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Original Research

Correlation between Umbilical Cord Torsion and Doppler Parameters of the Umbilical Artery: A Single-Center Retrospective Case-Control Study

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Abstract

Background: Umbilical cord torsion is one of the known causes of perinatal fetal death, adding to the increase in perinatal morbidity and mortality. However, there is no study on the relationship between umbilical cord torsion and the changes in umbilical artery Doppler parameters. **Methods**: The subjects included 962 pregnant women who were discharged from our hospital from January 2015 to November 2021 and were eligible for inclusion (415 in the study group and 547 in the control group). The measurement data of umbilical artery Doppler parameters (peak systolic velocity (PSV), systolic/diastolic ratio (S/D), resistance index (RI), pulse index (PI)) were collected from 21 to 40 weeks of gestation, and the differences among the collected parameters were statistically analyzed. **Results**: The peak systolic velocity (PSV) of umbilical artery were positively correlated with gestational age, while the Doppler resistance parameters (S/D, RI, PI) of the umbilical artery were negatively correlated with gestational age. The mean values of umbilical artery Doppler parameters (PSV, S/D, RI, PI) in the study group were significantly lower than those in the control group at the same gestational age ($p < 0.05$). **Conclusions**: The decrease of Doppler parameters in the umbilical artery in late pregnancy was significantly related to umbilical cord torsion, which may be used as a reason for prenatal ultrasound screening for umbilical cord torsion. In the future, we need to combine further perinatal and prognostic data to carry out a prospective study.

Keywords: prenatal ultrasound assessment; umbilical cord torsion; umbilical artery; color Doppler ultrasound

1. Introduction

The umbilical cord is critical for the normal development, survival and health of the fetus. The proper helix of the umbilical cord and its tissue structure provide some pressure protection for umbilical vessels [1,2]. The physiological torsion of umbilical cord can reach 6–11 weeks, and the torsion of umbilical cord can be more than 12 weeks [3]. Torsion of umbilical cord may lead to fetal growth restriction, premature delivery, meconium contamination of the amniotic fluid, and stillbirth [4–9]. Umbilical cord torsion is a known cause of perinatal fetal death [10]. Prenatal ultrasound has been exploring the ultrasonic manifestation of umbilical cord torsion, but no consensus has been reached [11,12]. At present, there is no study on the relationship between umbilical cord torsion and the changes of umbilical artery Doppler parameters. The purpose of this study is to explore the correlation between umbilical cord torsion and the changes in umbilical artery Doppler parameters, provide valuable information for prenatal ultrasound screening of umbilical cord torsion, and explore the possible mechanism of umbilical artery Doppler parameters changes during umbilical cord torsion.

2. Materials and Methods

This study was a retrospective control study. Pregnant women who underwent routine prenatal ultrasound examination and hospital delivery in our hospital from January 2015 to November 2021 were randomly collected.

Inclusion criteria:

(1) Pregnant women who gave birth in our hospital had a definite discharge diagnosis or pathological diagnosis of placental appendages;

(2) Low-risk pregnancy, including no pregnancy complications or major underlying diseases, such as gestational hypertension, gestational diabetes, placental previa, placental abruption;

(3) There was a record of prenatal ultrasound examination in our hospital, and the Doppler parameters of umbilical artery were measured in the free segment of umbilical cord during the examination;

(4) Singleton pregnancy.

Exclusion criteria:

(1) Severe fetal malformations or chromosome abnormalities;

(2) Pregnant women with single umbilical cord artery or other abnormal umbilical cord blood vessels;

(3) Stillbirth or induced labor due to other reasons.

