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REVIEW

Umbilical Vascular Thromboembolism: High-Risk Factors, Diagnosis, Management, and Pregnancy Outcomes: A Scoping Review

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Abstract: Umbilical vascular thromboembolism is a rare condition that can lead to serious consequences such as fetal hypoxia, fetal growth restriction, and even stillbirth. However, there is currently a lack of research on the pathology, pathogenesis, clinical management, and prognosis of this condition. Therefore, the purpose of this article is to analyze this condition's high-risk factors, clinical characteristics, pregnancy management, and discuss its corresponding pregnancy outcomes. Databases such as PubMed are searched using the relevant keywords of umbilical vascular thromboembolism in worldwide. And related information is analyzed such as maternal risk factors, fetal risk factors, umbilical cord and placental risk factors, and pregnancy outcomes. The literature search yields 113 articles, 64 of which meet the inclusion criteria for umbilical vascular thromboembolism. There are 4 retrospective cohort studies and 8 case series, the rest are all case reports. A total of 262 cases of umbilical vascular thromboembolism are found. The most common maternal complications and fetal related risk factors are diabetes (25 cases, 9.5%) and stillbirths (106 cases, 40.5%), respectively. Among these 262 cases, 98 (37.4%) cases are found by prenatal ultrasound to have umbilical vascular thromboembolism and the fetus is in a viable state with complete clinical information. In addition, considering the effectiveness and safety of low molecular weight heparin in thromboembolic conditions, twenty-four patients of umbilical artery thromboembolism attempted to use low molecular weight heparin during observation. Maternal diabetes was the highest risk factor for this condition. When umbilical artery thromboembolism occurs, the incidence of stillbirth increases. Premature patients with this condition can continue their pregnancy under close external monitoring. However, due to the small sample size, further research is needed.

Keywords: umbilical vascular thromboembolism, umbilical vein thromboembolism, umbilical artery thromboembolism, fetal growth restriction, umbilical vein varix, low molecular weight heparin

Background

The umbilical cord is an important channel for gas exchange, nutrient supply, and fetal metabolic product excretion between the mother and fetus. Normally, there are two umbilical arteries and one umbilical vein. When umbilical vascular thromboembolism (UVTE) occurs, umbilical blood flow is blocked, leading to fetal hypoxia, fetal growth restriction (FGR), and even stillbirth.[1] UVTE is relatively rare, with an incidence rate of only 1 in 1290 deliveries.[2] However, the incidence rate of UVTE in high-risk pregnant people is about 1/250[2]. More than half of UVTE was found in stillbirth autopsies, accounting for 18.7% of total stillbirths.[3] UVTE can occur in the umbilical vein and/or artery. Moreover, stillbirth usually occurs in the umbilical vein thromboembolism (UVT).[2,4] Umbilical artery thromboembolism (UAT) may lead to fetal distress, FGR, fetal organ infarction, and even stillbirth.[5,6] Therefore, it is particularly important to detect and diagnose UVTE before childbirth and implement proper pregnancy management. This study is the first attempt to summarize and analyze the high-risk factors, clinical characteristics, and pregnancy management of previously reported UVTE, and thus provide possible means for improving pregnancy outcomes.

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The underlying mechanisms of UVAT remains indeterminate with many experts resorting to Virchow's classic tripartite framework as an explanatory model. This triad encompasses venous stasis, vascular trauma, and a hypercoagulable state, all of which are postulated to contribute to the development of the condition.

Methods

A comprehensive search of PubMed, Medline, OVID, Cochrane, CINAHL, Web of Science, and DARE is undertaken to collect quantitative evidence about UVTE. The keywords used are as follows: "Umbilical cord" AND 'thrombus' OR 'thrombosis' OR "thromboembolism" OR "embolism" AND "fetal", or "umbilical" AND "thrombus" OR "thrombosis" OR "thromboembolism" OR "embolism" AND "fetal", or "Umbilical cord" AND "atresia" AND "fetal". Figure 1 shows the specific search strategy for UVTE related literature in this study.

The inclusion criteria encompass research articles, case series, and single case reports that focus on UVTE published between 1957 and 2023. These articles must detail clinical and pathological aspects, including the type, etiology, diagnosis, complications during pregnancy, treatment strategies, and pregnancy outcomes associated with UVTE. The language of the publications is limited to English or Chinese, with an English abstract mandatory for Chinese articles to ensure accessibility and comprehension. The exclusion criteria are: retrospective case studies and case reports with incomplete clinical data, non-English or non-Chinese literature. This article also extracts all cases related to UVTE from published articles on stillbirth, and uses Microsoft Excel to collect, organize, and analyze related information of UVTE such as maternal risk factors, fetal risk factors, umbilical cord and placental risk factors, and pregnancy outcomes. Finally, common features as well as similarities and differences among these descriptive reports are extracted for critical evaluation and comparison.

