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Original Research

Clinical Value of Prenatal Ultrasound in the Diagnosis of Fetal Ductus Venosus Abnormality

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Abstract

Background: The fetal ductus venosus (DV) is an important vessel that connects the umbilical vein (UV) to the proximal end of the inferior vena cava (IVC). DV abnormality often leads to poor fetal outcome. Thus, careful prenatal ultrasound for the diagnosis of DV abnormality is of major clinical significance. **Methods**: We conducted a retrospective analysis of 166 cases diagnosed with DV abnormality by prenatal ultrasonography. The type of DV abnormality, aberrant DV connection, and combination with intra- and extra-cardiac malformations were evaluated, together with pregnancy outcomes and chromosomal anomalies. **Results**: Prenatal ultrasound screening revealed that 137 of the 166 fetal cases with DV abnormality showed an absence of ductus venosus (ADV) accompanied by aberrant drainage of the UV (119 cases with intrahepatic shunt of the UV and 18 cases were extrahepatic shunt of the UV). Another 27 cases showed aberrant DV connections (9 cases with intrahepatic shunt of the UV and 18 cases with extrahepatic shunt of the UV). In addition, one case showed DV bifurcation accompanied by extrahepatic shunt of the UV, and one case showed DV atresia accompanied by intrahepatic shunt of the UV. Moreover, 72 cases were also diagnosed with intra- or extra-cardiac malformations. A total of 105 fetuses were born, including 79 with ADV, 24 with aberrant DV connection, 1 with DV bifurcation, and 1 with DV atresia. These were followed up for an average period of 12 months (range 1 to 24 months). Liver-function tests and cardiac ultrasound were performed postpartum. Pregnancy was terminated in 61 cases due to severe fetal deformities, which were confirmed by pathological anatomy after abortion. Only 28 cases underwent chromosomal examination, of which one case was diagnosed with trisomy 21 and another with trisomy 18. **Conclusions**: Prenatal ultrasound can clearly show fetal DV abnormalities and aberrant connections, as well as associated intra- and extra-cardiac malformations. This procedure can therefore provide comprehensive support for the diagnosis of fetal DV abnormality. Careful attention should thus be paid during prenatal ultrasound examination in order to obtain valuable information for prenatal consultation and subsequent procedures and care.

Keywords: prenatal diagnosis; ultrasonography; ductus venous abnormality

1. Introduction

The fetal ductus venosus (DV) is an important vessel that connects the umbilical vein (UV) to the proximal end of the inferior vena cava (IVC). The DV functions to carry oxygen-rich blood from the UV to the heart while bypassing the fetal liver [1]. It is critical for proper fetal circulation [2]. Normally, the DV gradually gets larger as the allantois and placenta develop, and then undergoes obliteration after birth to form a fibrous remnant known as the ligamentum venosum [3]. However, failure to close the DV shunt postpartum can lead to many adverse antenatal and perinatal outcomes. Kagan *et al*. [1] reported the DV could be absent during pregnancy, or could drain at an atypical site. The different types of DV abnormality are classified according to the drainage site (intra- or extra-hepatic), and whether they bypass the liver [1,4,5]. These include several typical abnormalities such as bypass of the UV to the hepatic system and draining into the right atrium, connection of the UV directly to the IVC via iliac veins, and drainage of the UV into the portal circulation [6]. Based on a comprehensive and retrospective review of cases presenting at our hospitals, in the present study we report four main types of DV abnormality. These are absence of ductus venosus (ADV) accompanied by aberrant drainage of the UV into other vessels, aberrant connection of DV, DV bifurcation, and DV atresia. These types are slightly different to the above typically reported abnormalities.

Recently, Contratti *et al*. [6] reported that ADV might result from fetal hydrops, chromosomal aberration, and portal vein absence, and that it could lead to various disease states and adverse outcomes. Importantly, abnormal blood flow through the DV can increases the risk of cardiovascular defects, fetal growth restriction, renal anomaly, perinatal death, and aneuploidy [7]. These observations highlight the importance of diagnosing fetal DV abnormalities.

Achiron *et al*. [5] reported that the fetal umbilical-portal-systemic venous network is an integral system, with fetal DV abnormality often resulting in shunts (mainly in-

trahepatic and extrahepatic) of the UV. Thus, fetal DV abnormality should alert physicians to carefully examine the course and shunts of the UV. DV abnormalities can occur alone or in combination with other congenital malformations [8]. Prenatal ultrasonography is the procedure of choice for the diagnosis of fetal DV abnormality. The present retrospective study reviewed 166 recent cases of DV abnormality that were diagnosed using prenatal ultrasonography. We investigated the aberrant DV connection, the type of abnormality, and combination with intra- and extra-cardiac malformations, as well as the pregnancy outcomes and chromosomal anomalies. The current results may serve as a reference for prenatal ultrasound workers and clinicians.