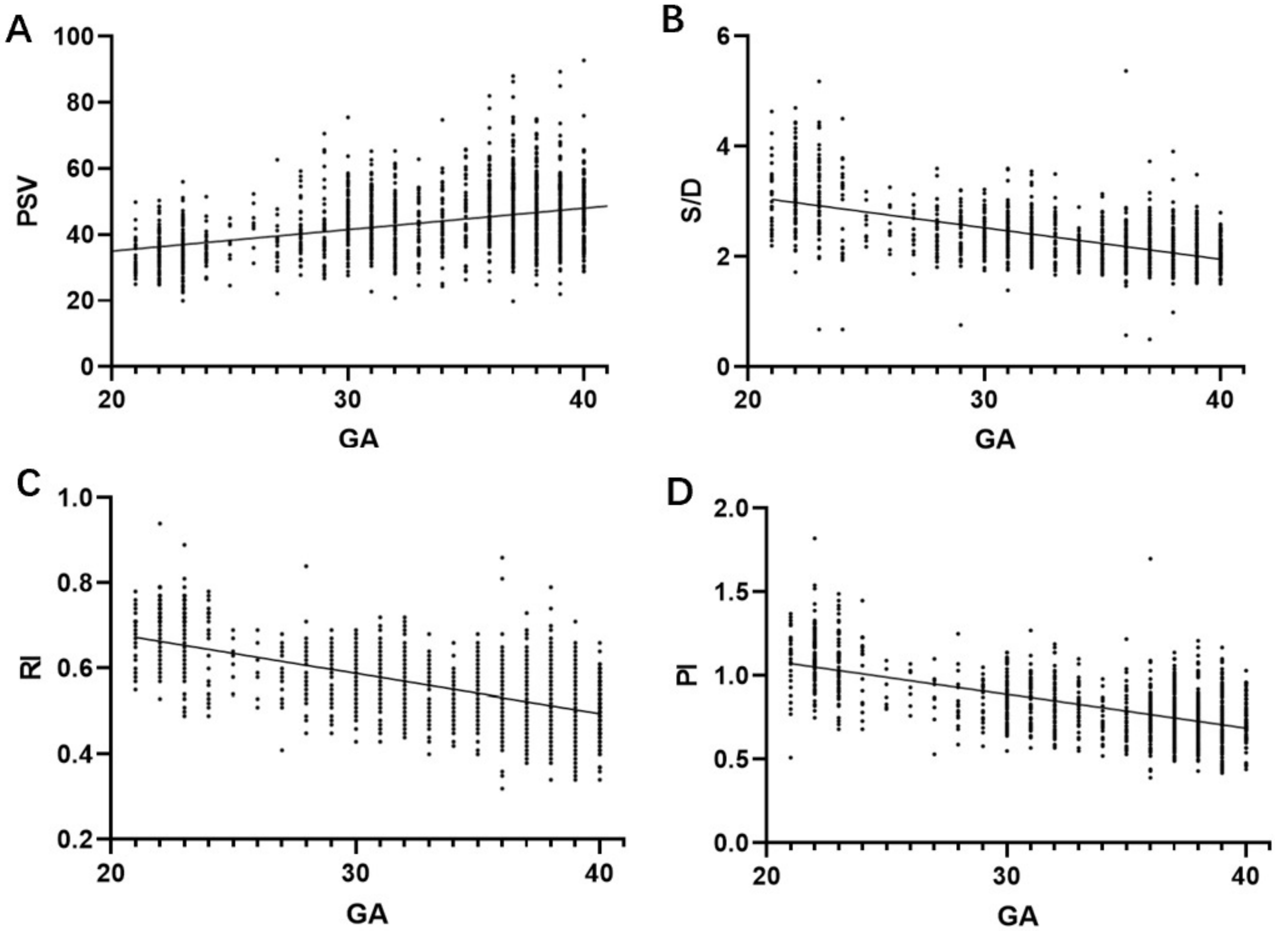

Fig. 1. PSV, S/D, RI, PI trend chart with gestational age (GA). (A–D) show the trends of PSV, S/D, RI, and PI with GA, respectively. PSV, peak systolic velocity; S/D, systolic/diastolic ratio; RI, resistance index; PI, pulsatility index.

Gestational age was calculated based on the last menstrual period. If the last menstrual period was unclear, it was calculated and recorded according to the NT (nuchal translucency) cycle after correcting the gestational age. Obstetricians evaluated the umbilical cord after delivery, and defined those who were discharged as having umbilical cord torsion as the study group. Those who were diagnosed as having no umbilical cord torsion were randomly selected as the control group. Torsion of the umbilical cord was defined as $>$12 coils [3]. The ethics committee of our hospital agreed to waive informed consent for this study.

The ultrasound instruments used were GE Voluson E10, GE Voluson E8 (GE Healthcare Austria GmbH & Co OG, Tiefenbach, Zipf, Austria), and Mindray Resona 70B (Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, Guangdong, China), with the probe frequency being 4–8 MHz. The free umbilical cord floating in the amniotic fluid was measured by Doppler, and the measurement angle was as parallel as possible to the direction of umbilical cord blood flow. Umbilical artery Doppler blood flow parameters, including peak systolic velocity (PSV), umbilical artery blood systolic/diastolic ratio (S/D), resistance index (RI) and pulse index (PI), were extracted from the scan at each gestational week from 21 to 40 weeks.

IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA) was used for data processing: (1) all umbilical artery Doppler blood flow parameters in the study group and the control group at 21–40 weeks gestation were evaluated according to gestational age. The mean of each gestational age measurement in the two groups was calculated. (2) The change trend of umbilical artery blood flow parameters for each gestational week was analyzed. (3) Logistic regression analysis was performed on the umbilical artery blood flow parameters of the study group and the control group at the same gestational age, with $p < 0.05$ indicating significant differences between the two variables. Regression analysis method was used to determine the missing values. (4) Quantitative data were expressed as mean $\pm$ standard deviation, and qualitative data were presented as ratios. The statistical significance of differences between the two groups was assessed using the independent-samples *t* test, chisquare test, and Fisher's exact test.

Table 1. Mean values and *t*-test of umbilical artery PSV, S/D, RI and PI between the study group and control group at different gestational weeks.

GA	Number		S/D				RI				PI				PSV			
	SG	CG	SG	CG	*t*	*p*-value	SG	CG	*t*	*p*-value	SG	CG	*t*	*p*-value	SG	CG	*t*	*p*-value
21	33	94	3.09	3.43	2.950	0.004	0.66	0.70	2.940	0.005	1.07	1.18	2.426	0.021	33.22	35.10	1.627	0.106
22	102	183	3.17	3.21	0.710	0.479	0.67	0.68	–0.718	0.474	1.10	1.11	0.017	0.986	35.38	35.06	–0.418	0.676
23	82	95	3.05	3.14	0.938	0.349	0.66	0.67	0.604	0.547	1.07	1.09	0.886	0.377	35.66	36.45	0.720	0.472
24	25	37	2.92	3.06	0.734	0.386	0.65	0.66	0.802	0.428	1.04	1.09	0.965	0.344	36.04	36.62	0.335	0.739
25	9	51	2.60	2.99	2.051	0.045	0.62	0.65	1.773	0.081	0.91	1.03	1.784	0.084	37.18	40.81	1.477	0.145
26	10	54	2.61	2.95	2.061	0.043	0.60	0.65	1.958	0.055	0.93	1.03	1.655	0.104	44.48	42.49	–0.882	0.381
27	17	28	2.44	2.77	2.368	0.022	0.58	0.62	1.899	0.064	0.86	0.96	1.616	0.115	37.99	42.61	2.102	0.041
28	35	49	2.46	2.73	2.677	0.009	0.59	0.62	2.156	0.034	0.85	0.96	2.823	0.006	41.20	45.01	2.279	0.025
29	47	80	2.45	2.67	2.789	0.006	0.58	0.61	2.101	0.038	0.86	0.92	1.836	0.070	42.33	46.14	2.329	0.021
30	101	172	2.39	2.64	4.995	0.000	0.57	0.60	4.177	0.000	0.85	0.91	3.171	0.002	44.84	47.01	2.273	0.024
31	111	153	2.40	2.57	3.142	0.002	0.57	0.60	2.833	0.005	0.84	0.89	2.092	0.038	43.47	47.09	3.607	0.000
32	97	132	2.36	2.54	3.239	0.001	0.56	0.59	2.910	0.004	0.82	0.89	3.024	0.003	42.81	47.79	4.362	0.000
33	50	71	2.27	2.44	2.153	0.033	0.54	0.58	2.221	0.028	0.81	0.87	1.939	0.056	41.36	48.74	4.817	0.000
34	47	60	2.12	2.43	4.695	0.000	0.52	0.57	3.748	0.000	0.73	0.85	3.106	0.003	44.08	49.16	2.755	0.007
35	54	69	2.18	2.39	2.870	0.005	0.53	0.56	2.209	0.029	0.76	0.85	2.794	0.006	45.76	49.64	2.409	0.018
36	128	212	2.14	2.31	3.890	0.000	0.52	0.55	3.050	0.002	0.75	0.83	3.392	0.001	46.91	50.30	3.478	0.001
37	243	321	2.13	2.27	3.579	0.000	0.52	0.54	2.632	0.009	0.75	0.80	3.237	0.001	46.38	50.58	4.923	0.000
38	183	279	2.11	2.25	3.706	0.000	0.52	0.54	2.552	0.011	0.73	0.80	3.878	0.000	46.59	50.78	4.825	0.000
39	202	293	2.07	2.20	3.855	0.000	0.50	0.53	3.065	0.002	0.73	0.78	3.065	0.002	45.79	51.00	6.256	0.000
40	96	110	2.06	2.17	2.293	0.023	0.50	0.53	2.201	0.029	0.72	0.78	2.071	0.040	47.16	51.13	2.831	0.005

GA, gestational age; SG, study group; CG, control group; PSV, peak systolic velocity; S/D, systolic/diastolic ratio; RI, resistance index; PI, pulsatility index.

