Shunt diameter in agenesis of ductus venosus with extrahepatic porto-systemic shunt impacts prognosis

Ori Shen, Dan V Valsky, Baruch Messing, Sarah M Cohen, Michal Lipschuetz, Simcha Yagel

Department of Obstetrics and Gynecology, Hadassah-Hebrew University Medical Centers, Jerusalem, Israel

Corresponding Author:
Prof. Simcha Yagel
Department of Obstetrics and Gynecology
Hadassah-Hebrew University Medical Centers
Jerusalem, Israel
simcha.yagel@gmail.com
Tel: +972 2 5844111
Fax: +972 2 5815370

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Abstract

Background*:* Agenesis of the ductus venosus (ADV) is a rare condition. This entity results from failure of the embryonic anastomosis between the primitive portal and systemic venous systems. Outcome is related to the associated anomalies, and may be affected by agenesis or underdevelopment of the fetal portal system. In ADV there are two variants of umbilical vein drainage: intrahepatic or extrahepatic (porto-systemic) shunt. It has been posited that the extrahepatic variant carries a poorer prognosis. However in the absence of associated anomalies there is still wide variation in outcome. We evaluated the portal system in cases of ADV, and aimed to identify parameters that might predict outcome.

Methods: We conducted a retrospective study of cases of ADV with extrahepatic shunt examined in two centers, and collected new cases prospectively. The route of the shunt was depicted using 2D and 3D ultrasound imaging. The diameter of the shunt in comparison with the umbilical vein was assessed as was the entire portal vasculature, in an attempt to characterize portal system and shunt developmental variations, and their possible impact on outcome. Bad outcome was defined as persistent morbidity or fetal or neonatal demise.

Results: 22 cases of ADV were identified: 9 retrospectively and 13 prospectively. Aberrant shunts from the umbilical vein were identified to the right atrium, coronary sinus, IVC and iliac vein. In 7/22 cases (32%) a wide connection was observed. In six of these seven cases (86%), outcome was bad, including four with severe associated anomalies and two children with hepatic dysfunction. In five of these cases cardiomegaly with tricuspid regurgitation was observed, as well as underdevelopment of the portal system. In only 5/15 cases of narrow shunt (33%) was the outcome bad, in all five bad outcome was related to associated anomalies.

Conclusion: In cases of ADV with extrahepatic shunt, portal system development is impacted by the diameter of the shunt. If the shunt is narrow, the portal system will have developed normally. A wide shunt is associated with underdevelopment or absence of the portal system. In cases of ADV with extrahepatic shunt, prognosis is determined by the severity of associated anomalies, the diameter of the shunt, and development of the portal system*.*

Introduction

Agenesis of the ductus venosus (ADV) is a rare condition with unknown prevalence in the general population. This entity results from a failure of the "critical anastomosis" between the portal-umbilical venous system and the hepatic-systemic venous system. The anatomy of the umbilical, portal and hepatic venous systems, and DV in the human fetus have been studied both pathologically[1] and sonographically [2-8] Briefly, the umbilical vein connects to the inferior branch of the left portal vein. Distal to this point is the portal sinus which is the sonographically prominent L shaped tubular structure curving to the right, at the level at which the standardized measurement of the fetal abdominal circumference is performed. Into this confluence of vessels, the inflow is from the umbilical vein from an anterio-inferior direction and the main portal vein entering from left to right. The outflow is to the right portal vein entering and branching within the liver, and the DV, which exits proximally to the main portal vein bifurcation in a posterior-superior direction to be joined by the hepatic veins and inferior vena cava, all in close proximity to the entrance into the right atrium.

When the DV is absent, there are two possibilities for umbilical vein drainage[9]. The first entails increased flow into the entire portal system ("intrahepatic shunt"). The second consists of an anomalous vascular connection between the umbilical vein, or one of the branches of the portal veins, into one of the hepatic veins, directly to a systemic vein, or into the heart, either to the right atrium or into the coronary sinus. When such an "extrahepatic" aberrant vessel is present the flow into the entire portal system depends on the volume shunted through the aberrant vessel.

Prognosis in ADV is impacted by the presence of any associated anomalies, the pathway of umbilical flow to the systemic venous circulation, and by the effects of hemodynamic stress, such as might be encountered in cases with placental dysfunction. Additional concerns are the possibility of postnatal hepatic dysfunction or cardiac failure [6, 9-12]. In both variants of ADV, that with a discrete aberrant portosystemic shunt (extrahepatic variant), and that without a distinct aberrant shunt (intrahepatic variant), a strong association exists between ADV and fetal death, hydrops, and structural and chromosomal anomalies. Even in cases without associated anomalies, it has been shown that the prognosis for the

extrahepatic variant is poorer[9], owing to the greater possibility of evolving cardiac failure. In some cases a persistent postnatal portosystemic shunt required placement of an occlusion device [13]. However, some of these cases are clinically silent; in the absence of other anomalies, it is possible that many such cases go undetected. Prognosis may also depend on the existence of a shunt draining from the umbilical vein to the systemic venous circulation [9, 10, 14-21].

We aimed to evaluate the portal system anatomy in cases of ADV with extrahepatic shunts, and examine how variations in this system, particularly the magnitude of the shunt, may affect outcome, especially in cases without associated anomalies.

Patients and Methods

We reviewed our computerized databases at Hadassah Mount Scopus and Shaare Zedek Medical Centers, two tertiary care centers in Jerusalem that see a mixed population of low- and high-risk women for their targeted organ scans, as well as women referred for evaluation of suspected fetal anomaly. All cases assigned a diagnosis of agenesis of ductus venosus (ADV) with an extrahepatic shunt to the systemic venous circulation from January 2002-June 2007 were extracted from our archives. From 2007 onwards we prospectively collected all cases and performed a comprehensive standardized assessment of the fetal umbilical vein, splenic vein, portal vein and branches, hepatic veins, pulmonary veins and systemic venous return systems. All prospective cases had 2D gray scale, color and spectral Doppler, as well as STIC volume acquisitions with 3D color and B-flow, and offline analysis of the venous vasculature. The anomalous shunt diameter was assessed qualitatively as either narrower than the umbilical vein at the shunt's widest point, or to be wider or equal to the UV diameter (defined as "wide shunt"). Flow pattern in the shunt reflected the flow pattern of the drainage site vessel. The presence or absence of the main portal vein with its normal inflow from the splenic vein was ascertained, and the portal system was qualitatively assessed to be normal or hypoplastic.

The diagnosis of ADV was made when the vessel was not demonstrated in its usual anatomic position by color Doppler. Two patients with an anomalous shunt but with a patent DV were identified during the study period. In cases where the

pregnancy continued, sonographic follow up to assess fetal growth as well as cardiac function was performed at 2-3 week intervals until labor was induced or occurred spontaneously.

Cases were a mix of referrals to our tertiary centers in ten cases and a primary diagnosis in the others. All exams were performed using a Voluson 730 Expert or E8 ultrasound machines (GE Medical Systems, Kretztechnik, Zipf, Austria).

Statistical note: proportions were compared with the $?^2$ test, all comparisons were two-tailed and $p<0.05$ was considered statistically significant.

Results

Twenty-two cases of ADV with an extrahepatic anomalous connection were identified, nine of them retrospectively extracted from our archives and 13 prospectively. Table 1 summarizes these cases. Post natal follow up duration was 6 months-5 years (mean 1.5 years). 18/22 cases (82%) had additional sonographic findings. In eight cases (36%) pregnancy was terminated because of associated structural or chromosomal anomalies. Eleven children (50%) are alive and well. Of these, all except one (with Ebstein's anomaly) had no or minor associated anomalies (Table 1). Five fetuses (23%) had partial or complete absence of the portal venous system (CAPVS), all associated with a wide shunt (Table 3). CAPVS was confirmed by post-mortem examination in 4 terminated fetuses, and by pediatric examination in one.

