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Original Research

The Value of Antenatal Ultrasound in Diagnosing Anatomical and Morphological Abnormalities of the Fetal Umbilical Vein

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Abstract

Background: Normally, fetal umbilical vein (UV) starts from the capillary network in the chorionic villus and accompanies the umbilical artery (UA). After leaving the placenta, it courses along within the umbilical cord. As the embryo develops, the proximal segment of both the right and left umbilical veins obliterate, and the distal end of the left umbilical vein enters the liver. The microvessels passing through the liver gradually merge and communicate with the hepatic sinus to form the ductus venosus, which then drains into the inferior vena cava (IVC). UV anatomical and morphological abnormalities in complex and variable forms often lead to poor fetal prognosis. In light of this, a thorough prenatal ultrasound providing detailed information on UV abnormalities is potentially clinically significant. **Methods**: The sonographic features and clinical data of fetuses diagnosed with abnormal umbilical vein anatomy and morphology by antenatal ultrasonography from January 2016 to December 2021 in Sichuan Provincial Maternity and Child Health Care Hospital were retrospectively analyzed. **Results**: A total of 403 fetuses were included in the study. Among them, 318 cases were diagnosed with intrahepatic persistent right umbilical vein, and 44 cases experienced intracardiac malformations, 34 cases with extracardiac malformations, and 14 cases with both intra- and extracardiac malformations. Three cases had double umbilical veins; 1 case with intracardiac malformation and 1 case with extracardiac malformation. Eighty cases were diagnosed with umbilical vein varix (manifested as intra- or extra-abdominal vein varix or umbilical vein aneurysm); 2 cases with intracardiac malformations and 11 cases with extracardiac malformations. Two cases were diagnosed with umbilical vein stenosis, with neither of them combined with other malformations. Among the 403 fetuses, 86 received genetic testing with 8 of them confirmed with chromosomal abnormalities and the remaining 78 being normal. Of the 8 cases, 7 were diagnosed with persistent right umbilical vein (PRUV) and 1 had umbilical vein stenosis. As related to pregnancy outcomes, 386 fetuses had no obvious abnormalities being observed during the subsequent 2 years' follow-up and 17 cases were terminated due to serious malformations. **Conclusions**: Antenatal ultrasound assists in the accurate diagnosis of anatomical and morphological abnormalities of the umbilical vein. For cases with no other malformations or chromosomal abnormalities, a better prognosis can be expected and careful follow-up is required, whereas for those with severe malformations or chromosomal abnormalities, the prognosis is often poor. Prenatal ultrasound should provide careful examination to determine whether the fetal umbilical vein has normal anatomy and morphology, thereby supporting better prenatal outcomes.

Keywords: antenatal; ultrasound diagnosis; umbilical vein

1. Introduction

In recent years, the technological advances in antenatal ultrasound has improved the study of the fetal umbilical vein and has resulted in an increasingly detailed classification of umbilical vein abnormalities. According to previous studies [1–4], the anatomical and morphological abnormalities of the fetal umbilical vein mainly include intrahepatic persistent right umbilical vein (PRUV), double umbilical vein, umbilical vein varix, and umbilical vein stenosis. The abnormalities may be associated with failure of vein closure, anastomotic or neovascular agenesis, secondary venous occlusion, or maternal hemodynamic changes [5,6]. In this study, a total of 45,623 patients were seen between 2016 and 2021, among which 403 were detected with umbilical vein abnormalities. The percentage was 0.8%. We analyzed the sonographic features and clinical data of 403 fetuses with anatomical and morphological abnormalities of the umbilical vein, aiming to provide sonographers and clinicians with more knowledge about this series of disorders for improved patient informed consent and better clinical decision-making.

2. Methods

2.1 General Data

The sonographic features and clinical data of 403 cases of fetuses diagnosed with anatomical and morphological abnormalities of the umbilical vein from January 2016 to December 2021 in Sichuan Provincial Maternity and Child Health Care Hospital were retrospective analyzed. The pregnant women were 19–42 years old, with