Table 2. Logistic regression analysis of S/D, RI, PI and PSV of the umbilical artery between the study group and the control group at 21–40 weeks of gestation.

GA	S/D		RI		PI		PSV	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
21	0.324 (0.139–0.753)	0.009	0.000 (0.000–0.030)	0.005	0.016 (0.001–0.246)	0.003	0.944 (0.877–1.015)	0.120
22	0.815 (0.520–1.277)	0.372	2.725 (0.054–137.377)	0.616	0.886 (0.183–4.292)	0.881	1.010 (0.970–1.051)	0.631
23	0.768 (0.461–1.277)	0.308	0.191 (0.002–20.673)	0.489	0.287 (0.043–1.920)	0.198	0.981 (0.941–1.023)	0.378
24	0.721 (0.338–1.539)	0.397	0.045 (0.000–39.299)	0.370	0.212 (0.011–4.122)	0.306	0.985 (0.912–1.065)	0.705
25	0.234 (0.044–1.256)	0.900	0.000 (0.000–27.335)	0.158	0.008 (0.000–1.839)	0.820	0.913 (0.803–1.037)	0.161
26	0.210 (0.043–1.024)	0.054	0.000 (0.000–1.847)	0.065	0.012 (0.000–1.224)	0.061	1.048 (0.938–1.170)	0.405
27	0.194 (0.037–1.004)	0.051	0.000 (0.000–1.335)	0.057	0.012 (0.000–1.344)	0.066	0.909 (0.819–1.009)	0.074
28	0.248 (0.082–0.746)	0.013	0.001 (0.000–0.587)	0.034	0.036 (0.002–0.589)	0.020	0.927 (0.868–0.989)	0.021
29	0.276 (0.109–0.701)	0.007	0.002 (0.000–0.580)	0.031	0.065 (0.005–0.920)	0.043	0.952 (0.910–0.996)	0.032
30	0.210 (0.101–0.436)	0.000	0.000 (0.000–0.016)	0.000	0.046 (0.008–0.277)	0.001	0.964 (0.932–0.997)	0.034
31	0.355 (0.185–0.680)	0.002	0.005 (0.000–0.206)	0.005	0.141 (0.024–0.842)	0.032	0.942 (0.911–0.975)	0.001
32	0.354 (0.178–0.705)	0.003	0.005 (0.000–0.264)	0.009	0.112 (0.019–0.673)	0.017	0.928 (0.895–0.962)	0.000
33	0.345 (0.129–0.927)	0.035	0.002 (0.000–0.430)	0.024	0.057 (0.005–0.690)	0.024	0.887 (0.838–0.938)	0.000
34	0.085 (0.023–0.311)	0.000	0.000 (0.000–0.025)	0.001	0.009 (0.001–0.145)	0.001	0.945 (0.903–0.989)	0.014
35	0.262 (0.098–0.699)	0.007	0.006 (0.000–0.687)	0.034	0.056 (0.005–0.598)	0.017	0.955 (0.915–0.997)	0.036
36	0.289 (0.152–0.550)	0.000	0.011 (0.001–0.194)	0.002	0.087 (0.020–0.372)	0.001	0.954 (0.928–0.980)	0.001
37	0.424 (0.262–0.687)	0.000	0.053 (0.006–0.495)	0.010	0.230 (0.080–0.661)	0.006	0.958 (0.940–0.976)	0.000
38	0.378 (0.223–0.642)	0.000	0.043 (0.004–0.449)	0.009	0.180 (0.058–0.557)	0.003	0.949 (0.928–0.971)	0.000
39	0.408 (0.244–0.682)	0.001	0.038 (0.004–0.354)	0.004	0.231 (0.079–0.678)	0.008	0.936 (0.915–0.958)	0.000
40	0.407 (0.177–0.935)	0.034	0.028 (0.001–0.876)	0.042	0.097 (0.014–0.673)	0.018	0.934 (0.991–0.999)	0.011

OR, odds ratio; 95% CI, 95% confidence interval; GA, gestational age; PSV, peak systolic velocity; S/D, systolic/diastolic ratio; RI, resistance index; PI, pulsatility index.

Table 3. Perinatal outcomes in the study group and the control group.