In 15/22 cases (68%) a narrow shunt was observed (Figure 1a-f). In 7/22 (32%) there was a wide portosystemic shunt (Figure 2a-f). Where it was measured, Doppler flow patterns in the shunt showed triphasic antegrade flow. The outcome of fetuses with a wide shunt was significantly worse than those with a narrow shunt (Table 2). Five cases with wide shunt had partial or complete CAPVS (Table 3). Of the three surviving children with a wide shunt, two have persistent hyperammonemia and hepatic dysfunction at the time of last follow up. An additional case has associated partial anomalous pulmonary venous drainage and is alive and well at the time of follow up. The shunt in this case closed spontaneously.

Two cases were diagnosed during the study period with patent ductus venosus and an extrahepatic shunt. In both, the shunt was from the left portal vein into a hepatic vein. In one case the shunt was narrow and closed spontaneously after birth. In the second case, the shunt was wide, and at six months the infant has hyperammonemia and is failing to thrive. An occlusion procedure is planned. In both cases the DV closed postpartum.

Discussion

Prenatal diagnosis of ADV is well known. In sonographic evaluation of the anomalous shunt color Doppler is indispensable, however for visualization of the shunt diameter, 2DUS and 4DUS with B-flow were found to represent the true dimensions of the shunt more reliably. 3DUS with color Doppler unfortunately was too prone to "bleeding" of the color beyond the vessel, to be suitable for measurement. In our study, babies in whom shunt diameter was equal to or exceeded that of the umbilical vein had significantly poorer outcome than those with a narrower shunt.

In a comprehensive review [9] of 86 published cases from a 10 year period (1996-2006), 45% of fetuses with ADV had associated major structural or chromosomal anomalies with no significant difference between the intrahepatic and extrahepatic variants. In ongoing pregnancies with no major anomalies survival was better in the intrahepatic variant, with all of the 13 reported cases surviving, while in the extrahepatic group only 20/29 survived. Nine of twenty survivors in the extrahepatic group and 1/13 in the intrahepatic group had congenital absence of the portal venous system (CAPVS).

Congenital absence of the portal venous system (sometimes referred to as congenital agenesis of the portal venous system, to distinguish it from acquired forms of portal vein anomalies) is a potentially serious condition. It is associated with extrahepatic anomalies, jaundice, hepatopulmonary syndrome, galactosemia, hyperammonemia, encephalopathy, biliary atresia, and hepatic tumors [22, 23]. Most of the reported cases appear in the pediatric literature; it is therefore unknown what proportion of CAPVS is associated with ADV. Its prevalence is unknown and it can manifest from the neonatal period into adulthood. CAPVS, also known as congenital extrahepatic portocaval shunt or

Abernethy malformation [24, 25] is classified into type 1, in which the entire venous return from the mesenteric and splenic veins bypasses the liver and drains systemically, and type 2, in which there exists a side to side shunt between the portal vein and a systemic vein diverting some flow away from the liver. Classification in the pediatric literature has been based on angiography, venography, computerized tomography, MRI, ultrasound or on intra-operative findings[23, 25-27]. We were not able to directly distinguish between the two types on prenatal sonography. However the 17 cases with a normal portal system appear to be type 2 shunts, as shown by the adequate portal system perfusion. It has been suggested that CAPVS may be associated with increased compensatory hepatic arterial proliferation and flow [17, 25]. Pediatric treatment options include various shunt occlusion procedures; balloon occlusion, coil embolization and open surgery [28-31]. Some cases will require liver transplantation [22, 32, 33]

Prenatal diagnosis of CAPVS has been infrequently reported. Some children may remain asymptomatic [34, 35]. In Contratti's report [10] CAPVS was confirmed post partum in 4/10 cases, all of whom had an additional sonographic finding. Three cases had cardiomegaly and one had IUGR and oligohydramnios. In one of these cases the infant died suddenly at the age of one year. In five additional cases with CAPVS, four survived [15, 36]. In a prenatal series of 9 cases[6], all 5 pregnancies with type 1 CAPVS were terminated. Of 4 cases with partial (type 2) CAPVS, 3 had a good outcome and the fourth suffered from mild hepatic dysfunction, elevated ammonia, and portal hypertension. Follow up continued for 2-10 years. Although not assessed by the authors, in all images produced in this series depicting the anomalous shunt, the shunt was wide, and the outcome was bad.

Our observation, similar to the above reports, confirms that a poor prognosis is most commonly determined by the presence of severe associated structural or chromosomal anomalies. Development of the portal system appears to be related to the maximal width of the shunt. If the shunt is narrow portal flow is maintained and the portal system will have developed normally; prognosis depends chiefly on the presence of associated anomalies. When the shunt is greater or equal in diameter to the umbilical vein, we speculate this may result, possibly by a "steal" mechanism, in diminished flow to the portal veins and to incomplete or anomalous development of the portal system. This is associated with long term complications.

A wide shunt is also strongly associated with other severe anomalies. In addition it may be difficult to accurately assess the fetal portal circulation, and shunt size may be a marker of poor portal development. Our study highlights the variation in severity of outcome in ADV fetuses with extra-hepatic shunt: the poor prognosis that has been observed in some of these fetuses in the absence of associated anomalies seems to stem from anomalous portal system development, which may be impacted by shunt dimension. It is also possible that prenatal diagnosis and timely treatment of large shunts improves prognosis in survivors.

When ADV with an extrahepatic shunt is seen, a meticulous search for associated anomalies and karyotyping are warranted. An effort should be made to depict the portal venous anatomy, especially when a wide shunt is present. If the portal system is absent or underdeveloped, the prognosis is guarded and the patient should be counseled on the possibility of long term complications, including the need for liver transplantation. When the portal system is intact and there are no associated anomalies a good outcome can be expected. In all cases careful frequent antenatal scans are required to detect signs of hydrops, which is not uncommon in these cases [9]. To better understand the prognosis of cases with prenatal diagnosis of porto-systemic shunts with ADV, more cases and long term follow up will be required.

LEGENDS TO FIGURES:

Figure 1: Narrow extrahepatic shunt to the IVC in agenesis of ductus venosus.

A: Agenesis of DV with narrow shunt, imaged in HDPD. Carets indicate the shunt, note that it is narrower than the umbilical vein (UV). IVC, inferior vena cava; Ao, aorta.

B: The same case, imaged in B-flow. Carets indicate the shunt. Owing to the greater sensitivity of B-flow in showing vessel dimensions, the difference in UV and shunt diameter is more marked. UV, umbilical vein; IVC, inferior vena cava; Ao, aorta.

C: At the level of the stomach (St) the portal venous system is shown to be developing normally. RPV, right portal vein.

D: The heart and abdominal great vessels in HDPD. The narrow shunt is marked with carets. UV, umbilical vein; IVC, inferior vena cava; Ao, aorta.

E: B-flow image of the heart and abdominal great vessels. Carets indicate the narrow shunt. MPV main portal vein; LPV, left portal vein; ARPV, anterior right portal vein; PRPV, posterior right portal vein.

F: Transverse view of the fetal abdomen with HDPD, showing the normally developed portal system. UV, umbilical vein; ARPV, anterior right portal vein; PRPV, posterior right portal vein.