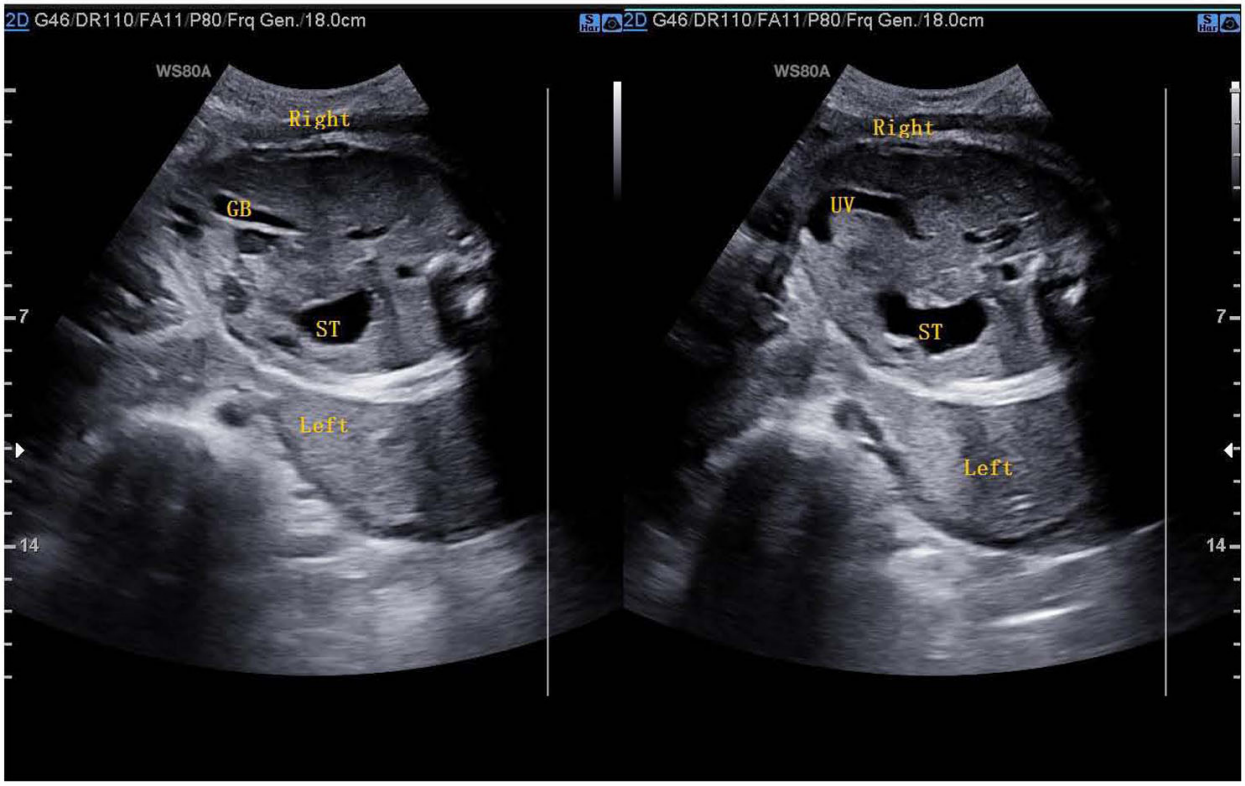

Fig. 1. Intrahepatic persistent right umbilical vein (PRUV). The left image shows the location of the gall bladder between the umbilical vein and the gastric bubble in a two-dimensional ultrasound image; the right image shows that the portal sinus curves towards the gastric bubble in a two-dimensional ultrasound image. UV, umbilical vein; ST, stomach; GB, gallbladder.

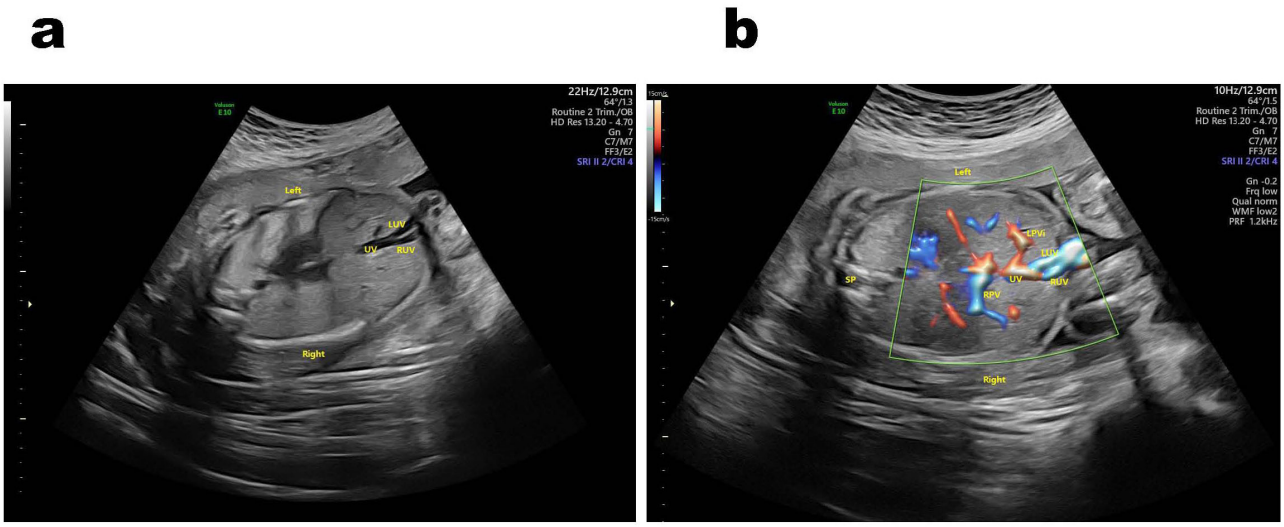

Fig. 2. Case No. 1 of double umbilical veins. The two umbilical veins converged to form a common umbilical vein after entering the liver, which partly connected with the left portal vein, and partly with the ductus venosus and then drained to the proximal end of the inferior vena cava. (a) Two-dimensional ultrasound images. (b) Color Doppler images. SP, spine; UV, umbilical vein; RUV, right umbilical vein; LUV, left umbilical vein; RPV, right portal vein; LPVi, left inferior portal vein.

a mean age of (30.6 ± 8.2) years; the gestational age determined by ultrasound ranged from 20–33 weeks, with a mean of 23.3 ± 6.1 weeks. Inclusion criteria: healthy pregnant women who underwent fetal systematic and targeted examinations at 22–30 weeks of gestation during which the fetus was found with anatomical and morphological abnor-