2. Materials and Methods

2.1 Materials

This retrospective study evaluated 166 fetuses diagnosed with a DV abnormality by prenatal ultrasonography at the Chengdu University Hospital of Traditional Chinese Medicine and the Sichuan Provincial Maternity and Child Health Care Hospital from January 2014 to December 2020. Mothers were aged between 18–40 years, with a mean of 25.5 years (standard deviation of 9.2 years). The gestational age was between 11–24 weeks, with a mean of 18.0 weeks (standard deviation of 5.3 weeks), as assessed by obstetric ultrasonography. Two mothers had a ventricular septal defect (VSD), 4 had patent foramen ovale (PFO), 5 had an atrial septal defect (ASD), while the remaining 155 mothers reported no heart-associated conditions.

The inclusion criteria were: pregnant women in good health, with no special past or family history, and who underwent routine prenatal ultrasound examination of the fetus between 11 to 24 weeks of pregnancy in our hospital. The exclusion criteria were: pregnant women with severe congenital disease (not suitable for pregnancy), or with abdominal wall fat hypertrophy causing poor fetal image quality.

2.2 Apparatus

Color Doppler ultrasound was performed using GE Voluson E8 (GE Healthcare, Milwaukee, WI, USA), Samsung WS80A (Samsung Medison, Seoul, Republic of Korea), Philips EPIQ 7 (Philips Medical Systems, Bothell, WA, USA) and Mindray Resona 8S (Mindray, Shenzhen, Guangdong, China) instruments. This allowed comprehensive screening of the fetus using a trans-abdominal volumetric probe (probe frequency 1–8 MHz). If a DV abnormality was found, further checks were conducted on the UV, portal vein, hepatic vein and IVC, as well as for intra- or extracardiac anomalies. The final diagnosis was made by two qualified physicians after performing separate ultrasound examination of the same case. This study followed standard medical ethics principles.

2.3 Indicators of Fetal Ductus Venosus Abnormalities

The 166 cases were analyzed for the type of abnormality, aberrant DV connection, combination with intra- or extra-cardiac abnormality, pregnancy outcome, and chromosomal anomaly.

2.4 Ultrasound Images of Normal Fetal Ductus Venosus

Ultrasound image features of normal fetal DV were: (1) bright blood flow signals on color Doppler were observed for the expected site of DV; (2) spectral characteristics of the blood flow were an S-wave in ventricular systole, D-wave in ventricular diastole, and a-wave in atrial systole. In normal circumstances, the a-, S- and D-waves are above the baseline. However, the a-wave in the atrial systole can be absent or reversed in rare fetuses [9]. The 166 fetuses in the current study included 143 fetuses with a normal a-wave, two fetuses with an absent a-wave, and 21 fetuses with a reversed a-wave.

3. Results

3.1 Specific Types of Fetal Ductus Venosus Abnormalities, Their Connections, Combinations with Intra- or Extra-Cardiac Anomalies, and Correlations with Pregnancy Outcomes and Chromosomal Anomalies

Prenatal ultrasound screening revealed 166 cases with a DV abnormality. These were classified into four groups: (1) Aberrant connection of the UV in 137 cases. Of these, 119 had an intrahepatic shunt of the UV (110 cases connected to the portal vein and 9 to the hepatic vein) and 18 had an extrahepatic shunt (8 cases connected to the IVC and 9 cases connected directly to the right atrium, and one case joined to the hemiazygos vein of the left atrium). (2) Aberrant DV connection in 27 cases. Of these, 9 had an intrahepatic shunt of the UV (all with DV connected to the hepatic vein) and 18 had an extrahepatic shunt of the UV (9 cases of DV connected to the middle or distal end of the IVC, and 9 cases of DV connected to the coronary sinus [CS]). (3) One case with DV bifurcation accompanied by extrahepatic shunt of the UV. The DV started from the UV (portal sinus), bifurcated proximally (one arm to the CS and the other to the IVC) and then entered the right atrium. (4) One case with atresia of the DV accompanied by intrahepatic shunt of the UV, which was connected to the portal vein. Furthermore, of the 166 fetuses with a DV abnormality, 72 cases with intra- or extra-cardiac malformations were identified, of which 67 were diagnosed with ADV accompanied by aberrant drainage of the UV, and the other 5 with an aberrant DV connection.

Information was also collected on the pregnancy outcome for the 166 fetuses. A total of 105 infants were born without significant postnatal abnormalities. Trans-abdominal ultrasound confirmed the results were consistent with those of prenatal ultrasound diagnosis. Unfortunately, 61 pregnancies were terminated due to severe malformation, with 58 cases of ADV accompanied by aberrant drai-

Table 1. Profile of 166 cases with fetal DV abnormality.