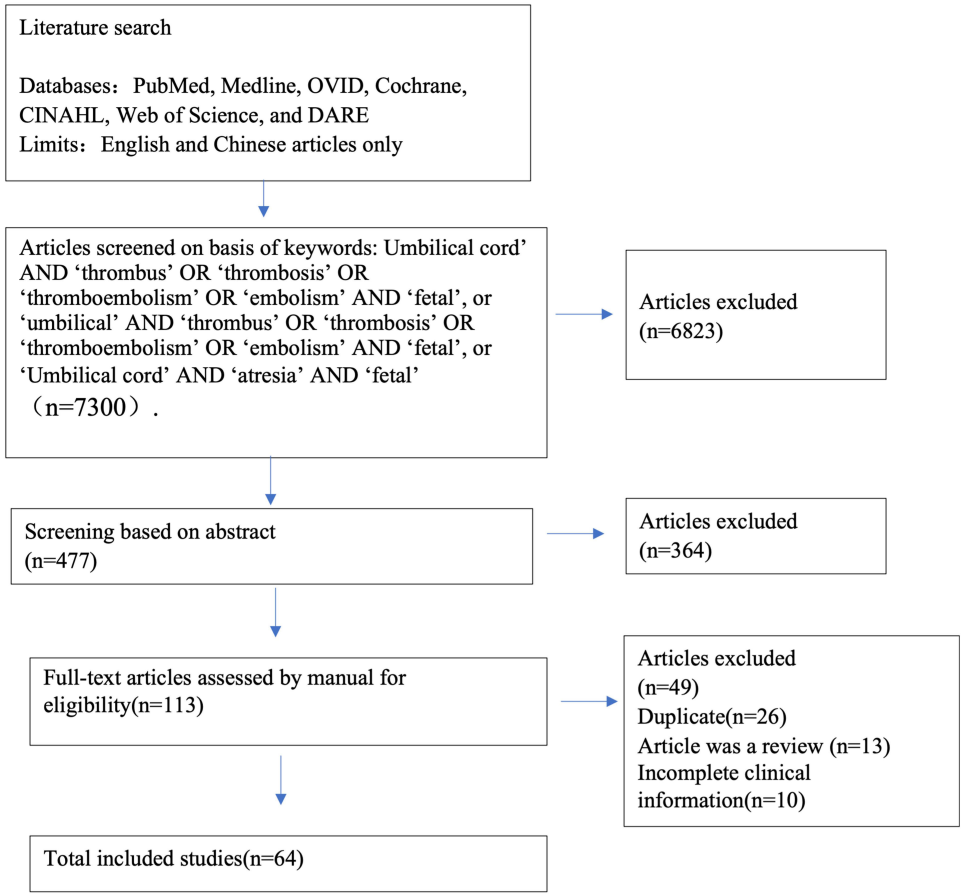

Figure 1 Shows the search strategy and keywords of this study. Two independent reviewers searched the corresponding databases and verified relevant literature one by one, excluding irrelevant, duplicate literature, and literature with incomplete clinical data.

Results

The literature search yields 113 articles, 64 of which meet the inclusion criteria for UVTE.[1,2,5–66] There are 4 retrospective cohort studies[1,2,7,66] and 8 case series,[1,2,6,8–11,61] and the rest are all case reports.[12–60,63–65] A total of 262 cases of UVTE are found. These results have generated relatively enough sufficient relevant articles, including case studies, case series, and retrospective cohort studies.

Most of the existing research classified UVTE based on the location of occurrence, and their main focuses were on UAT.[6–10,66] In addition, Heifetz[2] reported that the most common type of UVTE is UVT. Table 1 lists the frequency of UVTE. Most cases of UVTE are found during postpartum pathological examination, and 98 cases are found to have UVTE on prenatal ultrasound, and the fetus was in a viable state with comprehensive clinical information.

Summary of Risk Factors

Maternal Related Risk Factors

At present, it is unclear whether the occurrence of UVTE is related to certain maternal pregnancy complications or complications. Most scholars[5,7–9] explain it using Virchow's triad of venous stasis, vascular injury, and hypercoagulability.[67] A retrospective cohort study by Wu et al[7] found that gestational diabetes mellitus is an independent risk factor for the occurrence of UAT. In addition, pregnancy induced hypertension may be closely related to the occurrence of UVTE.[7,9,66] However, it is not clear how pregnancy induced hypertension and gestational diabetes mellitus can lead to UVTE. It may be due to imbalance of endothelial vasodilation and contraction factor expression induced by hyperglycemia and hypertension can lead to endothelial damage, coagulation dysfunction, and ultimately triggering UVTE.[68] Only 4 cases of positive anticardiolipin antibody are found in the 262 cases of UVTE in this study.[1,21,32] However, based on the fact that patients combined with positive antiphospholipid antibodies exhibit a hypercoagulable state of blood, antiphospholipid antibodies not only affect coagulation factors in the blood, but can also affect cofactors, protein C/S. In addition, they may activate the procoagulant components of endothelial cells and initiate coagulation cascade reactions.[63–65] Although Virchow's triad[67] suggests that hypercoagulability may lead to UVTE, only 37 patients underwent D-d dimer examination.[9,21,61,66] But there was only one case with abnormality (10.33 ng/mL),[61] the others all showed no abnormalities. These data indicate that D-dimer cannot yet be recognized as a reflecting factor of UVTE. Table 2 shows all the maternal related risk factors: there are many maternal complications in the 262 cases of UVTE, most of which are diabetes (25 cases, 9.5%).