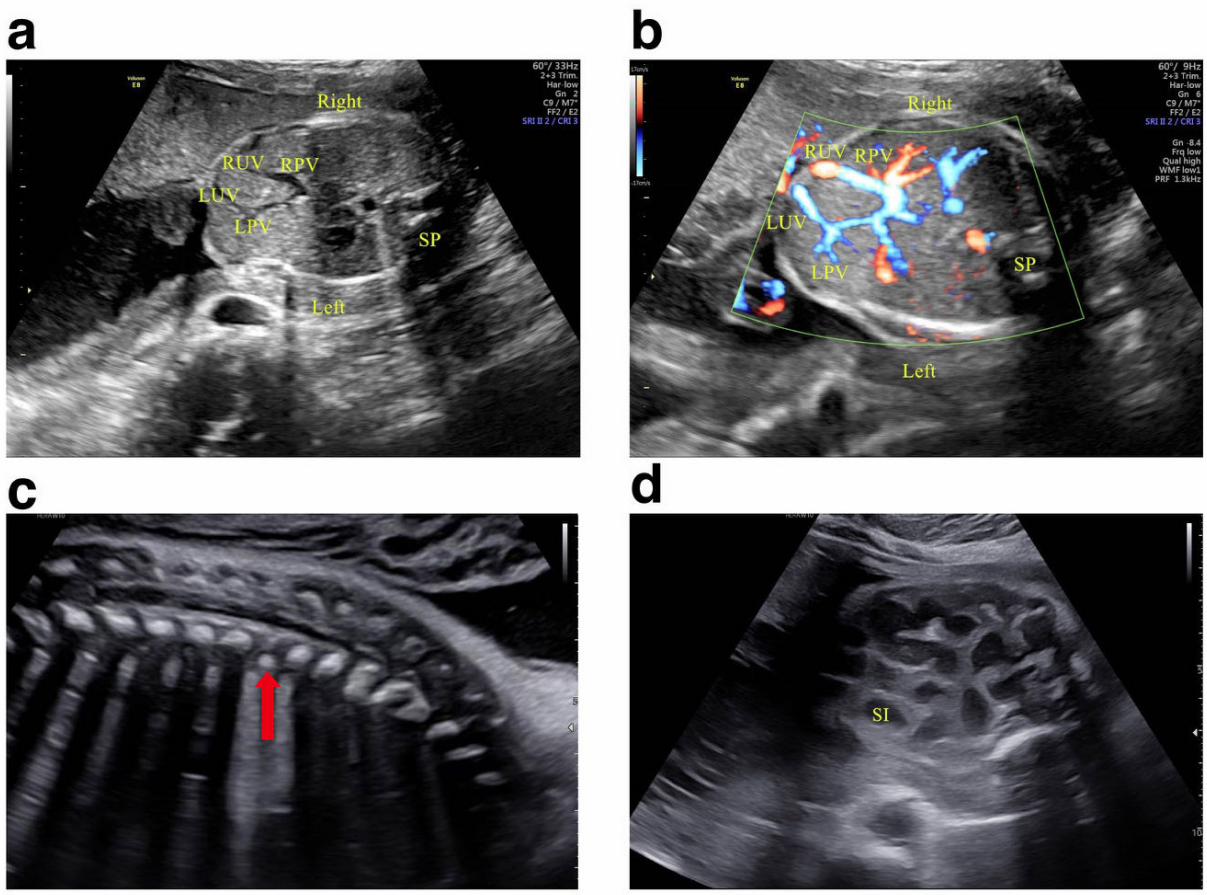

Fig. 3. Case No. 2 of double umbilical veins. The umbilical vein gave off one left and one right branch after entering the liver. The right one connected to the right portal vein and the left one connected to the left portal vein, which converged at the portal sinus and then through the ductus venosus draining to the proximal end of the inferior vena cava. (a) Two-dimensional ultrasound images. (b) Color Doppler images. (c) Hemivertebra (where the arrow points). (d) Small intestine dilation. SP, spine; RUV, right umbilical vein; LUV, left umbilical vein; LPV, left inferior portal vein; RPV, right portal vein; SI, small intestine.

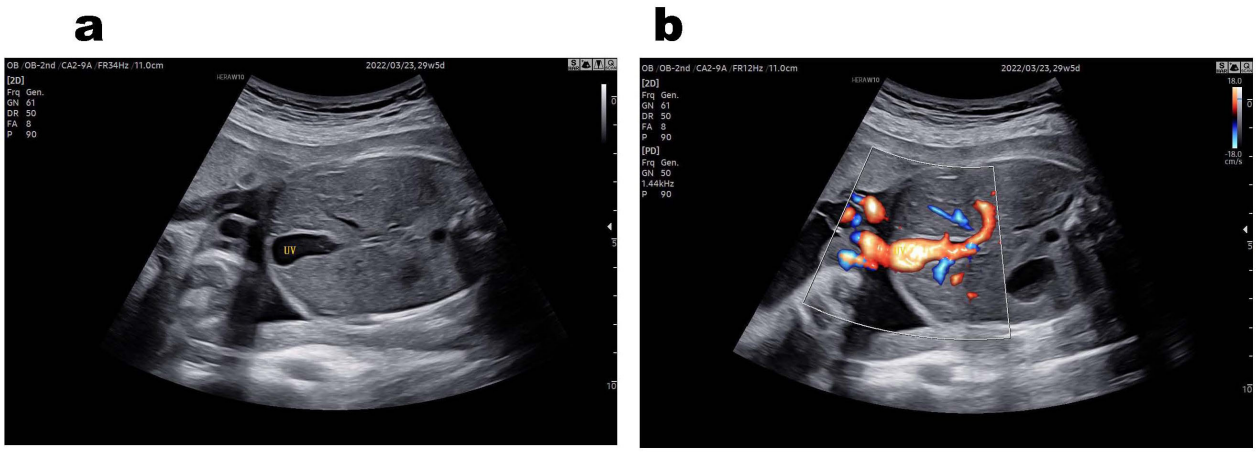

Fig. 4. Intra-abdominal umbilical vein varix. (a) Two-dimensional ultrasound images. (b) Color Doppler images. UV, umbilical vein.