Characteristics	Study group	Control group	χ^2	*p*-value
Number of nuchal cords				
One loop	84 (20.2)	133 (24.3)	2.678	0.431
Two loops	18 (4.3)	20 (3.7)		
Three loops	2 (0.5)	4 (0.7)		
Mode of delivery				
Vaginal delivery	208 (50.4)	331 (60.5)	4.619	0.033
Cesarean delivery	207 (49.9)	216 (39.5)		
Fetal heart rate abnormality during labor	7 (1.7)	2 (0.4)	4.444	0.044
Emergency cesarean delivery	78 (18.8)	63 (11.5)	9.992	0.002
Meconium staining of amniotic fluid				
I°	11 (2.7)	5 (0.9)	28.010	0.000
II°	49 (11.8)	31 (5.7)		
III°	15 (3.6)	3 (0.7)		
Low Apgar score ($\leq$7 at 1 minute)	20 (4.8)	9 (1.6)	8.131	0.007
Neonatal intensive care unit admission	50 (12.0)	31 (5.7)	12.336	0.001
Small for gestational age	10 (2.4)	7 (1.3)	1.736	0.221
Birth weight, g	3126.99 $\pm$ 509.81	3290.48 $\pm$ 376.38	5.495*	0.000
Gestational age at delivery of 37 weeks	382 (92.0)	538 (98.4)	22.477	0.000
Abnormal amniotic fluid volume				
Polyhydramnios	11 (2.7)	3 (0.5)	14.490	0.001
Oligohydramnios	32 (7.7)	21 (3.8)		

Data are shown as mean $\pm$ standard deviation or n (%). Fisher's exact probability method was used. *Independent-samples *t*-test was used.

PSV, S/D, RI, PI trend chart with gestational age plotted using GraphPad Prism version 9.5.0 for Windows (GraphPad Software, Boston, MA, USA, https://www.graphpad.com/).

3. Results

This study included 1608 pregnant women who delivered in our hospital (666 in the study group and 942 in the control group). According to the inclusion exclusion criteria, 646 pregnant women (251 in the study group and 395 in the control group) were excluded, and 415 pregnant women in the study group and 547 pregnant women in the control group were included. The two groups of pregnant women ranged in age from 21 to 44 years, with a mean age of 31 years (no difference between the two groups, $p >$ 0.05). A total of 4215 umbilical artery Doppler flow parameters were collected in the study group (1676 in the study group and 2543 in the control group), with each including the peak rate of umbilical artery contraction (PSV) and the umbilical artery flow resistance parameters (S/D). Some of the studies lacked the resistance parameters RI (missing 19) and PI (missing 75). The average values of umbilical artery Doppler parameters in the study group and the control group at different gestational ages are shown in Table 1, demonstrating that the average values of PSV, S/D, RI and PI of umbilical artery in the study group were lower than those in the control group at different gestational ages.

As shown in Fig. 1, the correlation analysis of umbilical artery flow parameters (PSV, S/D, RI, PI) and gestational age in the study group and control group respectively revealed that the peak velocity of umbilical artery contraction (PSV) was positively correlated with gestational age in both groups, while the correlation parameters of umbilical artery Doppler resistance (S/D, RI, PI) were negatively correlated with gestational age in both groups (R_{PSV} 0.374 *vs.* 0.538, $R_{S/D}$ 0.617 *vs.* 0.619, R_{RI} 0.616 *vs.* 0.563, R_{PI} 0.602 *vs.* 0.622, $p > 0.05$).

After filling in the missing values by regression analysis, logistic regression analysis demonstrated that at weeks 22–27, the umbilical artery Doppler parameters of both the study group and the control group were greater than 0.05, while in weeks 28–40, the weekly umbilical artery Doppler parameters were less than 0.05, with statistical significance as shown in Table 2.

Table 3 summarizes the relationships between umbilical cord torsion and perinatal outcomes. The incidences of, fetal heart rate abnormalities during labor (1.7% *vs.* 0.4%, p = 0.044), and meconium staining of amniotic fluid (18.1% *vs.* 7.3%, p = 0.000) were significantly higher in the study group and control group.

Admission to the neonatal intensive care unit was significantly associated with torsion of the umbilical cord (12% *vs.* 5.7% , p = 0.001). Low Apgar score ($\leq$7 at 1 minute) was also significantly associated with torsion (4.8% *vs.* 1.6%, p = 0.007).