Figure 2: Wide extrahepatic shunt in agenesis of ductus venosus.

A: The heart and abdominal vessels in ADV with wide extrahepatic shunt, imaged in HDPD. Carets indicate the shunt, which is shown to be wider than the umbilical vein (UV). Ao, aorta; CT, celiac trunk; UA, umbilical artery.

B: The heart and great vessels imaged in B-flow. Carets indicate the shunt, which still appears wider than the umbilical vein (UV). Ao, aorta; CT, celiac trunk; UA, umbilical artery.

C: Transverse abdominal plane of the same case with 3DUS and HDPD, showing the umbilical vein (UV) and absence of the portal venous system. Compare figure 1c.

D: Sagittal view showing the heart and abdominal vessels in HDPD, and absence of the portal venous system. UV, umbilical vein; RA, right atrium.

E: The same view in B-flow. UV, umbilical vein; RA, right atrium.

F: Transverse view at the level of insertion of the umbilical cord shows absence of the portal venous system. UV, umbilical vein.

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Table 1: Venous connection, shunt diameter, associated anomalies, and outcome in 22 fetuses with absence of ductus venosus and extrahepatic umbilical venous drainage

Case	Age Parity	GA	Venous connection	Shunt diameter (W/N)	Portal system	Additional sonographic findings	Karyotype	Outcome	Pathology
1	32Y G2P1 TWIN A	23	coronary sinus	N	normal	Ebstein anomaly	N	AW (surgery)	
2	31Y G2P1	26	coronary sinus	N	normal	LSUA	N	AW	
3	33Y G1	15	Rt. atrium	N	normal	D- TGA, PS, VSD	N	TOP	confirmed
4	24Y G1	23	Rt. atrium	N	normal	/	N	AW	
5	24Y G3P2	26	Rt. atrium	N	normal	LSUA, AVSD, PLSVC	trisomy 21	TOP	confirmed
6	24Y G1	15	IVC	N	normal	AVSD, HLHS, D-TGA	N	TOP	refused
7	34Y G7P6	21	IVC	N	normal	VSD, LSUA	N	AW	
8	29Y G2P1	27	IVC	N	normal	Nuchal edema	trisomy 21	TOP	confirmed
9	20Y G1	23	Lt. iliac vein	N	normal	severe growth restriction	Chromosome 2 mosaic	Fetal death	refused
10	30 G2P1	25	Rt. iliac vein	N	normal	/	N	AW	
11	34Y G4P3	29	Rt. iliac vein	N	normal	mild cardiomegaly	N	AW	
12	35Y G3P2	18	Rt. hepatic vein	N	normal	/	N	AW	
13	35Y G4P1	22	Rt. hepatic vein	N	normal	VSD	N	AW	

Case	Age Parity	GA	Venous connection	Shunt diameter (W/N)	Portal system	Additional sonographic findings	Karyotype	Outcome	Pathology
14	31Y G5P2AB2	28	Rt. hepatic vein	N	normal	/	N	AW	
15	37y G4P3	34	Rt. hepatic vein	N	normal	RVH, RAA	N	Coil embolization AW	
16	21Y G5P2AB2	23	Rt. atrium	W	normal	IPAPVC	N	AW	
17	27Y G2P1	23	Rt. iliac vein	W	normal	Truncus, VSD, PLSVC clenched hands	trisomy 18	TOP	confirmed
18	30Y G4P3	25	coronary sinus	W	abnormal	Cardiomegaly, TR, ASD, PLSVC	N	hyperammonemia	
19	28Y G1 TWIN B	22	IVC	W	abnormal	Cardiomegaly, TR , Pleuropericardial effusion	N	Hyperammonemia Coil embolization (twice)	
20	26Y G2P1	23	IVC Azygos shunt	W	abnormal	TR, interrupted IVC, cardiomegaly, PLSVC	N	TOP	confirmed
21	27Y G4P2AB1	25	IVC	W	abnormal	Cardiomegaly, TR, Lt. isomerism, heterotaxy syndrome, interrupted IVC, PLSVC	N	TOP	confirmed
22	39Y G7P4AB	27	IVC	W	abnormal	Cardiomegaly, TR, LSUA, severe AS, Pericardial effusion	N	TOP	confirmed

GA-gestational age at initial diagnosis, W/N wide or narrow shunt diameter, RVH-right ventricular hypertrophy, RAA-right aortic arch, AW-alive and well, TGA-transposition great arteries, PS-pulmonary stenosis, VSD-ventricular septal defect, TOP-termination of pregnancy, IVC-inferior vena cava, PLSVC-persistent left superior vena cava, LSUA-left single umbilical artery, AVSD-atrioventricular septal defect, HLHS-hypoplastic left heart syndrome, AS-aortic stenosis, IPAPVC- Infradiaphragmatic partial anomalous pulmonary venous connection, Pathology – confirmed: PM confirmed ultrasound findings; refused: PM was refused by the parents.

Table 2: Outcome of fetuses with narrow shunt vs wide shunt

	Narrow shunt (n=15)	Wide shunt (n=7)	*p*
Associated severe anomalies	6/15 (40%)	7/7 (100%)	<0.05
Pregnancy termination, IUFD	5/15 (33%)	4/7 (57%)	NS
Abnormal portal system	0/15 (0%)	5/7 (71%)	<0.05
Alive and well	10/15 (67%)	1/7 (14%)	<0.05

IUFD: intrauterine fetal death

Table 3: Portal system malformations in cases with wide shunt connection

Case #	Venous Connection	Portal System Anomaly	Outcome
18	CORONARY SINUS	Left portal veins only	Hyperammonemia
19	IVC	Partial left portal veins only	Hyperammonemia
20	IVC – AZYGOS SHUNT	Partial left and partial right portal system	TOP
21	IVC	No portal system detected	TOP
22	IVC	No portal system detected	TOP

TOP - termination of pregnancy.