malities of the umbilical vein. Exclusion criteria: cases with very poor ultrasound image quality due to thick abdominal subcutaneous fat. The study was approved by the Medical Ethics Committee of Sichuan Provincial Maternity and Child Health Care Hospital (Approval No. 20220330-035) and all pregnant women signed the informed consent form.

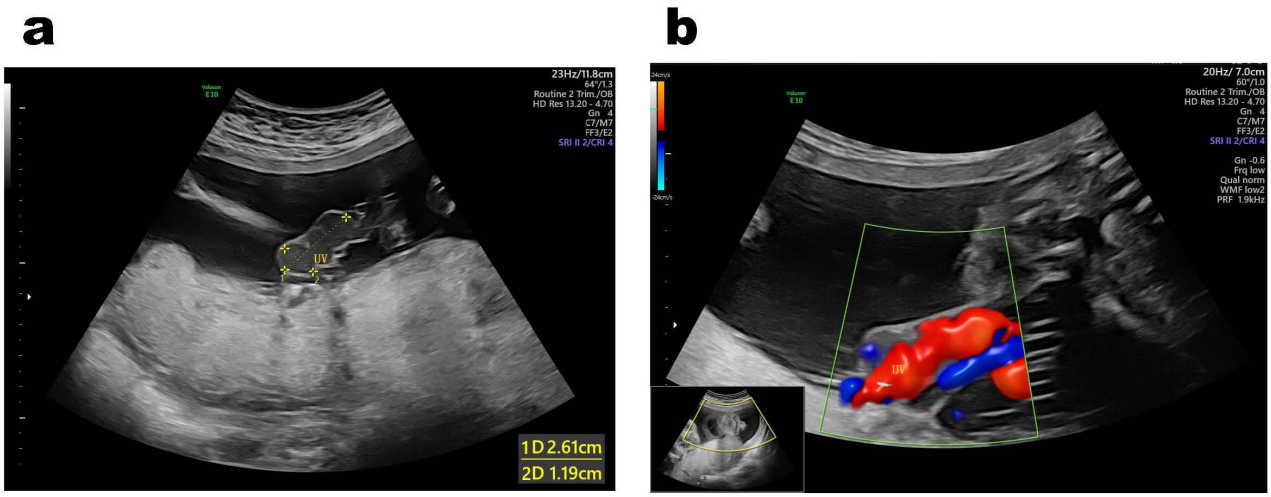

Fig. 5. Extra-abdominal umbilical vein varix. (a) Two-dimensional ultrasound images. (b) Color Doppler images. UV, umbilical vein.

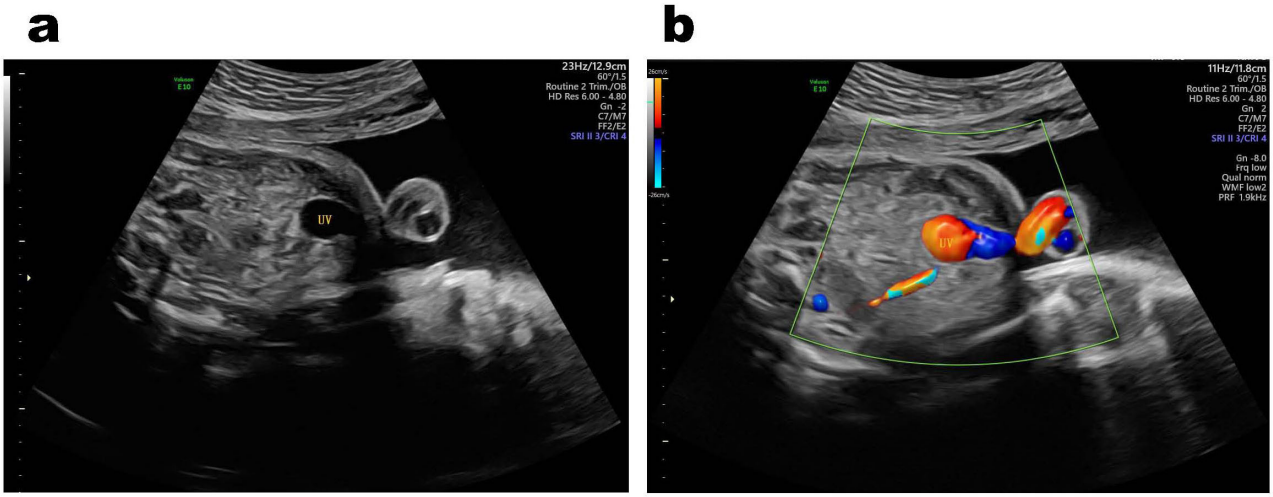

Fig. 6. Umbilical vein aneurysm. (a) Two-dimensional ultrasound images. (b) Color Doppler images. UV, umbilical vein.