Fetal Related Risk Factors

With the existence of UVTE, the mortality rate of the fetus increases, which may be related to the size of the thrombosis, the degree of vascular obstruction, and the presence or absence of other conditions in the fetus.[2,5,6,8,10,11,23] UVTE can lead to FGR.[1,2,5,6,8–13,15,16,23,25,28,30,31,33,34,40,41,44,46,61,66] And a large number of studies have shown that UVTE can cause stillbirth in the third trimester.[1,2,6,7,9–11,13,16,18,22,35–37,41,42,45,46,48,50,52,54,55,57,64,66] Newborns are prone to metabolic acidosis, thrombocytopenia, neonatal arterial thrombosis, portal vein thrombosis, cerebral palsy after

Table 1 Types According to the Occurrence Location of UVTE

Types according to the occurrence location of UVTE	No. of cases [Reference]
Umbilical vein thromboembolism	80[1,2,9,12,13,16,19,22,23,29,31–34,37,38,42,44,45,47,48,51,54–57]
One umbilical artery thromboembolism	134[1,2,5–10,14,15,17,18,20,21,24,26,28,30,36,41,43,46,49,52,59,61]
Two umbilical artery thromboembolism	3[1,2]
UVT combined with single umbilical artery thromboembolism	10[1,2,34,58]
UVT combined with double umbilical artery thromboembolism	21[1,2,60,64]
Undistinguished from UVT or UAT	14[11,25,34,40,50,53]

birth.[2,9,11,12,20,27,31,44,65] UVTE can also cause neonatal asphyxia[2,8,9,21,23,24,26,27,30,36,41,44,60] and increase the number of newborns transferring to NICU,[8,9,12,21,23,26,28,44] with a hospital stay of 7–39 days and an average of 19.8 days.

FGR occurs very frequently in UAT.[2,6,8,9,61,66] In addition, a large number of case reports on UVTE indicate that both UVTE and FGR can coexist, indicating that UVTE can be closely related to the occurrence of FGR.[1,5,11–13,15,16,23,25,28,30,31,33,34,40,41,44,46]

Among these 262 cases of UVTE, a total of 106 stillbirths (40.5%) and other common risk factors associated with UVTE, such as FGR, are shown in Table 2. A total of 173 cases of newborn biological sex are provided in the literature, including 97 males and 76 females, with a male to female ratio of 1.28:1.[1,2,5–60,62,65] Currently, only a total of 8 cases with UVTE underwent prenatal fetal chromosome karyotype examination with no abnormalities results.[5,18,23,36,37,41,42]

This study reviewed all 262 cases and found that only 12 cases had abnormal fetal movement,[9,50,54,61,64] while 15 cases had suspicious or unresponsive fetal heart rate monitoring.[8,12,14–16,44,46,58,60,61] This indicates that when UVTE occurs, because of the compensatory effect of another normal umbilical artery or incomplete closure of the vascular lumen, most pregnant people do not experience typical fetal distress symptoms such as reduced fetal movement, all of which suggests the importance of ultrasound examination in the diagnosis of UVTE. All other newborns' conditions are also shown in Table 2.

Table 2 Maternal Related Risk Factors and Fetal Related Risk Factors

Maternal Related Risk Factors	No. of cases	Fetal Related Risk Factors	No. of cases
Diabetes	25[1,2,5–7,9,48,58,66]	Stillbirth	106[1,2,6,7,9–11,13,16,18,22,35–37,41,42,45,46,48,50,52,54,55,57,64,66]
Hypertension	14[1,7–9,16,34,66]	FGR	56[1,2,5,6,8–13,15,16,23,25,28,30,31,33,34,40,41,44,46,61,66]
Oligohydramnios	8[2,8–10,13]	Fetal distress	22[7,8,10,12,16,18,20,31,37,41,42]
Polyhydramnios	8[1,40]	Abnormal fetal heart electronic monitoring	15[8,12,14–16,44,46,58,60,61]
Intrauterine transfusions	7[13,24,32,48,53]	Abnormal fetal movement	15[9,50,54,61,64,66]
Immune system diseases	5[58,66]	Fetal edema	5[13,31,32,37]
Positive anticardiolipin antibody	4[1,21,32]	Peak systolic flow velocity increase of the middle cerebral artery	1[14]
Negative Rh blood group	4[13,48,53,64]	Prenatal fetal chromosome karyotype	8[5,18,23,32,36,37,41,42]
Subclinical Hypothyroidism	2[9]	Intrauterine infection	1[8]
Hypothyroidism	3[1,8,61]	Neonatal respiratory distress	2[8]
Hepatitis B virus infection	3[8,58,61]	Neonatal hypoglycemia	1[12]
Intrahepatic cholestasis of pregnancy	2[8]	Neonatal death	12[2,11,41]
Obesity	2[1]		
SARS-CoV-2 infection	2[17]		
Syphilis	1[63]		
Fever	1[8]		
Fetomaternal hemorrhage	1[30]		
Chronic nephritis	1[8]		
Maternal thrombophlebitis	1[2]		
Severe Protein S Deficiency	1[40]		
Cordocentesis	1[66]		
Selective Termination in Dichorionic Diamniotic Twin Pregnancy	1[65]		