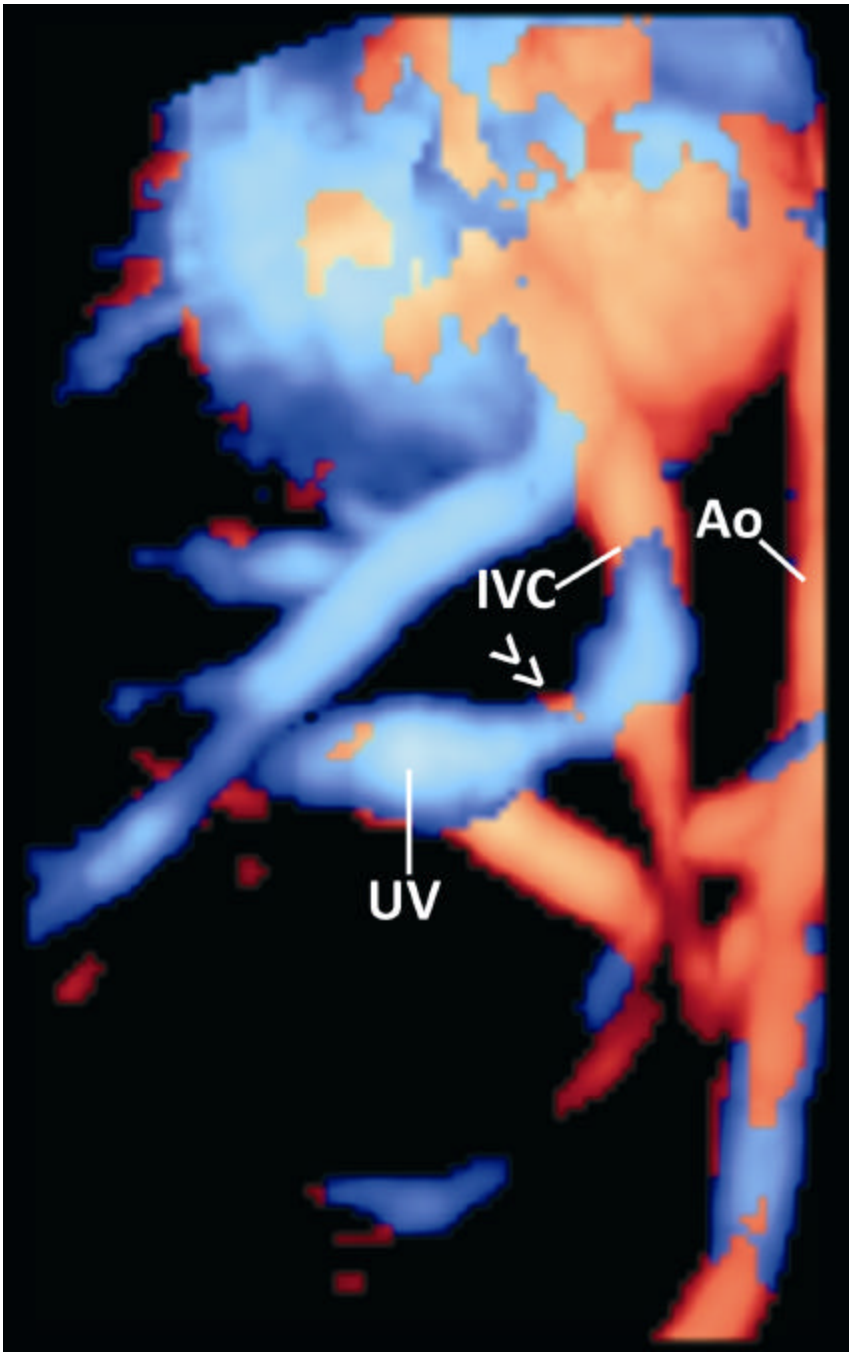
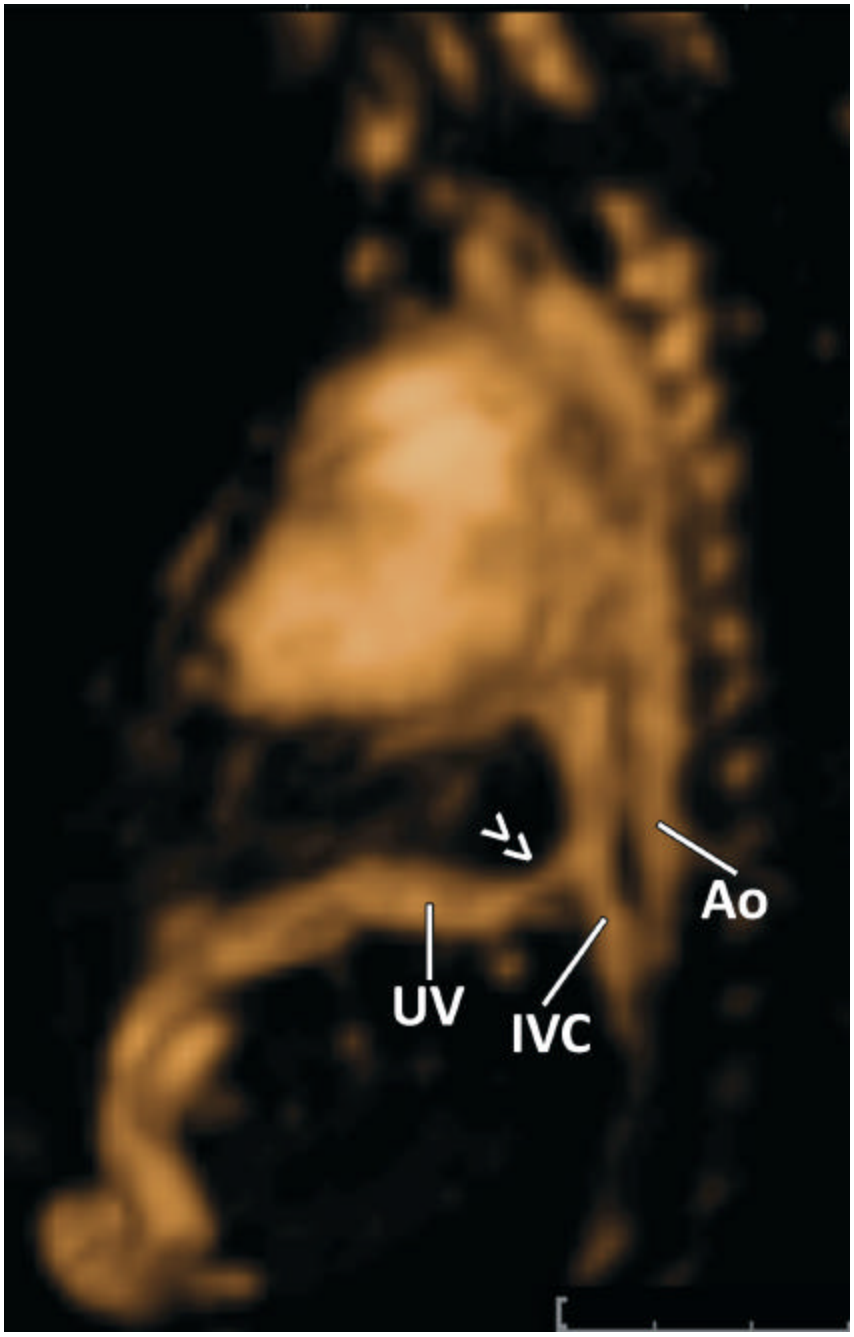
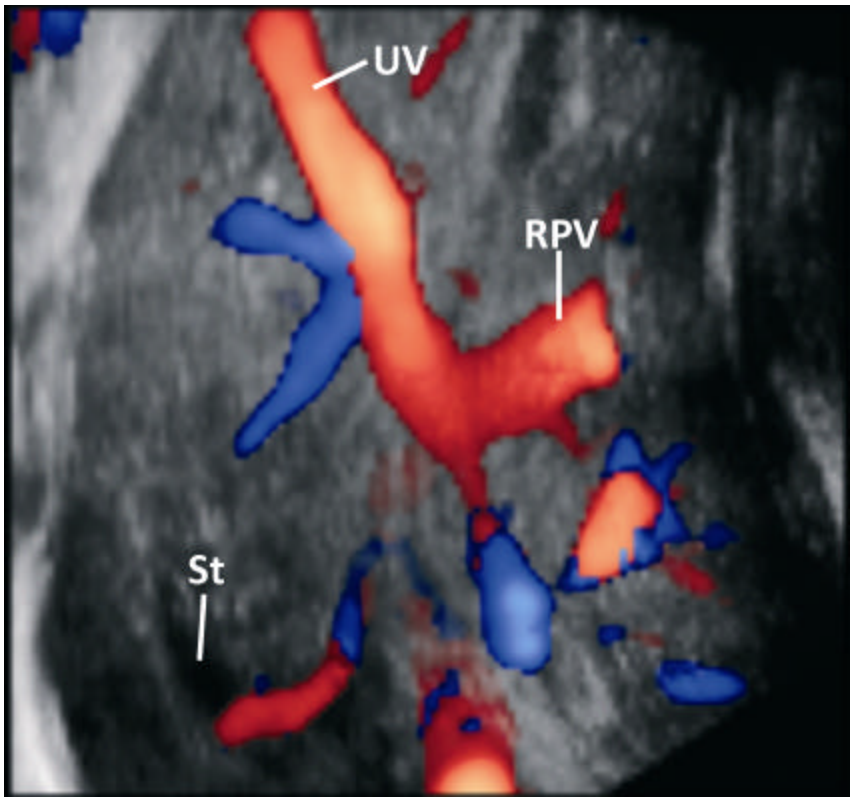