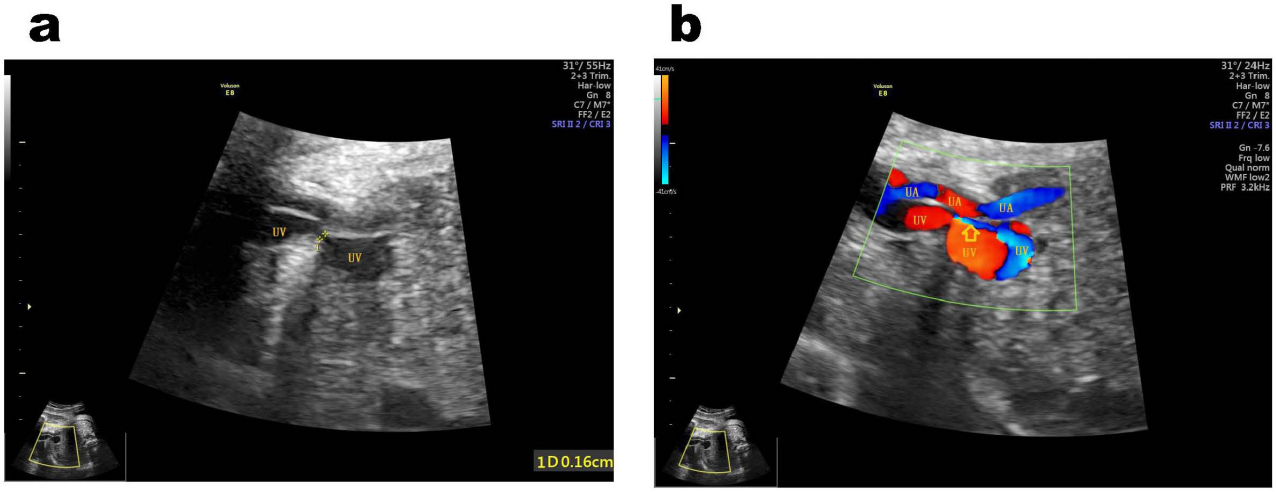

Fig. 7. Umbilical vein stenosis in the middle segment. (a) Two-dimensional ultrasound images. (b) Color Doppler images. UV, umbilical vein; UA, umbilical artery.

Table 1. Intra- and extracardiac malformations of the 403 fetuses with UV abnormalities and their outcomes.

Type/Case No.	Intracardiac malformations	Extracardiac malformations	Pregnancy outcome
Intrahepatic persistent right umbilical vein (PRUV)			
1	Persistent truncus arteriosus, Single Ventricle (SV) and Single Atrium (SA)	Single umbilical artery	Induction
2	Transposition of the great arteries, ventricular septal defect (VSD)	Diaphragmatic hernia	Induction
3	Rhabdomyoma of the left ventricular wall	Absence of the hepatic segment of the inferior vena cava (IVC)	Born
4	Anomalous pulmonary venous connection (intracardiac), SV and SA	Single umbilical artery	Induction
5	Anomalous pulmonary venous connection (subcardial), atrioventricular septal defect (AVSD), pulmonary atresia	Absent radius with varus deformity of hand	Induction
6	Double outlet right ventricle	Vegetation outside the nostril	Induction
7	Double outlet right ventricle, mitral atresia, AVSD	Single umbilical artery, choroid plexus cyst	Induction
8	Fallot tetralogy pulmonary atresia double superior vena cava	Cleft lip and cleft palate multicystic dysplastic kidney with renal pelvis dilatation	Induction
9–10	Fallot tetralogy	None	Induction
11	Pulmonary atresia	Enlarged posterior fossa	Induction
12–13	Right-sided aortic arch with left-sided ductus arteriosus, aberrant left subclavian artery	None	Born
14–15	Coarctation of the aorta	None	Born
16–20	Tricuspid valve dysplasia	None	Born
21–27	AVSD	None	Born
28–30	VSD	None	Born
31	VSD	Microtia, microphthalmia, nasal bone dysplasia	Born
32–35	VSD	None	Born
36	Aberrant right subclavian artery	Talipes varus	Born
37–39	Aberrant right subclavian artery	None	Born
40	Double superior vena cava	Ventriculomegaly	Born
41	Double superior vena cava	Duplex kidney	Born
42	Mitral atresia	Intrahepatic calcification	Induction
43–44	Pericardial effusion	None	Born
45–46	None	Cleft lip and cleft palate	Induction
47	None	Cerebellar dysplasia	Induction
48–49	None	Pleural effusion	Born
50	None	Absence of both kidneys	Born
51–54	None	Nasal bone dysplasia	Born
55	None	Craniosynostosis	Born
56	None	Bilateral syndactyly	Born
57	None	Pelvic kidney	Born
58–61	None	Intrahepatic calcification	Born
62–64	None	Single umbilical artery	Born
65–318	None	None	Born
Double, UVs			
1	Persistent truncus arteriosus	Small intestine dilation with hemivertebra, single umbilical artery	Induction
2–3	None	None	Born
UV varix			