Umbilical Cord and Placental Related Risk Factors

The pathogenesis of UVTE is not yet clear. UVTE may be related to the following umbilical cord issues: (1) Cord velamentous insertion on the placenta; (2) Severe infection of the umbilical cord; (3) Nuchal cord, twisting of umbilical blood vessels, stenosis, and knots; (4) Hematoma caused by intravascular puncture and blood transfusion through the umbilical cord.[1,5,22,29,43,47,48,55–67] Wei et al[8] conducted a retrospective study on 8 cases of UAT and found that 4 of them had umbilical cord abnormalities, such as hypercoiling, velamentous insertions, strictures, true knots, and cystic and vascular malformations. A retrospective study by Wang et al[61] found that up to 70% of 10 patients with UAT were combined with umbilical cord torsion. Zhu et al[9] found 10 cases of UAT in third trimester pregnancy that there were 2 cases of hypercoiling, 1 case of excessively short cord, 1 case of excessively long cord, and 1 case of umbilical cord inflammation.

Among these 262 cases of UVTE, various kinds of umbilical cord abnormalities are found, including 34 cases of nuchal cord.[1,2,7,28,34,46,49,60,64] Heifetz[2] found that out of 52 cases of UVTE, 10 cases had umbilical cord marginal insertion, 9 cases had hypercoiling, 9 cases had nuchal cord, 9 cases had funisitis, 5 cases had excessively short cord, 1 case had excessively long cord, and 3 cases had Umbilical cord true knot. Among the 11 cases of UAT reported by Sato,[10] 9 cases were combined with umbilical cord abnormalities, such as marginal cord insertion, short cord with twist, long cord, and funisitis. Above-mentioned results and all other umbilical cord conditions are shown in Table 3.

Shilling et al[6] conducted pathological examinations on the placenta of 7 patients with UAT and found that 1 case was combined with placental dysfunction, 2 cases were combined with distal villous immaturity, and 5 cases were combined with fetal thrombotic vasculopathy. Placental pathological examination of 11 cases of UAT reported by Sato et al[10] all suggested necrosis of the umbilical artery wall.

Table 3 Umbilical Cord and Placental Related Risk Factors

Umbilical Cord Related Risk Factors	No. of Cases	Placental Related Risk Factors	No. of Cases
Nuchal cord	34[1,2,7,28,34,46,49,60,64]	Meconium staining	11 [2,8,12,16,24,25,28,30,35]
Umbilical cord hypercoiling	37[1,2,5,8–10,13–15,18,29,32,47,61,64]	Chorioamnionitis	10[1,2,8–10,26,32]
Funisitis	13[1,2,9,34]	Mural thrombi	6[10]
Umbilical cord marginal insertion	18[1,2,6,10,20,22,61]	Infraction	6[10]
Excessively short cord	14[2,6,9,10,20,38,44,61]	Fetal thrombotic vasculopathy	5[6,51]
Excessively long cord	9[2,9,14,15,28,46,49,52,58]	Small	2[8,12]
Umbilical cord true knot	11[1,2,8,49,61]	Distal villous immaturity	2[6]
Hemorrhage	8[2,36]	Large	1[34]
Velamentous cord insertion	4[8–10]	Acute thrombosis of major chorionic vessels	1[1]
Umbilical yellow staining	2[1,8]	Circumvallate type	1,[34]
Umbilical cord cyst	1[8]	Flat	1[34]
		Focal retroplacental hematoma	1[39]
		Multifocal chorangiomatosis	1[37]
		Chorangiosis	1[10]
		Occlusion of stem vessels	1[10]
		Placenta accreta	1[9]
		Placental emboli	1[44]
		Uteroplacental insufficiency	1[6]

Some UVTE cases are combined with meconium staining,[2,8,12,16,24,25,28,30,35] so some scholars believe that the occurrence of UVTE is related to meconium staining. Intrauterine infection or vascular necrosis caused by meconium may lead to endothelial damage to the umbilical vascular, resulting UVTE.[12] The content of placental pathological examination in 262 cases of UVTE are also shown in Table 3.

Pregnancy Management and Pregnancy Outcome

At present, obstetricians mainly decide the timing and method of terminating pregnancy based on the condition of the mother and fetus and the gestational age.