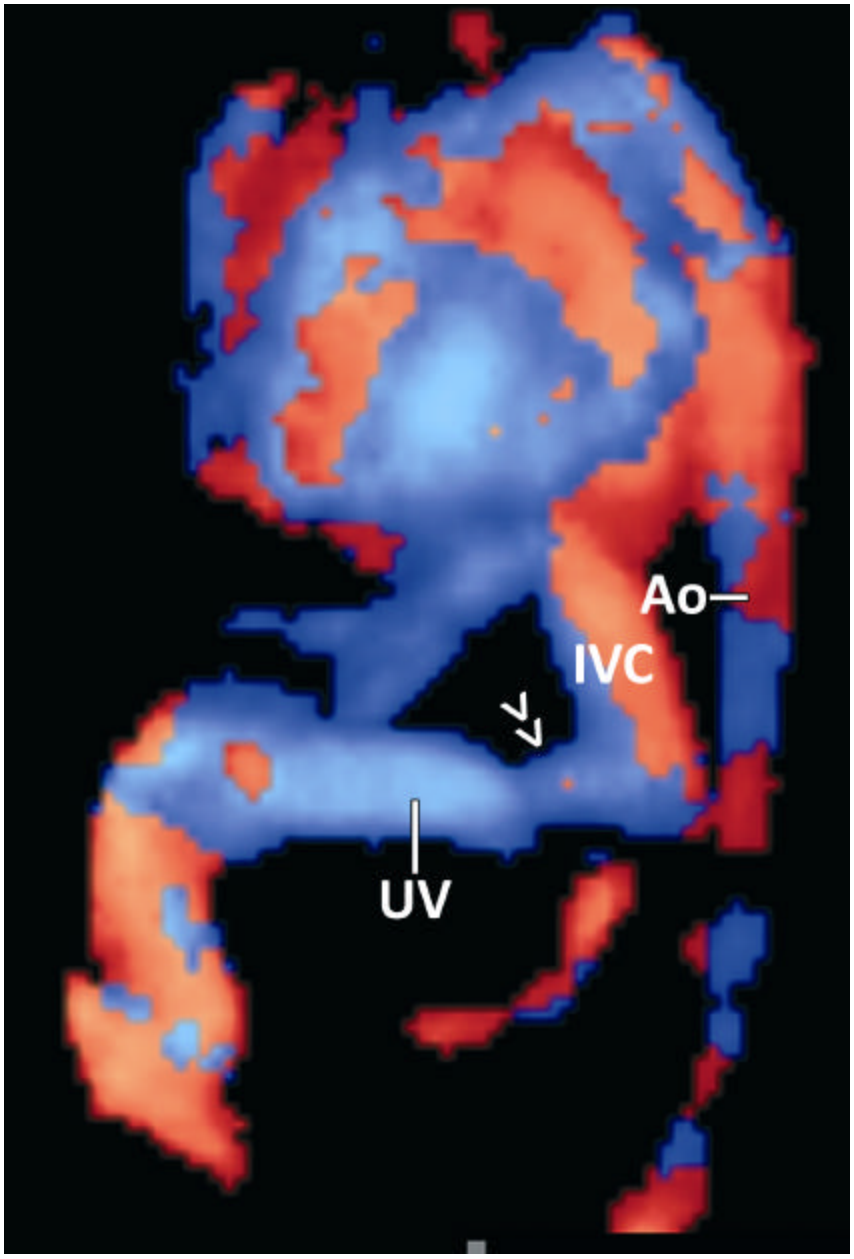
Figure 1: Narrow extrahepatic shunt to the IVC in agenesis of ductus venosus.
A: Agenesis of DV with narrow shunt, imaged in HDPD. Carets indicate the shunt, note that it is narrower than the umbilical vein (UV). IVC, inferior vena cava; Ao, aorta.



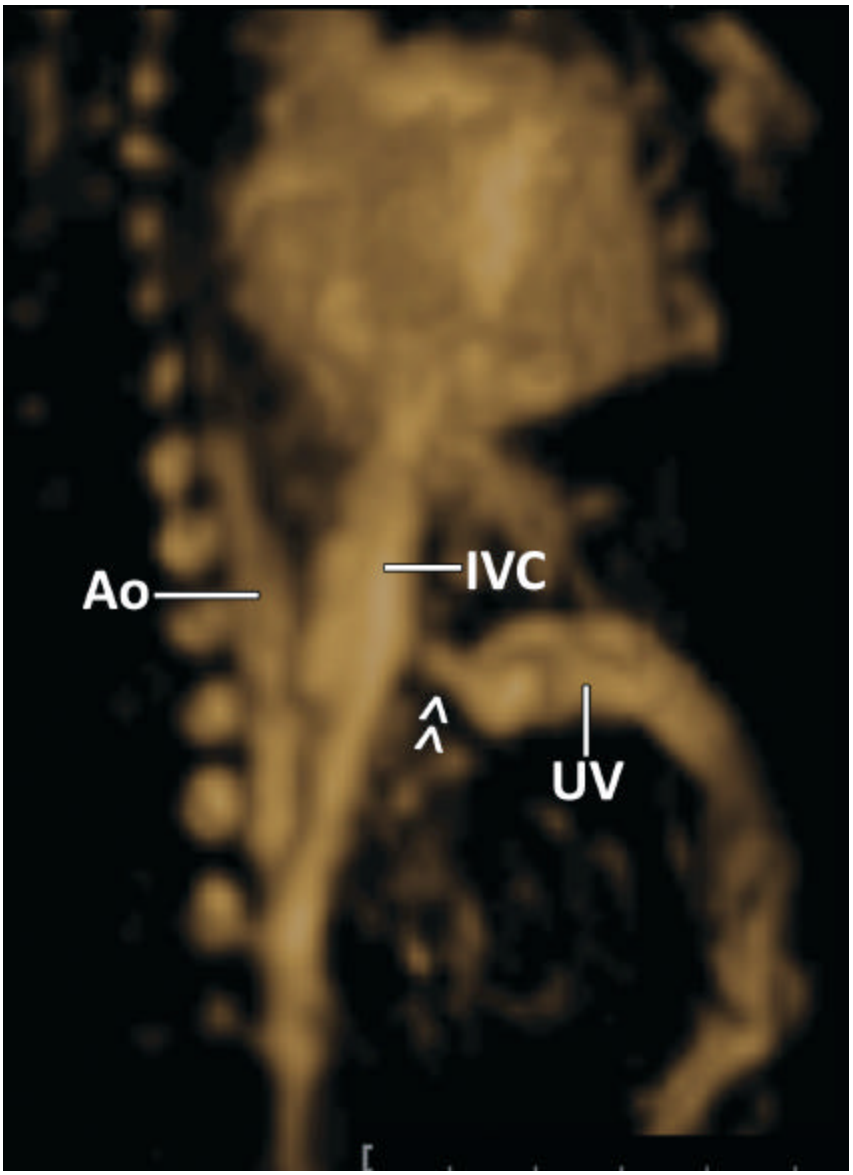
B: The same case, imaged in B-flow. Carets indicate the shunt. Owing to the greater sensitivity of B-flow in showing vessel dimensions, the difference in UV and shunt diameter is more marked. UV, umbilical vein; IVC, inferior vena cava; Ao, aorta.