Table 1. Continued

Type/Case No.	Intracardiac malformations	Extracardiac malformations	Pregnancy outcome
1	VSD	None	Born
2	Pericardial effusion	None	Born
3–5	None	Renal pelvis dilatation	Born
6	None	Dacryocystocele with lateral ventricular dilatation	Born
7	None	Absence of both kidneys	Induction
8	None	Hypospadias	Born
9	None	Nasal bone dysplasia	Born
10–11	None	Left-sided IVC	Born
12	None	Enlarged posterior fossa	Born
13	None	Talipes varus	Born
14–80	None	None	Born
UV stenosis			
1–2	None	None	Born

2.2 Instruments and Methods

Sonographic examinations were performed using diagnostic color Doppler ultrasound machines such as GE E8 (GE Healthcare, Milwaukee, WI, USA), Samsung WS80A (Samsung Medison, Seoul, Korea), Philips EPIQ 7 (Philips Medical Systems, Bothell, WA, USA), Mindray Resona8S (Mindray, Shenzhen, Guangdong, China). Utilizing 1.0–8.0 MHz transabdominal volumetric probes. In a comprehensive and systematic manner, all fetuses were screened for any signs of malformations. The screening starts with observation of the visceral position: for normal cases whose gastric bubble nestles under the left hemidiaphragm, the probe was then inched along the extra-abdominal segment of the umbilical vein until its entrance in the fetal abdomen, following the intra-abdominal segment, its course, inner diameter, and anastomosis from the entrance to the ductus venosus were carefully observed, and when necessary its flow velocity was measured. For cases with abnormal visceral position, a thorough scan was performed for any sign of intra- or extracardiac malformations. According to the newly updated guidelines by the American Heart Association (AHA), American Institute of Ultrasound in Medicine (AIUM), the American Society of Echocardiography (ASE) [7]: a complete fetal heart examination encompasses the following views (please note that these are still-frame images): visceral situs, four-chamber view and four-chamber view with CD (color Doppler), septal view and septal view with CD, left ventricular outfow tract and left ventricular outfow tract with CD, right ventricular outfow tract and right ventricular outfow tract with CD, three-vessel and trachea view and three-vessel and trachea view with CD, aortic arch view and aortic arch view with CD, ductal arch view and ductal arch view with CD, bicaval view and bicaval view with CD, pulmonary veins return with CD, pulmonary veins spectral pulsed-wave Doppler (SPWD) (one left), pulmonary veins SPWD (one right), ductus venosus with CD, ductus venosus SPWD, mitral valve SPWD, tricuspid valve SPWD, aortic valve SPWD, pulmonary artery valve SPWD, aortic valve annulus biometry in systole, pulmonary valve annulus biometry in systole, tricuspid and mitral valve annulus biometry in diastole, umbilical artery and vein with CD. The final diagnosis was made jointly by two physicians qualified in antenatal diagnosis after separate examinations. All cases were followed up.

For statistical analysis, SPSS 19.0 (IBM Corp., Armonk, NY, USA) was used for data analysis, and the categorical data is expressed in rates.

3. Results

3.1 Sonographic Features of the Anatomical and Morphological Abnormalities of the Fetal Umbilical Vein

The antenatal ultrasound detected the following: ① a total of 318 cases of intrahepatic PRUV where the right umbilical vein entered the liver and connected with the right portal vein, the portal sinus curved towards the gastric bubble, and the gallbladder was located between the umbilical vein and the gastric bubble in all 318 cases (Fig. 1); ② 3 cases of double umbilical veins with 1 case having two umbilical veins that merged into one common umbilical vein after entering the liver, partly connected to the left portal vein, and partly to the ductus venosus which drained to the proximal end of the inferior vena cava (Fig. 2) while in the other 2 cases, the umbilical vein gave off two branches after entering the liver, with the right branch connecting with the right portal vein, and the left branch with the left portal vein, which converged at the portal sinus and drained through the ductus venosus into the proximal end of the inferior vena cava (Fig. 3); ③ 80 cases of umbilical vein varix where the course of the umbilical vein and its connections with the portal vein after entering the liver was normal, while the varices were found in the intra- or extra-abdominal segment (Figs. 4, 5 respectively) as well as in the form of a venous

Table 2. Genetic testing of the 403 fetuses with UV abnormalities.

Type/No.	Whether did the genetic testing (Yes/No)	Results
Intrahepatic PRUV		
1	Yes	Trisomy-18
2	Yes	371.8 kb of duplication at 10q26.3
3	Yes	A ~17.19 kb of heterozygous deletion at 16p13.3; thalassemia
4	Yes	21pstk+
5	Yes	T (3; 9) (q21; p24)
6	Yes	1q43 duplication
7	Yes	357.5 kb of duplication at 1q21.1
8–78	Yes	Normal
79–318	No	/
Double UVs		
1–2	Yes	Normal
3	No	/
UV varix		
1–4	Yes	Normal
5–80	No	/
UV stenosis		
1	Yes	Trisomy-21
2	Yes	Normal

aneurysm (Fig. 6); ④ 2 cases of stenosis in the middle section of the umbilical vein with the image showed narrowing of the middle section of the umbilical vein (Fig. 7) with a reduced inner diameter of 1.2 mm and 1.6 mm and a blood flow velocity of 98.35 cm/s and 109.65 cm/s respectively. Images obtained one month later showed that the inner diameters were about 4.2 mm and 4.5 mm and the blood flow velocities were 39.62 cm/s and 35.89 cm/s respectively.