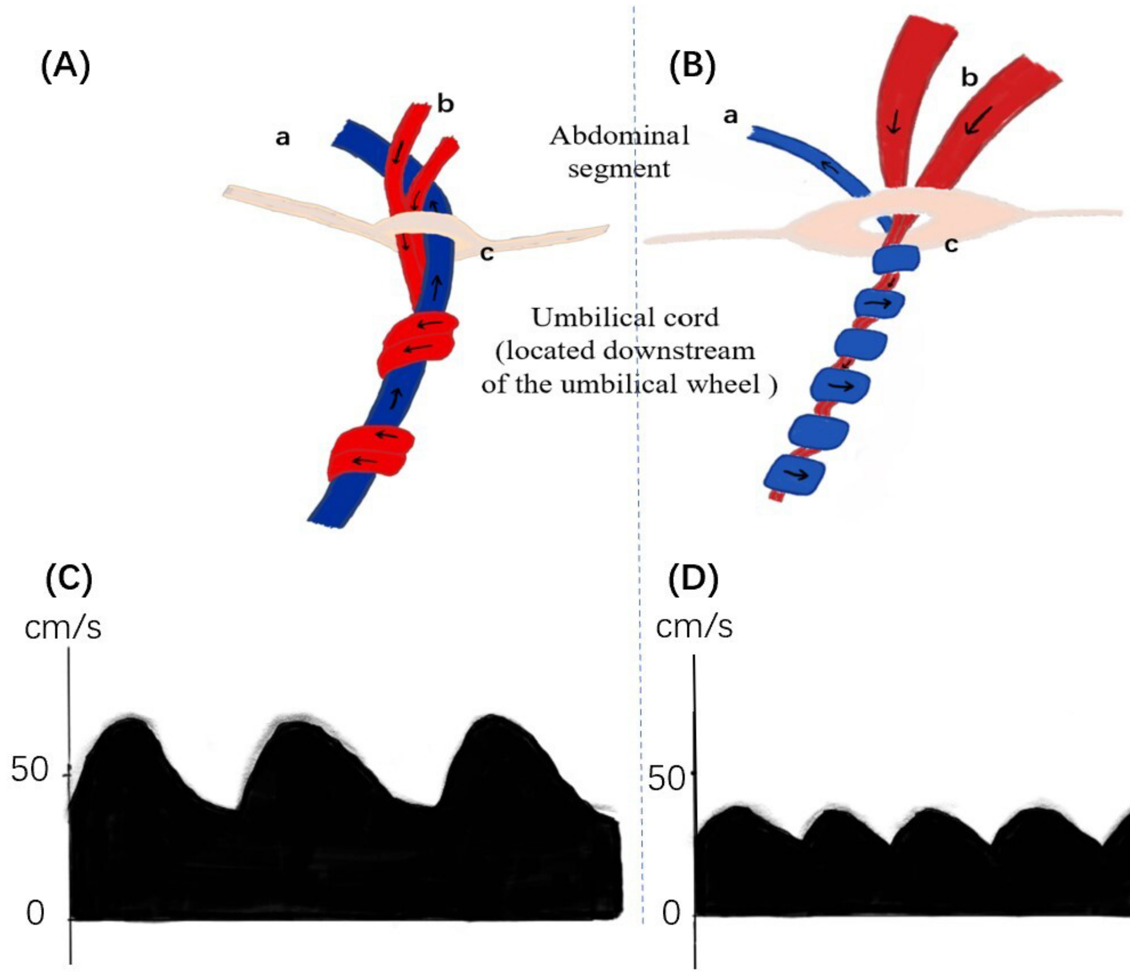

Fig. 2. The umbilical cord (located downstream of the umbilical wheel). (A) When the normal umbilical cord passes through the umbilical wheel, there is no stenosis of the umbilical artery. (B) When the umbilical cord is twisted, the umbilical artery at the umbilical wheel is narrowed due to torsion, and the peak systolic velocity and resistance of the umbilical artery downstream of the umbilical wheel is reduced. (C) Normal umbilical artery Doppler waveform. (D) When the umbilical cord is twisted, the umbilical artery changes with low velocity and low resistance. a, umbilical vein; b, umbilical artery; c, the umbilical wheel.

The mean neonatal weight was significantly lower in the study group and control group (3126.99 $\pm$ 509.81 g *vs*. 3290.48 $\pm$ 376.38 g, p = 0.000). Abnormal amniotic fluid volume was significantly associated with torsion (10.4% *vs*. 4.3%, p = 0.007).

4. Discussion

This was a single-center retrospective case-control study. The results demonstrated that the peak velocity of umbilical artery contraction (PSV) was positively correlated with gestational age in both the study group and the control group, and the values of the umbilical artery Doppler resistance related parameters (S/D, RI, PI) were negatively correlated with gestational age.