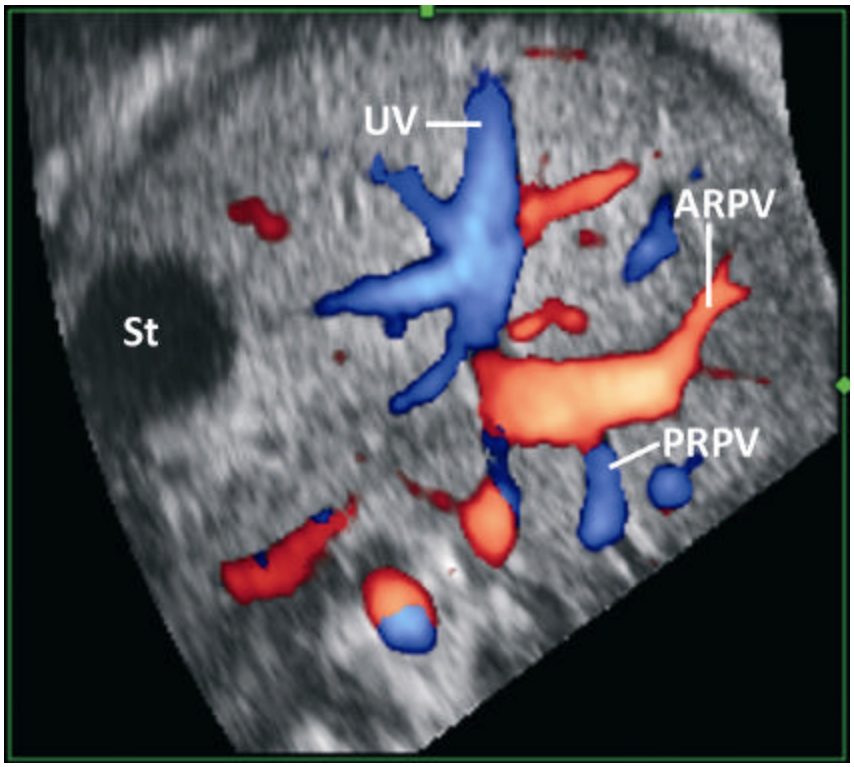
C: At the level of the stomach (St) the portal venous system is shown to be developing normally. RPV, right portal vein.



D: The heart and abdominal great vessels in HDPD. The narrow shunt is marked with carets. UV, umbilical vein; IVC, inferior vena cava; Ao, aorta.



E: B-flow image of the heart and abdominal great vessels. Carets indicate the narrow shunt. MPV main portal vein; LPV, left portal vein; ARPV, anterior right portal vein; PRPV, posterior right portal vein.



F: Transverse view of the fetal abdomen with HDPD, showing the normally developed portal system. UV, umbilical vein; ARPV, anterior right portal vein; PRPV, posterior right portal vein.