3.2 Abnormal Case Combinations with Intra- or Extracardiac Malformations and Pregnancy Outcomes

For all the abnormal cases, their pregnancy outcomes were as follows: ① for the 318 fetuses of intrahepatic PRUV, 44 cases had intracardiac malformations, 34 cases with extracardiac malformations, and 14 cases with both intra- and extracardiac malformations. Eventually, 303 fetuses were born and the other 15 were underwent labor induction due to severe deformities; ② for the 3 cases of double umbilical veins, 1 case had an intracardiac malformation and 1 case with extracardiac malformation. Eventually, 2 fetuses were born and one underwent labor induction due to severe malformation; ③ for the 80 cases of umbilical vein varix, 2 cases had intracardiac malformations and 11 cases with extracardiac malformation. Eventually, 79 cases were born and the other 1 case underwent labor induction due to severe malformations; ④ for the 2 cases of umbilical vein stenosis, no malformations were observed. Both cases were born and followed up for 2 years, and no obvious abnormalities were seen (Table 1).

3.3 Genetic Testing

Among the 403 fetuses, 86 received genetic testing with 8 of them confirmed with chromosomal abnormalities and the remaining 78 being normal. Of the 8 cases, 7 were diagnosed with PRUV and 1 with umbilical vein stenosis. See Table 2.

4. Discussion

4.1 Embryonic Development of the Umbilical Vein

The umbilical vein imports oxygen and nutrients from the mother and delivers them to the fetal circulatory system via the fetal liver and the inferior vena cava in order to support the growth and development of the fetus. The umbilical vein originates from the chorionic villus, starts from the placenta and enters the embryo via the umbilical cord [8]. The umbilical vein initially exists as a paired vessel consisting of the right and left umbilical vein during early fetal life; then during the 4th week of fetal development, the proximal ends of the two veins gradually obliterate, while the distal end of the left one persists and enlarges to accompany the umbilical artery. In the 6th week of the development, the umbilical vein enters the abdominal cavity of the fetus and a portion of it drains into the sagittal portion of the left portal vein curving like an L-shaped tube towards the right to supply nutrients to the liver; the other part of it drains into the ductus venosus and then to the proximal end of the inferior vena cava and then the right atrium [9,10]. Due to pressure changes after birth, the umbilical vein obliterates and its fibrous remnant forms a cord that becomes the round ligament of the liver [11].

4.2 Fetal Intrahepatic Persistent Right Umbilical Vein

The intrahepatic PRUV forms when the left umbilical vein atrophies while the right umbilical vein remains open, enters the abdominal cavity of the fetus, connects to the right branch of the portal vein, then joins to the proximal end of the ductus venosus which drains to the inferior vena cava [12]. The specific causes remain unclear but its occurrence might be related to lack of folic acid during early pregnancy, usage of teratogenic drugs, exposure to external pressure, or the formation of microthrombi. Ultrasound diagnosis of PRUV is based on the positional relationship of the umbilical vein, gallbladder, and gastric bubble, as well as the specific course of the umbilical vein as it joins the

portal vein. The diagnosis can be made in a standard transverse section of the abdomen with the following signs: the portal sinus curves in a tubular arc and points towards the left, the persistent right umbilical vein connects to the right portal vein, no umbilical vein connects to the left portal vein, and the gallbladder is located between the umbilical vein and the gastric bubble. All the 318 cases with PRUV in this study had the above ultrasound findings. It should be noted that the gallbladder can also be inferiorly located to the umbilical vein, a situation when missed diagnosis or misdiagnosis can easily happen. Therefore, we place emphasis on the observation of the pointing direction of the portal sinus and the site where the umbilical vein joins the portal vein. The determination of the position of the gallbladder can also be used to assist the diagnosis. Initial ultrasound findings of fetal intrahepatic PRUV invites a more detailed and comprehensive scan for any signs of combination with other malformations [13]. In this study, 28.6% (91/318) of fetuses were found with other malformations, mainly cardiovascular, urinary, skeletal, and neurological, a finding that is consistent with the literature [14]. Among the 318 cases, 303 fetuses were born, and the other 15 cases were terminated due to severe malformations. Intrahepatic PRUV without other malformations has a better prognosis and does not require any special management after birth; for those with other malformations, the prognosis mainly depends on the severity of the malformations.

4.3 Double Umbilical Veins

A four-vessel umbilical cord with two veins and two arteries occurs when both the left and right umbilical veins do not regress during embryonic development. This study found 1 case with 2 umbilical veins entering the liver and joining to form a common umbilical vein, which partly connected to the left portal branch and partly to the ductus venosus and then drained to the proximal end of the inferior vena cava. In the other 2 cases, the right umbilical vein connected to the right portal branch, and the left umbilical vein connected to the left portal branch, which converged at the portal sinus, then to the ductus venosus and eventually drained to the proximal end of the inferior vena cava. Numerical abnormalities of umbilical cord vessels are rare and often overlooked during antenatal ultrasound scans. A case with 4 arteries and 1 vein in the umbilical cord has been reported [15], and the mother had a bicornuate uterus, suggestive of the associations between the numerical abnormality of umbilical cord vessels and maternal uterine anomalies. Another case has been reported with 2 arteries and 2 veins on the fetal side of the umbilical cord with 2 arteries and 1 vein on the placenta side [16]. Considering the various aberrations, the examination of the number of umbilical cord vessels using color Doppler in the second trimester of pregnancy should include careful inspection of at least three locations: the umbilical cord's entrance to the fetal abdomen, the connection site in the placenta, and the floating segment of the umbilical cord. Double umbilical vein is often associated with other anomalies. In this study, 1 case was terminated due to combination with persistent truncus arteriosus, with the other 2 fetuses being born and their follow-ups for two years showed no obvious abnormalities. Better prognosis can be expected if there are no combined malformations [17].