Type	NO	Extra-cardiac malformation	Intra-cardiac malformation	Outcome
ADV with				
① Umbilical vein connected to portal vein				
-	1–14	Neck hygroma (NH) with overall cutaneous oedema	N/A	induction
-	15–25	NH with cutaneous oedema and hydrothorax	N/A	induction
-	26–31	NH with cutaneous oedema, hydrothorax	Persistent truncus arteriosus (PTA)	induction
-	32–34	NH with cutaneous oedema	single atrium and single ventricle (SA and SV)	induction
-	35–36	NH with cutaneous oedema	SA, SV and PTA	induction
-	37–39	NH with cutaneous oedema, omphalocele	N/A	induction
-	40–43	Increased NT	N/A	born
-	44	Neck hygroma	Tetralogy of Fallot and Persistent left superior vena cava (PLSVC) and coronary sinus dilatation	induction
-	45	Exencephaly	N/A	induction
-	46	Gastroschisis	N/A	induction
-	47	NH and spina bifida	N/A	induction
-	48	NH and situs inversus	N/A	induction
-	49	NH and talipes (right foot)	N/A	induction
-	50	Limb-body wall complex (LBWC) with left leg defect	N/A	induction
-	51	NH, holoprosencephaly with beaked nose	Atrioventricular septal defect and ventricular disproportion	induction
-	52	NH, omphalocele	Atrioventricular septal defect and ventricular disproportion	induction
-	53	Holoprosencephaly, talipes (left foot), and overlapping fingers of both hands	N/A	induction
-	54–110	N/A	N/A	born
② Umbilical vein connected to hepatic vein				
-	1	NH with cutaneous oedema	N/A	induction
-	2	Increased NT	N/A	born
-	3	NH with cutaneous oedema and hydrothorax	N/A	induction
-	4	Omphalocele, ulnar polydactyly (right hand), genitals abnormalities, rhizomelia	N/A	induction
-	5–9	N/A	N/A	born
③ Umbilical vein connected to inferior vena cava				
-	1	Nasal bone maldevelopment	N/A	born
-	2	Increased NT	N/A	born
-	3	NH with cutaneous oedema	single ventricle and PTA	induction
-	4	NH with cutaneous oedema and hydrothorax	N/A	induction
-	5–8	N/A	N/A	born
④ Umbilical vein connected to right atrium				
-	1	Bilateral talipes	PLSVC and coronary sinus dilatation	induction
-	2	Duodenal atresia	N/A	induction
-	3–4	Hydrothorax and Hydroperitoneum	N/A	born
-	5	Nasal bone maldevelopment	PLSVC and coronary sinus dilatation	induction
-	6–9	N/A	N/A	born

Table 1. Continued.

Type	NO	Extra-cardiac malformation	Intra-cardiac malformation	Outcome
⑤ Umbilical vein connected to left atrium				
-	1	Horseshoe kidney, hydrothorax and hydroperitoneum, intracranial cystic lesions	PTA, ventricular septal defect, ventricular disproportion and aberrant drainage of pulmonary veins	induction
Aberrant DV course				
① DV connected to hepatic vein				
-	1	Situs inversus	N/A	born
-	2	Interrupted IVC in the renal segment with dilated azygos vein	N/A	born
-	3	Esophageal atresia with tracheoesophageal fistula (TEF)	N/A	induction
-	4–9	N/A	N/A	born
② DV connected to the middle or distal part of IVC				
-	1	N/A	Atrioventricular septal defect and ventricular disproportion	induction
-	2–9	N/A	N/A	born
③ DV connected to CS				
-	1	N/A	Tetralogy of Fallot and cardiomegaly	induction
-	2–9	N/A	N/A	born
DV Bifurcation				
-	1	N/A	N/A	born
DV Atresia				
-	1	N/A	N/A	born

DV, ductus venosus; ADV, absence of ductus venosus; ADV with, ADV combined with the following 5 types of umbilical vein's aberrant connections; NT, nuchal translucency; IVC, inferior vena cava; CS, coronary sinus; N/A, not applicable.

nage of the UV, and 3 cases of aberrant DV connection. These were also confirmed by pathological anatomy following induced labor (Table 1).

Only 28 of the 166 fetuses underwent chromosomal analysis. Of these, one case was confirmed as trisomy 21, with ADV and the UV connected directly to the IVC. One other case was confirmed as trisomy 18, with the DV connected to the CS. The remaining 26 cases showed normal chromosomal findings.

3.2 Types of Fetal Ductus Venosus Abnormality and Their Ultrasound Features

Fetal DV abnormalities were due to aberrant drainage of the UV, aberrant DV connection, DV bifurcation, and DV atresia. Their features as observed by ultrasound were:

(1) ADV with the UV connected to the portal vein (Fig. 1a), the left hepatic vein (Fig. 1b-L), the middle hepatic vein (Fig. 1b-M), the right hepatic vein (Fig. 1b-R), the IVC (Fig. 1c), the right atrium (Fig. 1d), or the left atrium (Fig. 1e).

(2) Aberrant DV connection: the DV was not connected to the proximal end of the IVC, but rather to the hepatic vein (Fig. 2a), the middle part or the distal end of the IVC (Fig. 2b), or the CS (Fig. 2c).