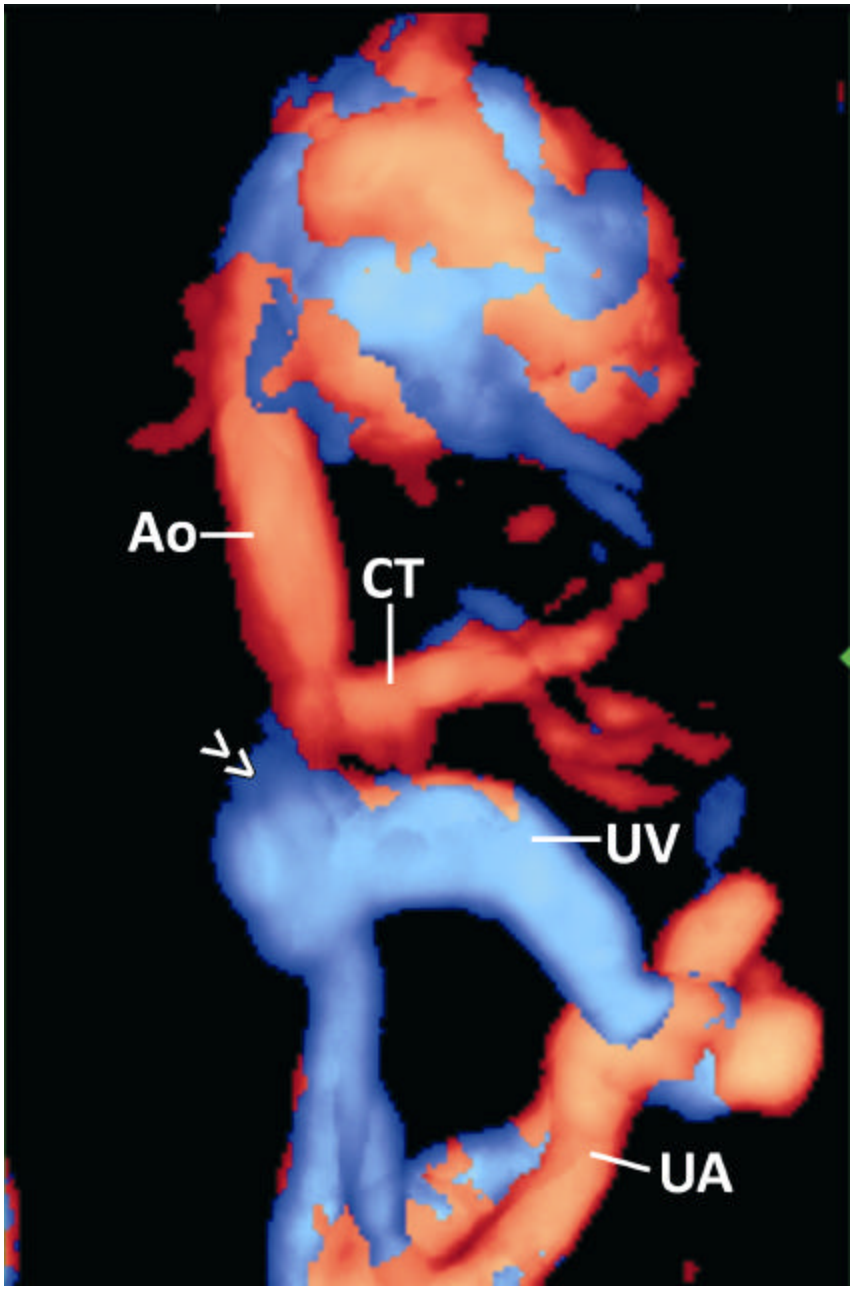
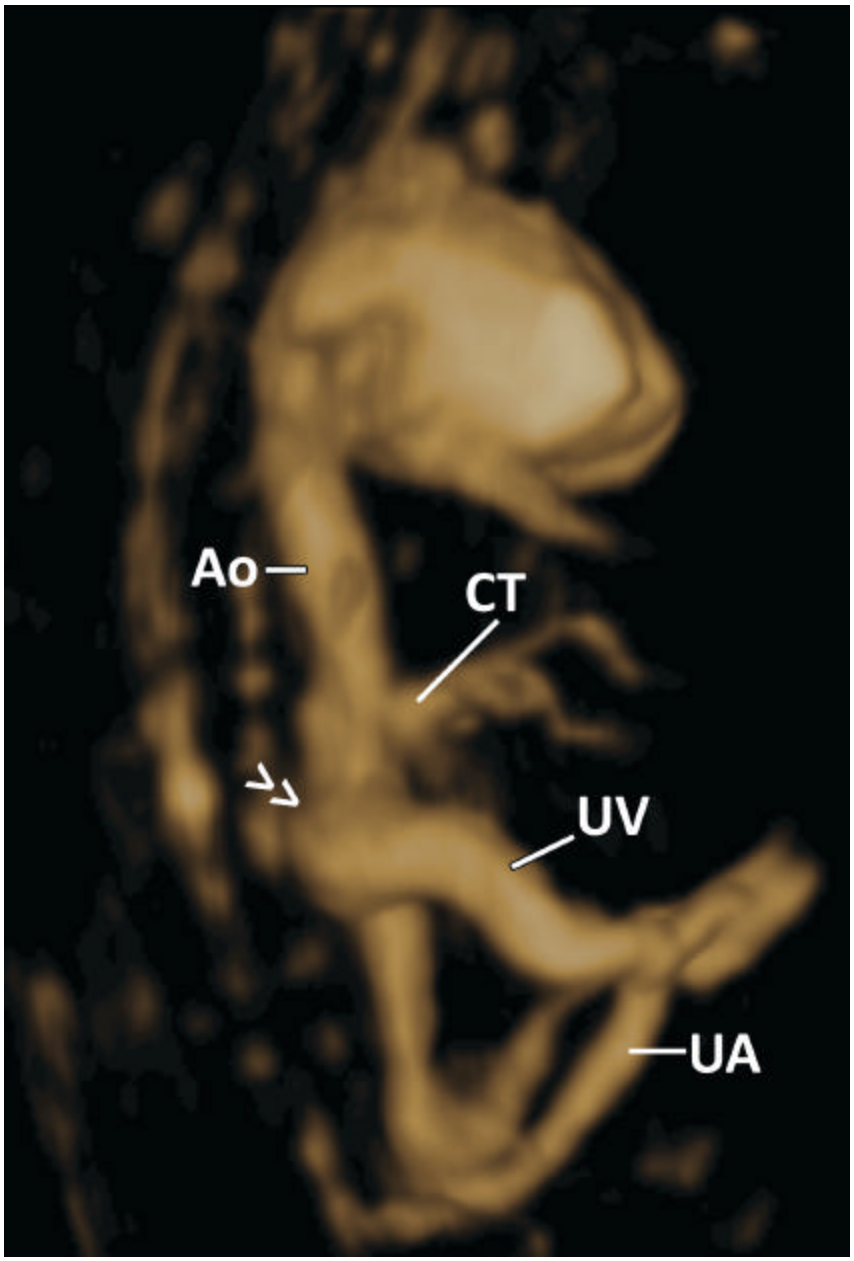
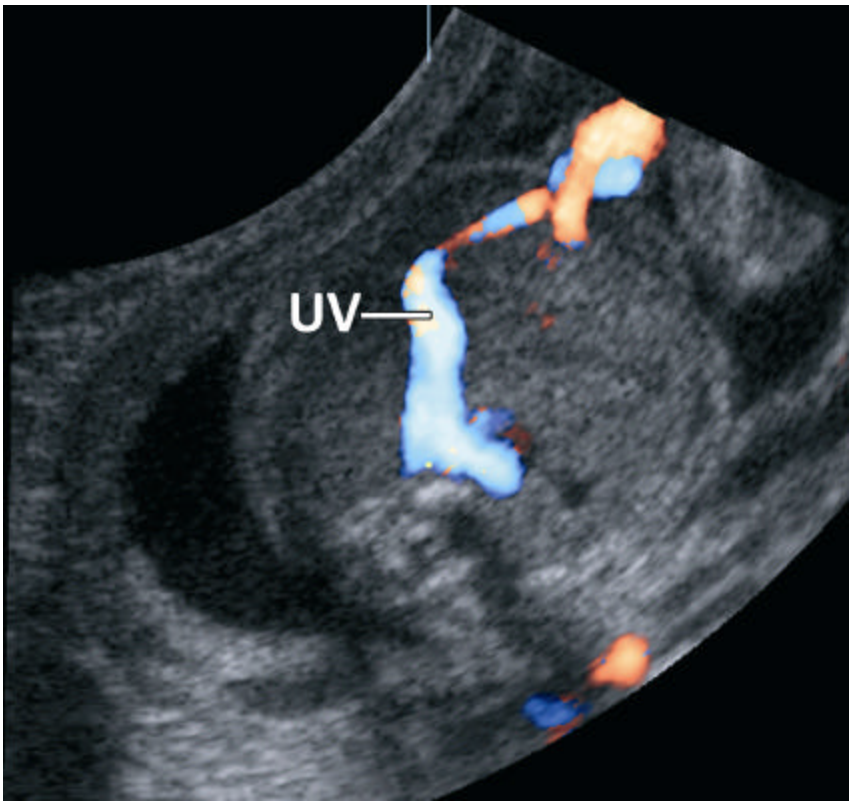


Figure 2: Wide extrahepatic shunt in agenesis of ductus venosus.

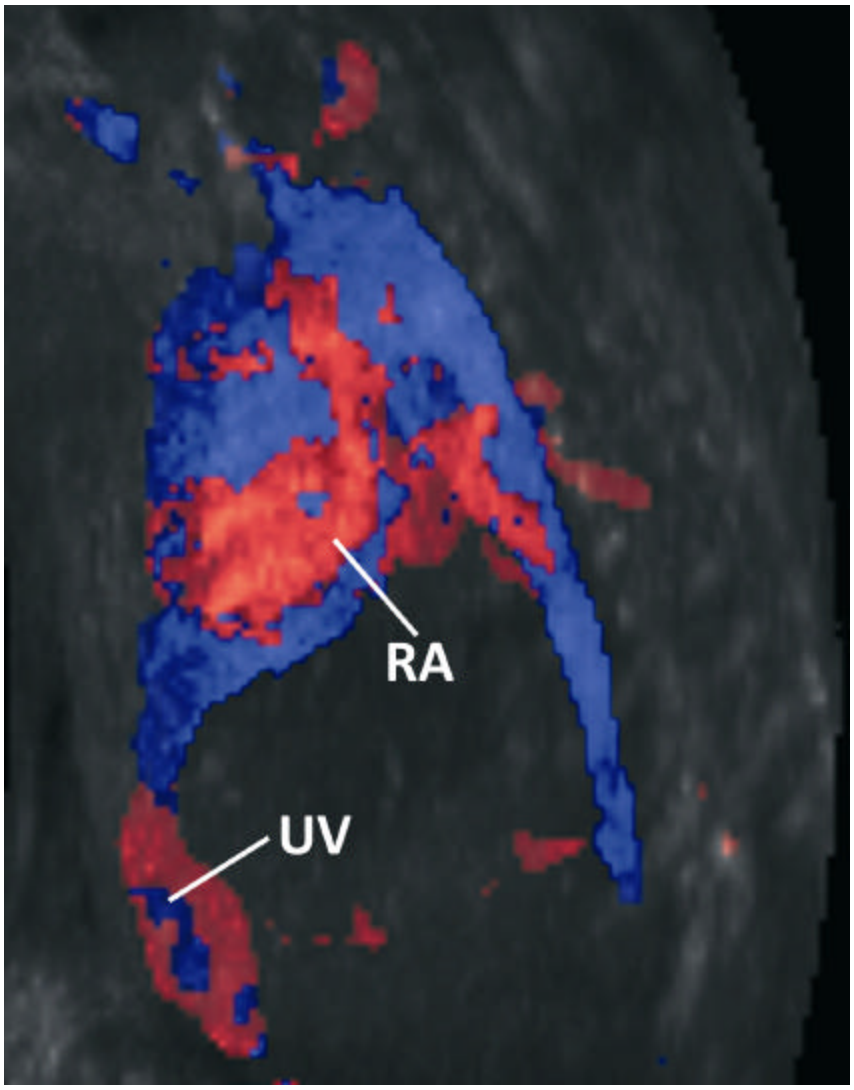
A: The heart and abdominal vessels in ADV with wide extrahepatic shunt, imaged in HDPD. Carets indicate the shunt, which is shown to be wider than the umbilical vein (UV). Ao, aorta; CT, celiac trunk; UA, umbilical artery.