4.4 Fetal Umbilical Vein Varix

Umbilical vein varix can be seen in the form of intra-abdominal umbilical vein varix, extra-abdominal umbilical vein varix, and umbilical vein aneurysm [18,19], among which the intra-abdominal varix is the most prevalent while the extra-abdominal varix and umbilical vein aneurysm are rare [20]. Normally, the internal diameter of the intra-abdominal umbilical vein in normal fetuses grows proportionately with the increase of gestational age. The incidence of umbilical vein varix reported in the literature is about 1/400–1/2000, and the diagnostic criterion is that the widest inner diameter of the intra-abdominal umbilical vein is $\geq$9 mm or wider than half of the inner diameter of the neighboring extra-abdominal segment [21,22]. Umbilical vein varix may occur due to narrowing of the umbilicus, weakness of the wall, dilatation of the vein after compression, or partial loss of smooth muscle in the vessel wall [23]. Umbilical vein varix may lead to thrombosis due to altered hemodynamics and can also result in adverse outcomes such as hemolytic anemia, fetal heart failure, fetal edema and intrauterine fetal death [23–25]. Therefore, the presence of an umbilical vein varix requires close ultrasound follow-up throughout pregnancy [26]. In this study, umbilical vein varix combined with other malformations accounted for 16% (13/80), mainly being urinary, neurological, and cardiovascular malformations. Isolated umbilical vein varix may have a good prognosis, and when combined with other severe malformations can lead to adverse outcomes [27]. Among the 80 cases, 79 fetuses were born and 1 case was terminated due to combination with bilateral renal agenesis. Both intra- and extra-abdominal umbilical vein varix show laminar flow, and umbilical vein aneurysms mainly show turbulence, which can be easily confused with persistent extra-hepatic vitelline vein aneurysms [28], and therefore requires further careful examination to make a differential diagnosis.

4.5 Fetal Umbilical Vein Stenosis

Studies have reported [29] that umbilical vein blood flow increases exponentially throughout pregnancy, and the mean diameter of the umbilical vein at the umbilicus is about 2.8 to 5.9 mm at 20 to 40 weeks of gestation, whereas the mean flow velocity is 34 to 41 cm/s, which peaks at 39 weeks of gestation, and then decreases slightly until 42 weeks. If the internal diameter of the umbilical vein is smaller than the mean internal diameter for the gestational week and the blood flow velocity increases, the possibil-

ity of umbilical vein stenosis should be considered. In this study, the blood flow velocity was about 100 cm/s in cases of umbilical vein stenosis, possibly due to the compression from uterine contraction of the umbilical vein at the abdominal wall in middle and late pregnancy. During follow-up, the internal diameter of the umbilical vein gradually widened and the flow velocity gradually returned to normal. Studies have reported [30] that staphylococcus aureus infection may induce spastic contraction of the umbilical vein, thereby causing inadequate perfusion in the fetal umbilical vein. However, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection does not have a significant effect on umbilical vein blood flow and cardiac function in uncomplicated fetuses [31]. Studies have reported [32] that narrowing of the cord at the umbilicus is common during mid to late pregnancy, and that the flow rate in the cord in 21% of fetuses can increase up to 300%, suggestive of a reduction in the diameter of the umbilical cord by at least 50%. Umbilical vein stenosis in this study were not associated with intra- or extracardiac malformations. Umbilical vein stenosis is strongly associated with pregnancy complications including intrauterine fetal death, intrauterine growth restriction and oligohydramnios.

Literature reported [33] shows that premature rupture of the fetal membrane is significantly associated with vitamin D deficiency in maternal plasma and neonatal umbilical cord blood. Therefore, observation of umbilical vein stenosis requires close follow-up and vitamin D levels in umbilical vein blood should be measured if necessary.

5. Conclusions

Sonographers should pay close attention to the inner diameter, blood flow velocity and confluence of the intra-abdominal segment of the umbilical vein during antenatal ultrasonography. Detailed examination assists a precise diagnosis of the anatomical and morphological abnormalities of the umbilical vein. A full and detailed screening should be conducted for possibilities of other malformations. For cases with anatomical and morphological abnormalities of the umbilical vein but without other malformations, a better prognosis can be expected and they should be closely followed up. For cases undergoing fetal echocardiography, at least two guidelines recommend us to detect and assess the anatomy of umbilical vein with color Doppler (AHA, AIUM and ASE) [7]. Attention should be paid to the inner diameter of the umbilical vein, blood flow velocity, and the presence of thrombus in order to support appropriate antenatal management in a timely fashion.

Availability of Data and Materials

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

Author Contributions

CZ conceived the study and literature review and drafted the manuscript. JZ and HW analyzed the data interpreted data. CZ and LH proposed the idea, and designed the work. LH revised the manuscript and supervised the whole study. XZ helped CZ to collect and analyze the data. XZ also checked the spelling, corrected mistakes in grammar and revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study protocol was reviewed and approved by the Ethics Committee of the hospital of Sichuan Provincial Maternity and Child Health Care Audit Committee, Approval No.20220330-035. Written informed consent was obtained from participants prior to the study.

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Conflict of Interest

The authors declare no conflict of interest.

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