(3) DV bifurcation (Fig. 3 and **Supplementary Video 1**): the DV starts from the UV (portal sinus) and then bifurcates proximally, with one arm to the CS and the other to the IVC, and then into the right atrium.

(4) DV atresia (Fig. 4): ultrasound images of the fetal abdomen show normal connection of the UV, but a thin, strongly echogenic band without any flow signal at the expected site of the DV with color Doppler.

4. Discussion

Fetal echocardiography requires well-trained operators and adherence to a pre-defined protocol. These are critical for ensuring high-quality cardiac scanning leading to improved detection rates and fetal outcomes [10]. Several scientific societies including the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), the American Heart Association (AHA), the American Institute of Ultrasound in Medicine (AIUM), and the Medicina Fetal Barcelona (BCN) recommend screening for the presence of DV as an essential part of fetal echocardiography [10]. The justification is that abnormal DV may result in poor fetal outcomes. Therefore, prenatal ultrasound for the diagnosis of fetal DV abnormality is of major clinical significance.

DV is an important vessel that connects the UV to the proximal end of the IVC. Its key role is to regulate blood flow and deliver blood containing oxygen and nutrients from the UV to the vital organs of the fetus, including the heart and cerebrum, thereby supporting fetal growth and development [11]. The various types DV abnormality may be associated with genetic mutations [12]. It has been reported previously that ADV may be accompanied by connection of the UV to the iliac vein, the left internal iliac artery, or the CS [13–15]. However, ADV cases in the present study showed connection of the UV to the portal vein, the IVC, the hepatic vein, the right atrium or the left atrium. Interestingly, the types of ADV reported previously were not found in the current study. This could be because the number of cases was limited, and hence further studies with more cases from a wider area are required. However, DV with aberrant connections to the middle part or distal end of the IVC, the CS, and the hepatic vein have been reported previously [16].

This study identified a novel case of DV bifurcation. The DV originated from the umbilical vein-portal sinus and bifurcated proximally, with one arm to the CS and the other to the IVC. This type is rare and may be associated with abnormal embryonic development. It is known that early embryonic development involves two UVs (left and right), with the left persisting and developing into the DV. However, if both of the veins persist it may result in abnormal DV branching.

Fetal DV atresia may be associated with hepatic fibrosis due to mastocytosis and to other systemic diseases [17]. Previous studies have shown that blood flow velocity does not affect DV morphology [18], which primarily reflects changes in cardiac blood volume. Any factor that affects the load into and out of the fetal heart, as well as vascular embryonic development, can alter DV structure and hence its hemodynamics. In addition, careful attention must be paid to DV closure, which leads to formation of the ligamentum venosum after birth. Within 1–2 weeks after birth, the UV closes to form the ligamentum teres hepatis, while the DV closes to form the venous ligament. It has been reported that familial liver disease is present in patients with the very rare condition of patent DV [19,20], suggesting it may be an inherited autosomal recessive disease. Hereditary patent DV should therefore be considered in patients who present with hepatic insufficiency and encephalopathy of unknown etiology.

A previous report showed that approximately one third of DV abnormalities are accompanied by aberrations in the portal venous system [21]. In the present work we observed intra- and extra-hepatic UV portosystemic shunting during examination for fetal DV abnormality. However, no further detailed ultrasound examinations were conducted on the fetal portal vein system. More recently, Karmegaraj *et al.* [22] reported on a fetus with extra-hepatic UV connected directly to the right atrium, ADV, and an intra-hepatic portal venous system (right and left portal veins). Moreover, the fetus showed clinical symptoms of Abernethy malformation type I. Considering the poor long-term outcome associated with an abnormal portal venous system, comprehensive ultrasound examination of the fetal portal vein system should be conducted in future whenever fetal DV abnormalities are encountered.