However, there are still some cases that choose to terminate pregnancy immediately due to fear of fetal demise.[8,9,12,16,18–21,23–26,36,41,44,50,55,56,60,65,66] There is currently one reported case involved a cesarean section at 25 weeks to terminate a pregnancy due to UVTE diagnosed by ultrasound.[26]

Zhu et al[9] reported 8 cases of UVTE with viable fetuses, with a gestational age ranging from 31+2 weeks to 38+1 weeks. All cases terminated pregnancy immediately after diagnosis, with 5 cases showing the result of non-stress test is not satisfied. Wei et al[8] reported 3 cases in which UAT was detected by ultrasound and fetal hypoxia on fetal heart monitoring resulted in immediate emergency cesarean section. The gestational ages were 32+ weeks, 35+ weeks, and 37+ weeks respectively. Jiang et al reported 31 cases of prenatal diagnosis of UAT, 9 of which chose to terminate the pregnancy immediately after diagnosis, and the average gestational age of the termination was 35.9±2.9 weeks.[66] In addition, there are a large number of case reports in which UVTE was diagnosed before delivery, the fetus was still viable, and the pregnancy was immediately terminated.[12,16,18–21,23,25,26,36,41,44,50,55,56,60,65] Among the 262 cases of UVTE in this review, only 40 cases are found by prenatal ultrasound to have UVTE and the fetus is in a viable state which choose to terminate the pregnancy immediately after diagnosis. The relevant data are shown in Table 4.

On the other hand, there are also currently a large number of reports of cases in which pregnancy continued after diagnosis of UVTE, especially patients with smaller gestational age.[8,13–15,18,29–32,40,43,47,48,54,57–59,61,62] Patient currently

Table 4 Cases Chose to Terminate Pregnancy Immediately After Discovered UVTE

Types of UVTE	No. of Cases and Reference	Gestational Age Weeks	Delivery Method	Newborn Condition
UAT	9[66]	35.9±2.9	Cesarean Section	Newborn alive(all)
	4[8]	32+	Vaginal delivery	Newborn Transfer to NICU; Alive
		35+	Vaginal delivery	Newborn Transfer to NICU; Alive; Neonatal Sepsis
		36	Vaginal delivery	Newborn with FGR Transfer to NICU
		37+	Vaginal delivery	Newborn alive
	2[9]	35 + 5	Cesarean Section	Newborn alive
		39	Cesarean Section	Newborn alive
	1[18]	38	Cesarean Section	Newborn alive
	1[20]	38	Cesarean Section	Newborn alive
	1[21]	37	Cesarean Section	Newborn Transfer to NICU; Alive
	1[24]	32	Cesarean Section	Newborn alive
	1[26]	25	Cesarean Section	Newborn Transfer to NICU; Alive Neonatal atrophy in the cerebrum and cerebellum
	1[65]	35+6	Cesarean Section	Newborn alive

(*Continued*)

Table 4 (Continued).

Types of UVTE	No. of Cases and Reference	Gestational Age Weeks	Delivery Method	Newborn Condition
UVT	4[9]	31+2	Cesarean Section	Newborn Transfer to NICU; Alive
		38 + 1	Cesarean Section	Newborn alive
		39 + 5	Cesarean Section	Newborn alive
		39 + 6	Cesarean Section	Newborn alive
	2[12]	40+1	Vaginal delivery	Newborn alive
		41	Vaginal delivery	Newborn alive
	1[16]	40	Vaginal delivery	Newborn alive
	1[19]	35	Cesarean Section	Newborn alive
	1[23]	32+3	Cesarean Section	Newborn with FGR Transfer to NICU; Alive
	1[36]	32	N/A	N/A
	1[41]	34	Cesarean Section	Neonatal asphyxia and death (lung hemorrhage)
	1[44]	31+4	Cesarean Section	Newborn Transfer to NICU; Alive
	1[50]	37	Cesarean Section	Newborn alive
	1[55]	32	Cesarean Section	Newborn alive
	1[56]	41	N/A	N/A
The site of embolism is unknown	2[9]	32 + 6	Cesarean Section	Newborn alive
		35+3	Cesarean Section	Newborn with FGR alive
	1[25]	40	Vaginal delivery	Newborn with FGR alive
UVT combined with one UAT	1[60]	39	N/A	N/A

diagnosed with UVTE who choose expectant observation extend gestational age up to 13 weeks with gestation age of 23 weeks when UAT was diagnosed.[61] The minimum observation period for diagnosis of UVTE was only 2 days. The patient was diagnosed with UAT at 36+5 weeks of gestation. Unfortunately, the patient eventually suffered stillbirth at 37 weeks of gestation.[18] Meanwhile, after being diagnosed with UVT, patients who chose expectant observation extended gestation up to 3 weeks + 5 days.[30] In the shortest case, stillbirth occurred after only 3 days of observation.[54]

What deserves our attention is that some obstetricians try to treat UVTE with LMWH to reduce the occurrence of fetal adverse events.[8,61,66] Wei et al[8] reported 2 cases of UAT treated with low molecular weight heparin. The condition was both found at gestational age of 24^{+}weeks, and the gestational age at termination of pregnancy was 34^{+}weeks and 35^{+}weeks, respectively. Both newborns survived and were combined with FGR. Wang et al[61] reported a retrospective study on UAT. 10 patients were treated with LMWH after UAT was detected by ultrasound. The average gestational age when diagnosed was 29.9±3.7 weeks, the average gestational age when pregnancy was terminated was 36.3±2.5 weeks, and the average gestational age extended was 6.4±4.2 weeks. Among these 10 cases, 5 cases had fetal distress and 5 cases were combined with FGR, but all fetuses were born alive. Wu et al[7] reported 30 cases of prenatal ultrasound suggesting UVTE. Among them, 22 cases with gestational age more than 32 weeks had immediate termination of pregnancy, and 8 cases with gestation age less than 32 weeks chose expectant observation. However, there were no significant differences in fetal outcomes between the immediate termination group and the expectant observation group. Jiang et al[66]