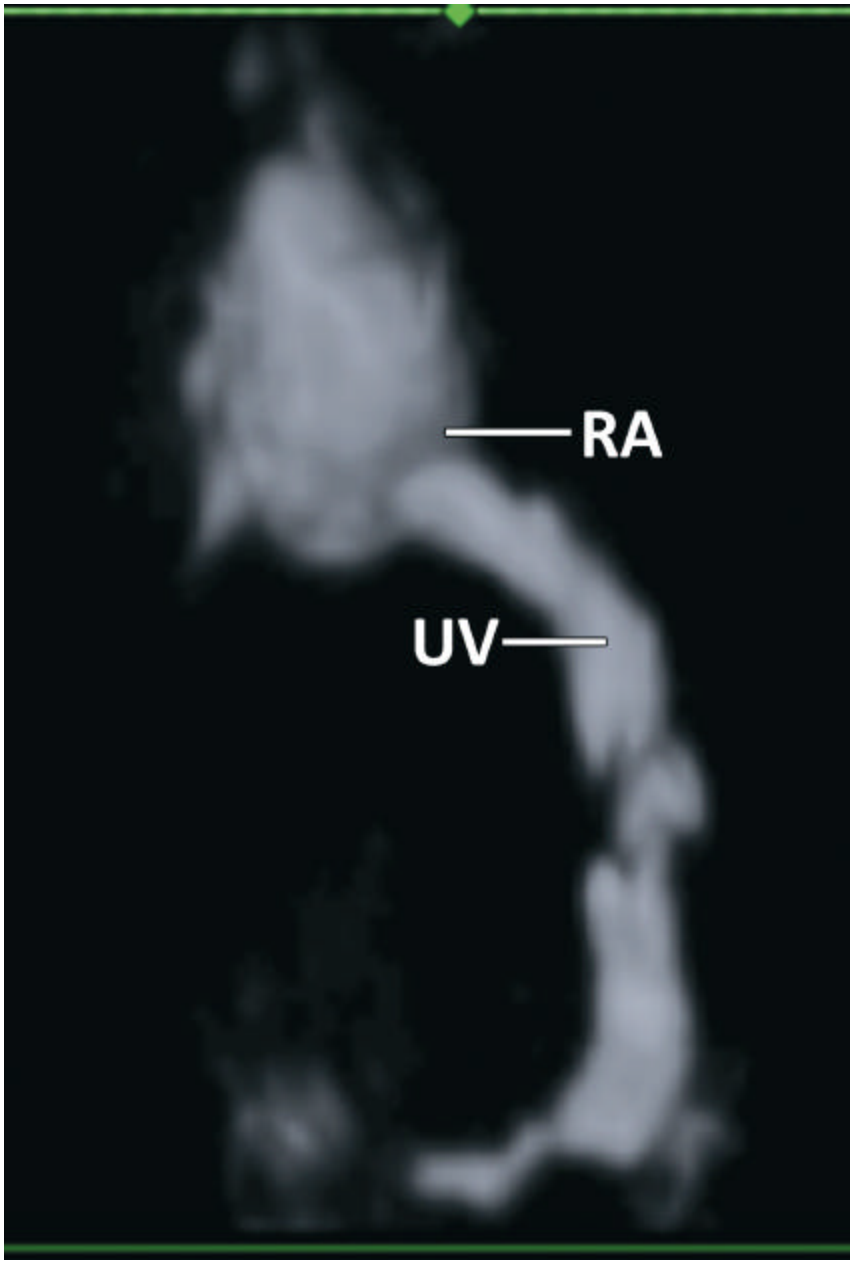
B: The heart and great vessels imaged in B-flow. Carets indicate the shunt, which still appears wider than the umbilical vein (UV). Ao, aorta; CT, celiac trunk; UA, umbilical artery.



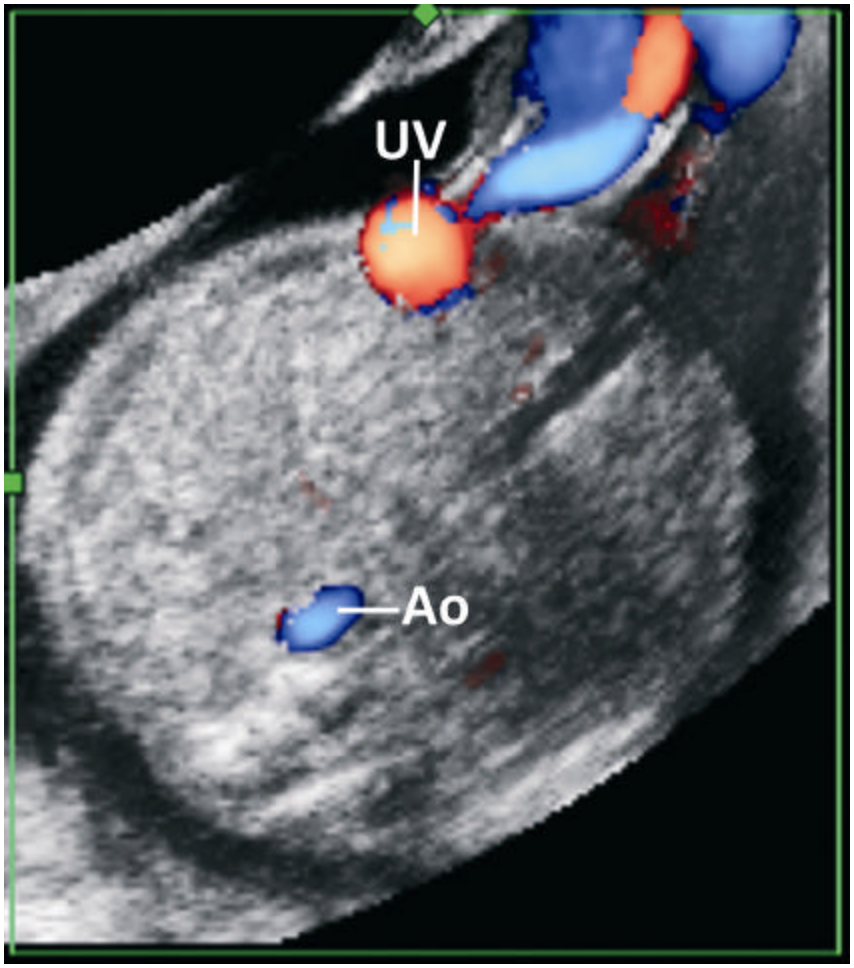
C: Transverse abdominal plane of the same case with 3DUS and HDPD, showing the umbilical vein (UV) and absence of the portal venous system. Compare figure 1c.



D: Sagittal view showing the heart and abdominal vessels in HDPD, and absence of the portal venous system. UV, umbilical vein; RA, right atrium.



E: The same view in B-flow. UV, umbilical vein; RA, right atrium.



F: Transverse view at the level of insertion of the umbilical cord shows absence of the portal venous system. UV, umbilical vein.