The occurrence of ADV in combination with partial

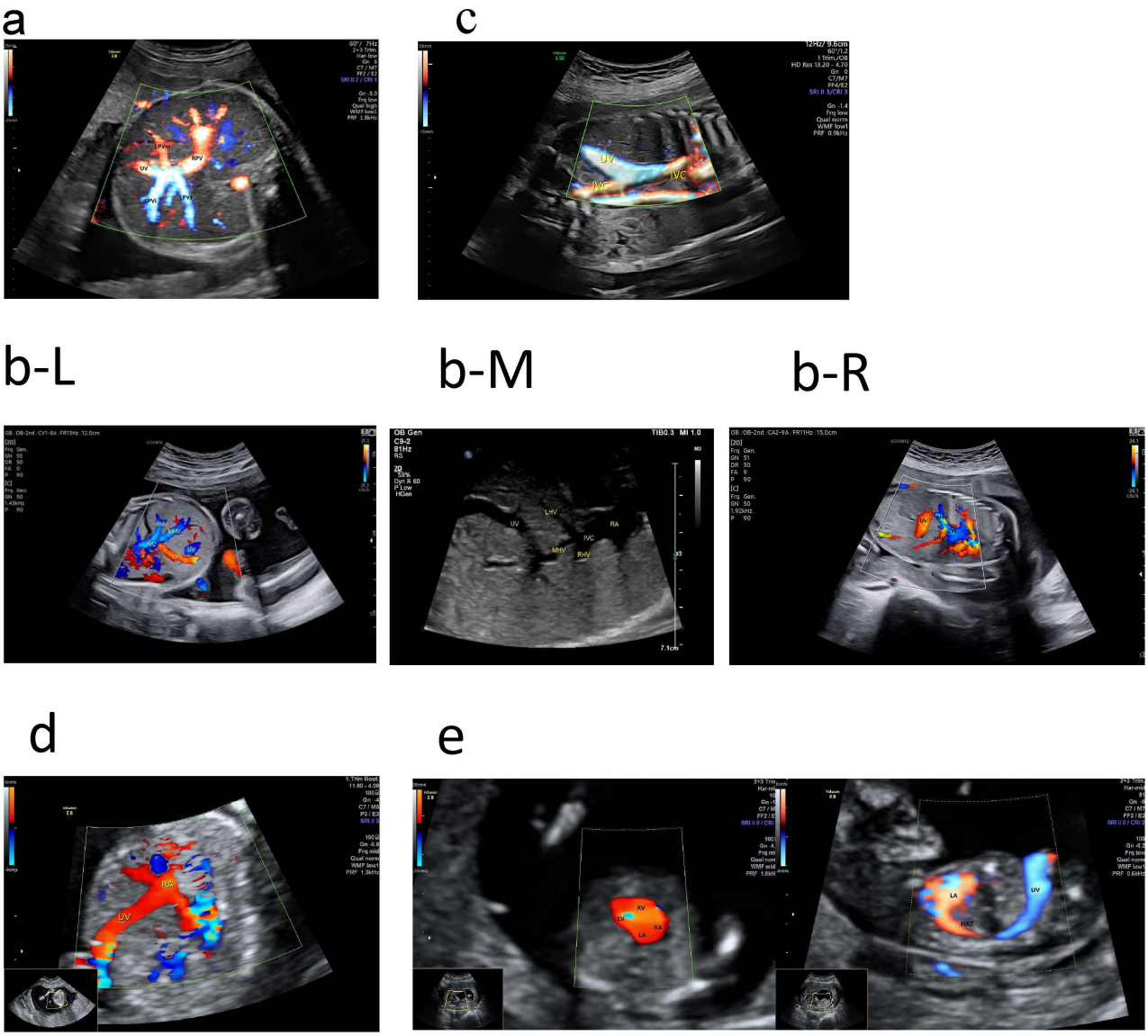

Fig. 1. Absence of ductus venosus (ADV) accompanied by aberrant drainage of the UV. (a) ADV with UV connected to the portal vein. (b-L) ADV with UV connected to the left hepatic vein. (b-M) ADV with UV connected to the middle hepatic vein. (b-R) ADV with UV connected to the right hepatic vein. (c) ADV with UV connected to the IVC. (d) ADV with UV draining directly into the right atrium. (e) ADV with UV connected to the hemiazygos vein and then draining into the left atrium. Left, four-chamber view showing the LA. Right, sagittal section showing drainage of the UV into the LA. UV, umbilical vein; LPVi, left portal vein inferior; LPVs, left portal vein superior; LPVm, left portal vein middle; RPV, right portal vein; IVC, inferior vena cava; LHV, left hepatic vein; RHV, right hepatic vein; MHV, middle hepatic vein; RA, right atrium; LA, left atrium; LV, left ventricle; RV, right ventricle; HAZ, hemiazygos vein.

loss of the liver [23] suggests there may be a close relationship between abnormal liver development and ADV. The latter reduces the supply of oxygenated blood to the liver, causing abnormalities in liver function and in the secretion of various differentiation factors, notably growth factors, cytokines and proteins. This may explain why abnormal liver development and ADV can occur simultaneously. Moreover, ADV often occurs in conjunction with fetal oedema, liver necrosis and calcification, congenital heart disease, chromosomal anomalies and aneuploidy [24]. In the current study, 72 of the 166 cases of fetal ADV occurred in combination with intra- and extra-cardiac malformations. ADV with aberrant connection of the UV and with malformations was the most common type of DV-related abnormality. Consistent with previous reports, the most commonly observed malformations were fetal hygroma and congenital heart diseases.