retrospectively analyzed 21 cases of expectant observation with extended gestational age after diagnosis of UAT, including 10 cases treated with LMWH and 11 cases simply observed with no other treatment. The diagnosed gestational age in the LMWH treatment group was 31.4±3.7 weeks, the median gestational age extended was 7.9 weeks (ranging from 4.6 to 9.4 weeks), and all newborns were born alive. In the expectant observation group, the median gestational age extended was only 0.6 weeks (ranging from 0 to 1.0 weeks) and 2 cases of fetal demise; comparing the gestational age extended, the difference between the two groups was statistically significant (P=0.002). Among the 262 cases of UVTE in this study, only 58 cases are found by prenatal ultrasound to have UVTE and the fetus is in a viable state which choose to observe. The relevant data are shown in Table 5.

Table 5 Cases Chose to Wait for Fetal Development After Discovered UVTE

Types of UVTE	No. of Cases and Reference	Gestational Age Weeks		Delivery Method	Newborn Condition
		Found	Termination		
UAT	1[5]	32+4	34+3	Cesarean section	Newborn alive
	4[8]	24+	37+	Vaginal delivery	Newborn alive
		30+	35+	Cesarean section	Newborn alive
		24+	34+	Cesarean section	Newborn Transfer to NICU; Alive; Neonatal jaundice
		24+	35+	Cesarean section	Newborn Transfer to NICU; Alive; Neonatal jaundice
	2[14]	37	37+6	Cesarean section	Newborn alive
		33+5	36+1	Cesarean section	Newborn alive
	2[15]	35+5	36+2	Cesarean section	Newborn alive
		31+3	37+4	Cesarean section	Newborn alive
	1[18]	36+5	37	Vaginal delivery	Stillbirth
	1[28]	32	34	Cesarean section	Newborn Transfer to NICU; Alive
	1[40]	29	37	Cesarean section	Newborn alive
	1[48]	28	34+6	Cesarean section	Newborn alive
	1[58]	27+1	34+3	Cesarean section	Newborn alive
	1[59]	33+2	36	Cesarean section	Newborn alive
	10[61]	23	38+6	Cesarean section	Newborn alive
		31	37+6	Cesarean section	Newborn alive
		26+1	34+4	Cesarean section	Newborn alive
		28+1	37+2	Cesarean section	Newborn alive
		28+2	38+3	Vaginal delivery	Newborn alive
		29+6	37+6	Cesarean section	Newborn alive
		30+5	32	Cesarean section	Newborn with FGR Transfer to NICU; alive
		31+3	37+1	Cesarean section	Newborn with FGR; alive
		31+3	31+6	Cesarean section	Newborn with FGR Transfer to NICU; alive
		31+6	37+4	Cesarean section	Newborn with FGR; alive
	1[62]	36+1	36+3	Vaginal delivery	Newborn alive
	21[66]	31.4±3.7	N/A	N/A	2 Newborns stillbirth

(*Continued*)

Table 5 (Continued).

Types of UVTE	No. of Cases and Reference	Gestational Age Weeks		Delivery Method	Newborn Condition
		Found	Termination		
UVT	2[13]	27	29	Vaginal delivery	Stillbirth
		32	34	Vaginal delivery	Stillbirth
	1[29]	31	34+5	Cesarean section	Newborn alive
	1[30]	38	38+3	Cesarean section	Neonatal asphyxia and death
	1[31]	31	36	Vaginal delivery	Newborn alive
	1[32]	25	27	Cesarean section	Newborn Transfer to NICU; Alive
	1[43]	25	27+3	Vaginal delivery	Newborn with FGR; Stillbirth
	1[47]	23+3	25+5	Vaginal delivery	Stillbirth
	1[54]	32	32+3	Vaginal delivery	Stillbirth
Two UAT	1[58]	30+4	31+1	Cesarean section	Newborn Transfer to NICU; Alive
UVT and one UAT	1[60]	28	32	Cesarean section	Neonatal asphyxia transfer to NICU; Alive

Regarding the management of UVTE patients who choose to observe, most scholars recommend increasing frequency of prenatal care, combined with fetal ultrasound and counting of fetal movements by the patient. Han et al[14] reported 2 cases diagnosed with UAT. The diagnosed gestational ages were 36 weeks and 33+5 weeks respectively. Fetal heart rate monitoring was performed twice a week and fetal biophysical scores and fetal middle cerebral artery peak systolic velocity were monitored once a week. And cesarean section was performed at 37+6 weeks of gestation and 36+1 weeks of gestation respectively, with extended gestational age about 2 weeks. Wu et al[7] shared their experience in the management of patients with UAT: daily home monitoring of fetal heart rate and weekly ultrasound examination to re-evaluate UAT status and hemodynamic status. When necessary, patients are hospitalized and oxygen, LMWH anticoagulation, magnesium sulfate, ritodrine hydrochloride or other tocolytic agents are used in doctor's discretion. Also, dexamethasone can be injected to accelerate the maturation of the fetal lungs. When fetal distress cannot be corrected, cesarean section should be immediately performed. In a case series of UAT reported by Wei et al[8] it was mentioned that when UAT patients choose to continue observation, it is recommended that the patient count fetal movements at home every day and perform fetal color ultrasound every week. Zhu et al[9] suggested that in patients who choose observation after discovering UVTE, in addition to observing various fetal ultrasound indicators and fetal movements, they should also combine electronic fetal heart rate monitoring and changes in maternal coagulation conditions, and they recommended that after completing treatment to promote fetal lung maturation, cesarean section should be performed to terminate the pregnancy to avoid adverse fetal outcomes.

