal), and pregnant women with umbilical artery thrombosis (UAT) groups. B: Comparison of Prothrombin Time (s) among control, normal and UAT groups. C: Comparison of Activated Partial Thromboplastin Time (s) among control, normal and UAT groups. D: Comparison of Thrombin Time (s) among control, normal and UAT groups. E: Comparison of Fibrinogen (g/L) among control, normal and UAT groups. The P -values indicates significant differences.

Our findings showed that in both UAT and non-UAT groups, the umbilical artery flow ultrasound indices S/D, RI and PI decreased significantly from mid to late pregnancy, while PSV increased significantly, which indicating that the demand for blood flow between the fetus and the mother is elevated as the fetus develops. The proportion of decrease in S/D and RI as well as the increase in PSV in the UAT group were greater than in the non-UAT group, revealing an increase in blood flow in the remaining vessel, which supports our hypothesis about the compensatory effect of blood flow in the described case. PSV can also be used as an observer of umbilical artery anomalies, something that is usually overlooked by previous studies, and reference ranges for PSV at different gestational times remains to be developed.

However, it is important to acknowledge the limitations of our study, such as the relatively limited number of cases due to the rarity of UAT, which may not fully represent all the changes in the disease process. Furthermore, as a retrospective study relying on past data and medical records, it may introduce selection bias and incomplete or inaccurate data. Therefore, future prospective cohort studies are needed to collect larger sample sizes to comprehensively understand the blood flow changes during the occurrence of UAT.

CONCLUSION

For the first time, here we demonstrate statistically significant changes in ultrasound indices of umbilical artery flow after the occurrence of UAT, which provides a basis for clinical follow-up of people at high risk for UAT. Our results show that PSV, which was previously overlooked, can be used as a diagnostic indicator for UAT, in combination with RI, PI and S/D. We also show that blood hypercoagulation during pregnancy is not sufficient for the cause of UAT.