The decision to induce labor for DV abnormality depends mainly on the severity of the combined intra- and extra-cardiac malformations, the presence of oedema, and on the presence of chromosomal anomalies such as aneuploidy [25]. In the present study, 105 fetuses were born

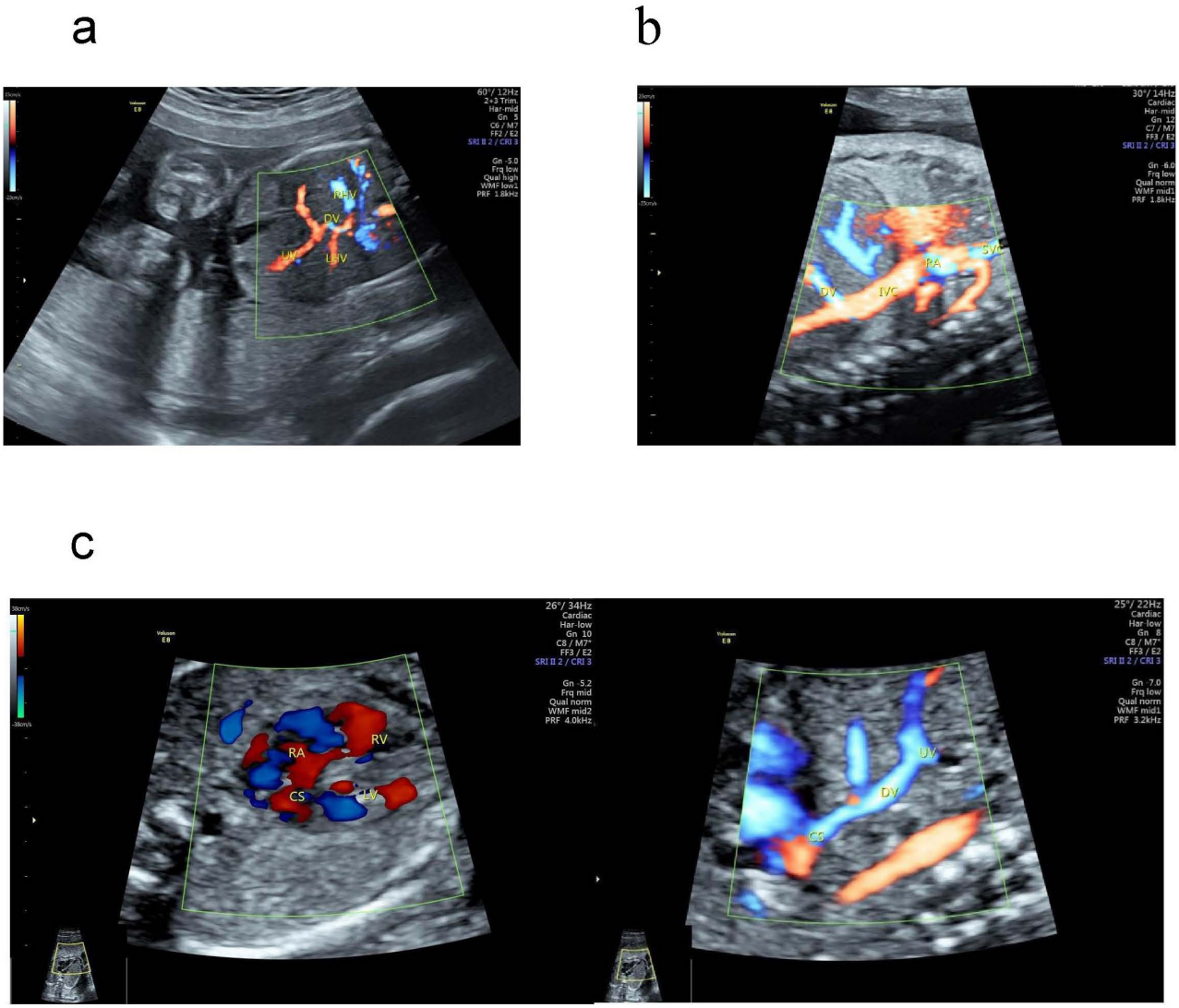

Fig. 2. Aberrant ductus venosus (DV) connections. (a) DV connected to the LHV. (b) DV connected to the distal end of the IVC. (c) Drainage of CS connecting the DV into RA. Left, four-chamber view clearly showing the connection of CS to RA. Right, sagittal view showing connection of the DV to CS. UV, umbilical vein; DV, ductus venosus; LHV, left hepatic vein; RHV, right hepatic vein; IVC, inferior vena cava; CS, coronary sinus; RA, right atrium; LV, left ventricle; RV, right ventricle.

and 61 pregnancies were terminated due to severe malformations. Fetuses with an intrahepatic shunt of the UV have good prognosis. Mild transient postpartum hyperammonemia was observed in two neonates, but resolved in the first week with symptomatic treatment. Furthermore, cardiac ultrasound examination showed no abnormalities. The prognosis of fetuses with an extrahepatic UV shunt is poor, and the healing time is long. In view of the importance of the UV drainage site in ADV, we conducted postnatal ultrasound examination of the portal system in 35 cases. Only one newborn was found to have partial absence of the portal vein, accompanied by high serum ammonia levels and abnormal liver function. This case was missed by prenatal ultrasound diagnosis. Fortunately, the shunt was closed via percutaneous catheterization, leading to gradual regeneration of collateral vessels and normalization of the serum ammonia level and liver-function tests at 2-years of age. The remaining 70 newborns did not undergo ultrasound examination of the portal vein system because they showed normal liver function and normal results with cardiac ultrasound.