Discussion

UVTE is a rare complication of pregnancy, which is currently difficult to discover through routine prenatal examination. UVTE includes UVT and VAT. Moreover, UVT can hinder blood flow, leading to fetal distress or even stillbirth.[2] UAT is a condition that ultrasound examination only shows one umbilical artery and blood flow signals during second to third trimester, even though the ultrasound examination can properly display two normal umbilical arteries during first and second trimester. UAT may lead to fetal distress, FGR, fetal organ infarction, neonatal cerebral palsy, maternal-fetal blood transfusion, and even stillbirth.[5,6] However, abnormal fetal heart rate monitoring, decreased fetal movements, changes in the number of umbilical arteries indicated by prenatal ultrasound, or thickening roots of umbilical blood vessels with slow blood flow can help us identify UVTE in the early stage.[7–9,11,12,18] Prenatal detection and diagnosis of UVTE, as well as implementing good pregnancy management, are particularly important for improving perinatal outcomes.

Incidence Rate of UVTE

At present, many scholars have reported the incidence rate of UVTE. A prospective study by Heifetz[2] showed that the incidence rate of UVTE during perinatal live birth was 1/1300, and the incidence rate of high-risk pregnancy combined with UVTE was 1/250[2]; UVT is more common than UAT; The incidence rate of UVT is 85%, and 15% of patients have UAT. Avagliano[1] found that the incidence rate of UVT was 10.1%, based on the autopsy of 317 fetuses of spontaneous intrauterine fetal demise, and 32 cases of UVT are found. The research of Wu et al[7] shows that the incidence rate of UAT is approximately 1 in 2524 deliveries, and only 3 (10%) of all 30 cases of UAT are found in the second trimester. Wei et al[8] discovered 8 cases of UAT in 8400 deliveries, which corresponds to an incidence rate of 0.8%. Zhu et al[9] investigated 29594 deliveries and found 10 cases of UVTE; Therefore, the incidence rate of UVTE was about 1 in 3000, with pure UVT approaching 50% and pure UAT in 30%. The incidence rate of UAT reported by Jiang et al[66] is 0.03% (31/99,651), which is consistent with that reported by Zhu et al.[9]

The results of 262 cases of UVTE counted in this study is different from the previous reports: The number of cases of UAT is more than that of UVT. The difference in this study from previous reports may be the reason that the multiple studies included in this study are retrospective studies and case reports on UAT, for there are less UVT being reported.

In addition, Heifetz[2] reported that the biological sex ratio of fetuses with UVTE was 1.74:1 (male: female). In 262 cases of UVTE in this study, for the first time, this paper records the biological sex of fetuses in each article one by one: there are 97 males and 76 females in total (86 cases fails to indicate sex of the fetus). Male fetuses slightly outnumbers female fetuses (1.28:1), which is basically consistent with the report of Heifetz.[2]

Finally, a total of 106 stillbirths are identified in this study. Among them, the number of UVT is significantly higher than that of UAT, as shown in Table 2, and the data also supports Heifetz's[2] view that UVT is more likely to cause stillbirth.

Diagnostic Methods for UVTE

With the improvement of ultrasound diagnostic technology and the increasing popularity of color ultrasound, growing cases of UVTE is discovered by ultrasound doctors and obstetricians. When color Doppler ultrasound detects a decrease in blood flow velocity accompanied by umbilical vein varix, UVT should be positively considered.[30,55–57]

Above all, UAT mostly occurs in the third trimester, and its ultrasound images normally show as "orange grasped with one hand".[7,15,44,66] This study reviewed all 262 cases and found that only 15 cases had abnormal fetal movement,[9,50,54,61,64,66] while 15 cases had suspicious or unresponsive fetal heart rate monitoring.[8,12,14–16,44,46,58,60,61] This indicates that when UAT occurs, because of the compensatory effect of another normal umbilical artery or incomplete closure of the vascular lumen, most pregnant people do not experience typical fetal distress symptoms such as reduced fetal movement, all of which suggests the importance of ultrasound examination in the diagnosis of UAT.