The results of this study revealed that there was no significant difference in the mean value of umbilical artery Doppler parameters between the study group and the control group at 21–27 weeks of gestation ($p > 0.05$). The values of umbilical artery Doppler parameters at 28–40 weeks gestation in the study group were lower than those in the control group. Logistic regression analysis showed that the difference was significant ($p < 0.05$). We hypothesized that umbilical cord torsion may begin early in the second trimester, and then gradually increase with gestational age. During the second trimester, the protective structure of the umbilical cord gives it some resistance to excessive torsion [1,2]. The changes of umbilical artery blood flow mechanics were not obvious, and the difference of Doppler parameters was not statistically significant. However, with the gradual aggravation of torsion in later pregnancy, the changes of umbilical artery blood flow mechanics were obvious, and the difference of Doppler parameters was statistically significant.

When the arteries in other parts of the human body are narrowed, the Doppler changes of the artery blood flow at the distal end of the stenosis are low-speed and low-

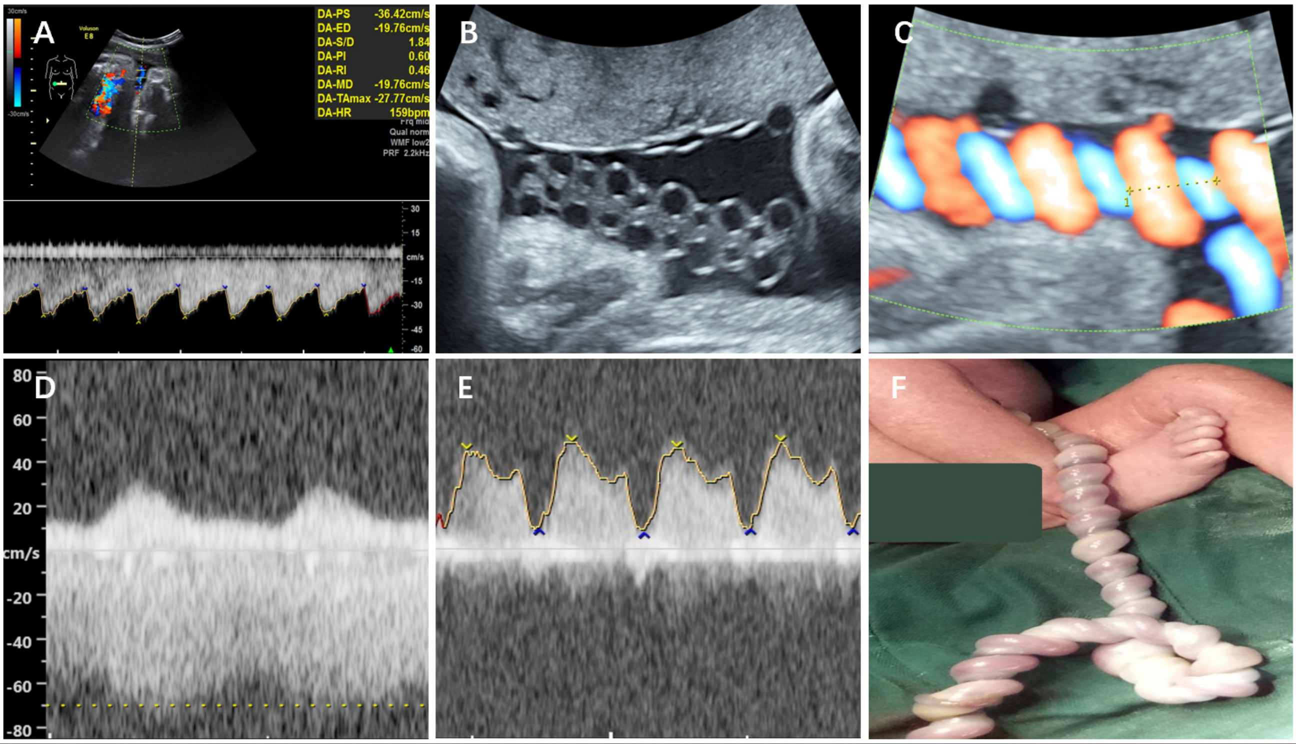

Fig. 3. A case of umbilical cord torsion. (A) Abnormal fetal heart monitoring at 32 weeks of gestation, frequency spectrum of umbilical cord free segment. PSV is lower than 5th%, S/D, RI, PI is lower than 10th%. (B) 2D image of high spiral umbilical (changing like chain). (C) Color Doppler image of high spiral umbilical (UCI 0.76). (D) The umbilical vein flow velocity at the umbilical wheel increased (PSV 69 cm/s). (E) Doppler spectrum of intravenous catheter (a notch significantly deepened, PI 1.22). (F) Umbilical cord torsion >30 weeks after birth. UCI, umbilical coiling index.