During early and mid-pregnancy, DV abnormalities can cause widening of the hepatic and portal veins, resulting in increased neonatal mortality. In late pregnancy, the abnormalities result in less blood flow back into the proximal IVC and compensatory changes in cardiac function, resulting in better prognosis after birth. Cardiac ultrasound examination found that cases with extrahepatic shunts were more prone to developing cardiac decompensation. This was manifested mainly as cardiomegaly and tricuspid regurgitation, consistent with previous observations by Berg *et al*. [26]. Fetuses with abnormal DV may experience neu-

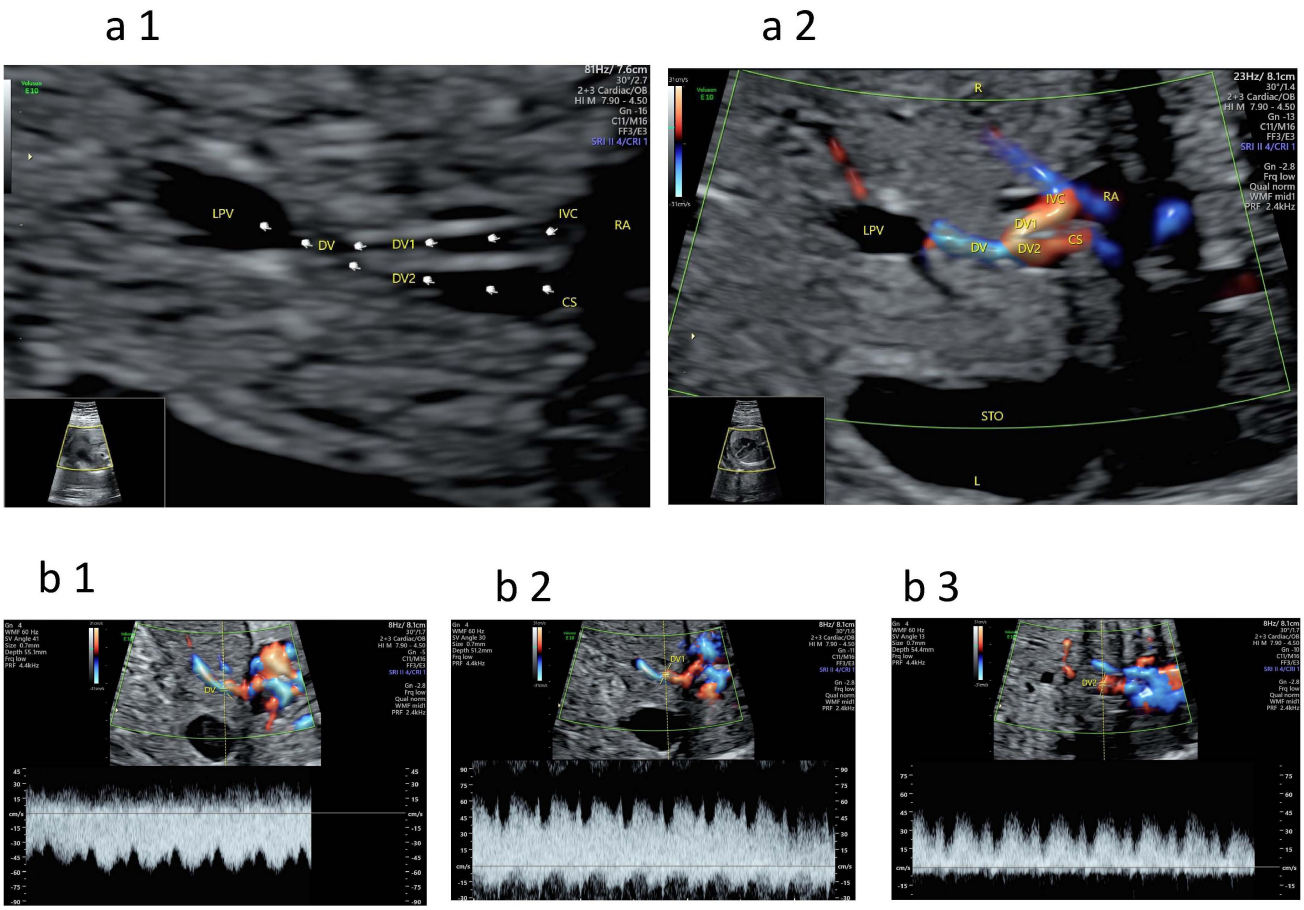

Fig. 3. DV bifurcation. (a1) Two-dimensional image of DV bifurcation. (a2) The DV starts from the UV (portal sinus), then bifurcates proximally (one arm to the CS and one to the IVC) before entering the right atrium. (b1) Blood flow spectral image of the DV. (b2) Blood flow spectral image of DV1. (b3) Blood flow spectral image of DV2. LPV, left portal vein; DV, ductus venosus; IVC, inferior vena cava; CS, coronary sinus; RA, right atrium; STO, stomach.