Pregnancy Monitoring and Perinatal Management of UVTE

The current difficulty in clinical management is that once UVTE is diagnosed, the management of pregnant people in preliminary gestational age is in a dilemma: what troubles obstetricians is the issue of iatrogenic premature birth caused by choosing immediate termination of pregnancy, while stillbirth occurred during continued pregnancy. Therefore, it is particularly necessary and practical to continue pregnancy, accurately monitoring fetal conditions, and avoid adverse outcomes such as stillbirth. However, there is no clinical guide or expert consensus for the diagnosis and treatment of this condition currently.

Some studies had shown that when UVTE was found, cesarean section should be performed immediately to terminate the pregnancy.[9,54,59] In addition, Zhu et al[9] suggested that when UVTE is discovered, the pregnancy should be terminated by cesarean section immediately after completing treatment to promote fetal lung maturation. Wu et al[7] predicted adverse pregnancy outcomes in fetuses with gestational age less than 34.8 weeks or abnormalities in the umbilical cord itself by constructing a risk model. Wu et al[7] divided 30 cases of UAT into emergency treatment group (more than 32 weeks) and expectant observation group (less than 32 weeks). The effects on fetal outcomes were the same between the two groups. Therefore, Wu et al[7] suggested that when UAT was observed early, expectant observation can be chosen, and when UAT was observed at a later gestational age or even near term, it was recommended to terminate the pregnancy. In addition,

Wu et al[7] also believed that when the fetus had umbilical cord abnormalities, it should be treated positively. Jiang et al[66] divided 21 cases of UAT (gestational age when diagnosed: 31.4±3.7 weeks) into the LMWH group (10 cases) and the observation group (11 cases). The median length of gestational age extended in the LMWH group was 7.9 weeks (4.6~9.4 weeks), all newborns lived; the median length of gestational age extended in the observation group was 0.6 weeks (0~1.0 weeks), and 2 cases of fetal demise; compared with the extended gestational age, the difference was statistically significant (P=0.002). This suggested that when UAT was diagnosed at an early gestational age and with poor neonatal viability, starting LMWH anticoagulant therapy as early as possible may be an effective treatment method.

Therefore, assisting patients in choosing expectant management or immediate termination of pregnancy depends on the gestational age and fetal condition. When UAT is observed and the gestational age is less than 28 weeks and the estimated fetal viability is poor, comprehensive consideration (such as neonatal complications and costs) should be taken into account and sufficient communication should be made with the patient and family before deciding whether to terminate the pregnancy immediately by cesarean section; When the gestational age is greater than 28 weeks and the fetal condition is relatively stable (fetal movement is normal, color ultrasound indicates normal peak systolic flow velocity of the fetal middle cerebral artery), expectant management can be chosen.

Attention should be paid to fetal movement during the observational period, and considering the effectiveness and safety, anticoagulation treatment by LMWH may improve pregnancy outcomes; Urgent cesarean section is recommended for near term and full-term patients. On the other hand, when UVT is observed, the fetal mortality rate is high.[2,13,43,47,54] Moreover, UVT is more likely to cause stillbirth during the expectant observation process.[13,43,47,54] Therefore, when the fetus experiences UVT, it is necessary to fully evaluate the fetal viability and neonatal care, and communicate with the patient and family members. When the fetus is expected to be viable, it is recommended to immediately terminate the pregnancy through cesarean section. However, due to the small sample size, further clinical verification is still needed.

Regarding the method of terminating pregnancy, pregnant people with UVTE are theoretically prone to adverse outcomes during vaginal delivery if the other unobstructed umbilical artery is compressed or secondary thromboembolism occurs. Therefore, pregnant people with UVTE usually choose cesarean section to terminate pregnancy. However, there are also many reports of successful vaginal delivery in UVTE cases. The delivery methods of 110 cases of UVTE with fetal survival are recorded, including 90 cases of cesarean, Fetal Related Risk Factors[5,7–9,12,14,15,18,20,21,23,24,27–30,34,35,38,40,41,44,48,50,55,58–66] 20 cases of vaginal delivery[7–9,12,16,18,22,25,31,33–35,38,39,42,45,49,61,62,66] with 2 cases of vacuum extraction[12,16] and 5 cases of induced labor.[8,31,62,66] Therefore, it can be inferred that UVTE is not an absolute indication for cesarean section, and vaginal delivery can be chosen. As such, the indications for cesarean section should be appropriately widened based on the maternal and fetal conditions.

Conclusion

After re-analyzing and summarizing the previous literature, this paper found that the ratio of male to female incidence of UVTE in the reported literature was 1.28:1. Maternal diabetes was the highest risk factor for UVTE. In addition, it was found that premature patients with UVTE could wait for fetal development by closely observing the fetal movement and regular ultrasound examination. If ultrasound examination in the second to third trimester reveals previously undiscovered single umbilical artery or umbilical vein varix, it is necessary to promptly consider UVTE. Pregnancy monitoring and perinatal management of UVTE need to be individualized, and the decision to expect treatment or terminate pregnancy depends on the gestational age and fetal condition. If it is found that the gestational age is near full term, emergency cesarean section can reduce adverse pregnancy outcomes, but UVTE alone is not an indication for cesarean section, and vaginal delivery can still be chosen.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study protocol was reviewed and decided by Medical Ethics Committee of West China Second University Hospital, Sichuan University that no ethics approval was required.

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