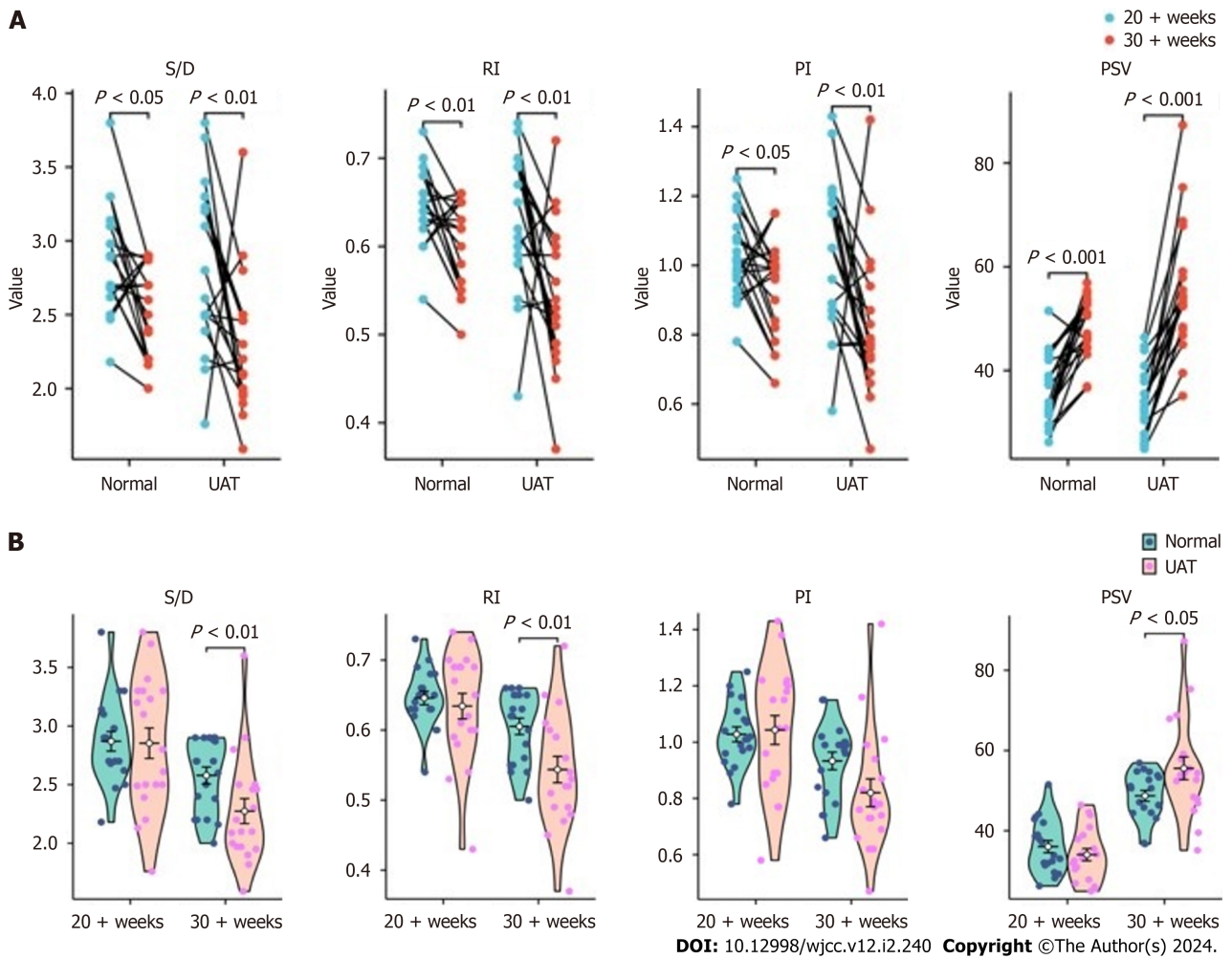


Figure 4 Statistical analysis of umbilical artery blood flow ultrasound indices of patients with umbilical artery thrombosis ($n = 19$) vs non-umbilical artery thrombosis women ($n = 19$). A: Second trimester vs third trimester; B: Umbilical artery thrombosis (UAT) patients vs non-UAT women. UAT: Umbilical artery thrombosis; S/D: Systolic-diastolic duration ratio; RI: Resistance index; PI: Pulsatility index; PSV: Peak systolic velocity.

ARTICLE HIGHLIGHTS

Research background

Umbilical artery thrombosis (UAT) is a rare condition that poses a serious threat to the lives of both the mother and the fetus. Its occurrence has been reported to be potentially associated with hypercoagulability in pregnant women. While ultrasound is a routine method for assessing umbilical artery blood flow, there is currently limited research on the blood flow changes before and after the occurrence of UAT.

Research motivation

Studies of changes in ultrasound flow indices before and after the onset of UAT can help in early detection and intervention to reduce the risk to the pregnant woman and the fetus.

Research objectives

The results of this study will help to understand the changes in blood flow before and after the onset of UAT and will hopefully lead to the use of ultrasound flow indices as an effective means of tracking the condition of people at high risk for UAT.

Research methods

In this study, blood flow ultrasound indices and coagulation parameters of patients before and after the occurrence of UAT were collected and analyzed statistically.

Research results

Patients with UAT did not display a significantly abnormal blood coagulation status compared with normal pregnant controls. In patients with UAT, the changes in ultrasound blood flow indices were significantly greater than normal

pregnant women.

Research conclusions

Hypercoagulability alone is not sufficient for the occurrence of UAT. Significant changes in ultrasound indicators after UAT were demonstrated. Peak systolic velocity can play important roles in the diagnosis of UAT.

Research perspectives

Prospective studies with large sample sizes can help to further explore the physiologic changes in the process of umbilical artery embolization by setting up well-defined control groups.

FOOTNOTES

Co-first authors: Si-Jie Hong and Li-Wei Hong.

Author contributions: Hong SJ and Hong LW contributed equally to this work, especially in data collection, analysis, and drafting of the initial manuscript; Zhong XH conceived the study; He XQ helped to revise the manuscript; all authors contributed to interpret data; all authors have read and approve the final manuscript.

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Institutional review board statement: The study was reviewed and approved by the research ethics committee (REC) of Xiamen Women and Children's Hospital (Approval No. KY-2023-081-K01).

Informed consent statement: This study is a retrospective study in which de-identified data was extracted from accumulative database, and the study complies with the Declaration of Helsinki of posing no more than minimal risk to participants. The research ethics committee of Xiamen Women and Children's Hospital approved the waiver of informed consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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