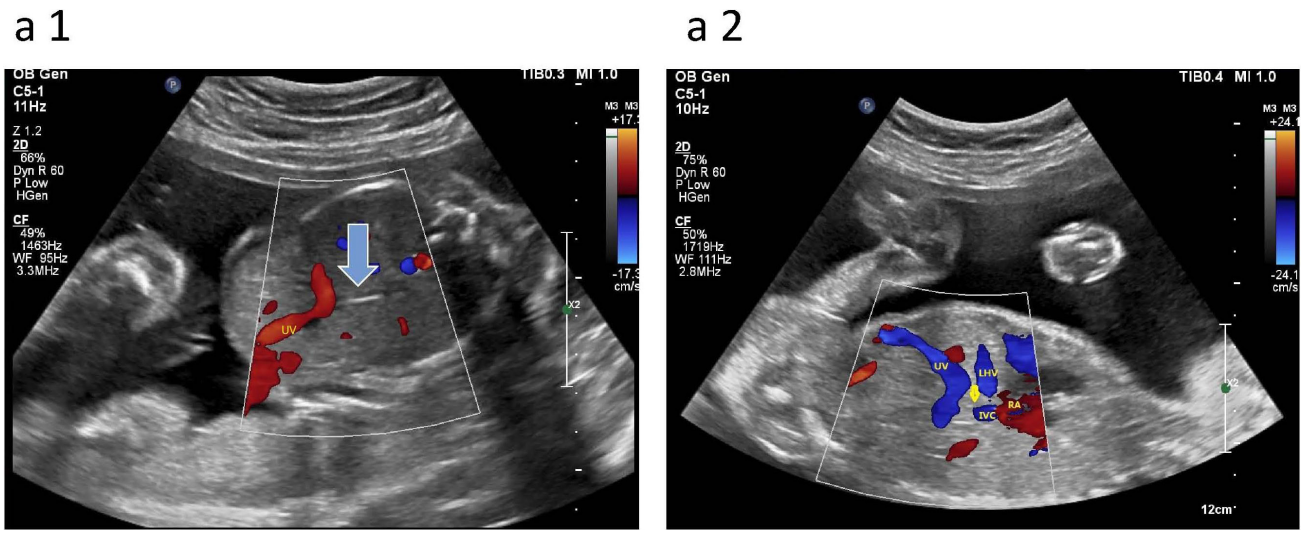

Fig. 4. DV atresia. (a1) Transverse view showing DV Atresia. The arrow represents the closed DV, with no blood flow signal detected inside. (a2) Sagittal view showing DV atresia. The arrow represents the closed DV, with no blood flow signal detected inside. DV, Ductus Venosus; UV, umbilical vein; LHV, left hepatic vein; IVC, inferior vena cava; RA, right atrium.

rological changes after birth and should therefore undergo follow up [27]. Routine prenatal ultrasound examination of the DV allows assessment of prognosis in pregnant women with hypertension or diabetes mellitus [28].

A correlation between DV abnormality and chromosomal anomalies has been reported [29,30]. In the current study, only 28 of the 166 fetuses underwent chromosomal analysis. One of these 28 cases showed trisomy 21 and another showed trisomy 18. The relationship between DV abnormality and chromosomal anomaly requires further investigation. Previous studies have shown that DV abnormalities are associated with Down's syndrome [31]. They may also be an indicator of Pallister-Killian syndrome (PKS) [32], a rare sporadic disorder with a short arm for chromosome 12p. Thus, we recommend routine chromosomal testing when fetal DV abnormalities are detected with ultrasound. This should provide comprehensive information for the prenatal consultation.

5. Conclusions

Prenatal ultrasound is readily accessible, affordable, and critical for the diagnosis of fetal DV abnormalities. It provides reliable evidence of ADV, aberrant DV connection, and combined intra- and extra-cardiac malformations. Prenatal ultrasound can provide general information for prenatal care and for subsequent decisions and treatment. Therefore, careful attention to the performance of the ultrasound procedure and meticulous observation of each section is critical.

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

HYY conceived the study. HYY and YK processed the images, drafted and revised the manuscript. CGZ, YZ and YK analyzed the data and interpreted data. HYY and LHH proposed the idea, and designed the work. LHH supervised the whole study, 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

The study was conducted in accordance with the Declaration of Helsinki. This study protocol was reviewed and approved by the Ethics Committee of the Sichuan Provincial Maternity and Child Health Care hospital (approval no. HUSLL 20211216). 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.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5007148.

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