pulsation changes, forming a "small slow wave" [13,14]. We believe that the Doppler changes of the umbilical artery blood flow during umbilical cord torsion are consistent with the changes of blood flow Doppler changes after arterial stenosis in other areas. Because umbilical cord torsion occurs mostly at the umbilical wheel [3], the umbilical artery at the umbilical wheel is narrowed by the torsion of the umbilical cord, resulting in "small slow wave" changes in the blood flow Doppler of the umbilical artery at the distal end of the umbilical wheel (Fig. 2).

The Doppler parameters of umbilical artery blood flow are the routine indexes of the prenatal ultrasound examination. At present, most of the poor pregnancy outcomes are related to the abnormal increase of umbilical artery blood Doppler resistance parameters [15–19]. When obstetricians suspect fetal distress or abnormal fetal movement, they usually pay more attention to the abnormal increase in Doppler resistance of umbilical artery blood flow. If there is no abnormal increase in Doppler resistance of umbilical artery blood flow, the conclusion is reached that the fetus is currently stable and the recommendation is that the fetus be reexamined in the future. During the time waiting for reexamination, it is possible that the fetus may die in the uterus due to torsion of the umbilical cord. Therefore, when the fetus has abnormal fetal heart monitoring and abnormal fetal movement, and the Doppler parameters of umbilical artery blood flow do not increase abnormally or actually decrease, the possibility of umbilical cord torsion should be considered. It has been reported that the high helix of umbilical cord is related to umbilical cord torsion [20–22]. It has been reported that when the umbilical cord is high helical, the umbilical vein blood flow velocity at the umbilical wheel will increase [23,24] or the a-wave reverse of the venous catheter will occur [25]. Therefore, when umbilical cord torsion is suspected, attention needs to be paid to the contents of unconventional ultrasound examination, such as umbilical cord helix, umbilical vein flow velocity and venous catheter spectrum.

Fig. 3 represent a case of a pregnant woman at 32 weeks of gestation with abnormal fetal heart rate monitoring. Ultrasound examination demonstrated a single umbilical artery.

The PSV of umbilical artery was 36.42 cm/s, S/D and 1.84 Magi was 0.46 and Pi was 0.60, in which PSV was lower than normal 5th% [26], and S/D, RI and PI were lower than 10th% [26] (Fig. 3A). The results suggested that there may be umbilical cord torsion. Therefore, we examined the shape of the umbilical cord and the blood flow of the venous catheter. It was found that the fetal umbilical cord spirally increased, UCI (umbilical coiling index) 0.76 [27]

(Fig. 3B,C), and the umbilical vein blood flow velocity at the umbilical cord wheel (PSV 69 cm/s) was higher than that of 95th% [24] (Fig. 3D). The a-wave notch of the fetal venous duct was significantly deepened and PI increased, which was larger than that of 95th% [26] (Fig. 3E). We considered the possibility of umbilical cord torsion, and the obstetrician performed a emergent cesarean section. The postoperative diagnosis confirmed umbilical cord torsion for 36 weeks (Fig. 3F). Postoperative pathology of the umbilical cord revealed two umbilical arteries (one of which was atretic) and one umbilical vein.

5. Conclusions

The decrease of umbilical artery Doppler parameters in late pregnancy is significantly correlated with umbilical cord torsion, which may be used as a reason for prenatal ultrasound screening for umbilical cord torsion. The Doppler characteristics of umbilical artery blood flow during umbilical cord torsion are consistent with the basic principle of the changes of blood flow Doppler parameters after vascular stenosis in other parts of the body. We suggest that a multicenter prospective cohort study is needed to further evaluate these findings.

Abbreviations

GA, gestational age; PSV, peak systolic velocity; S/D, systolic/diastolic ratio; RI, resistance index; PI, pulsatility index; NT, nuchal translucency; UCI, umbilical coiling index.

Availability of Data and Materials

The dataset generated and/or analysed during the study are available from the corresponding author on reasonable request.

Author Contributions

YL and DZ designed the research study. YL performed the research. YS provided help and advice on statistics. YL analyzed the data. YL and DZ wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. This study passed the exemption of informed consent in Peking University Shenzhen Hospital and the protocol was approved by the Ethics Committee of Peking University Shenzhen Hospital (Ethics number: 2022 NO.010).

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Conflict of Interest

The authors declare no conflict of interest.

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