

Prenatal Diagnosis of Agenesis of Ductus Venosus: A Retrospective Study of Anatomic Variants, Associated Anomalies and Impact on Postnatal Outcome

Pränatale Agenesie des Ductus venosus: retrospektive Analyse anatomischer Varianten, assoziierter Fehlbildungen und Einfluss auf das postnatale Outcome

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ABSTRACT

Purpose To assess the anatomic variants, associated anomalies and postnatal outcome of fetuses with a prenatally diagnosed agenesis of ductus venosus (ADV).

Materials and Methods Retrospective study of 119 cases with agenesis of ductus venosus diagnosed by prenatal ultrasound in two tertiary referral centers from 2006 to 2014. The type and location of the umbilical venous drainage site was not-

ed. Charts were reviewed for associated structural or chromosomal anomalies, pregnancy outcome and postnatal course.

Results In 24 cases (20.2 %) ADV was an isolated finding, while 95 cases (79.8 %) had associated anomalies. We identified 84 cases (70.6 %) with intrahepatic and 35 cases (29.4 %) with extrahepatic drainage of the umbilical vein. 58.8 % of neonates were alive at follow-up. There was no statistical association between drainage site and associated anomalies or outcome. Postnatal outcome was determined by the presence and severity of associated anomalies. There was no adverse outcome in the isolated group related to ADV. Overall, there were 6 persistent portosystemic shunts, 3 of them with a spontaneous closure, and one total agenesis of the portal venous system with lethal outcome.

Conclusion Postnatal outcome in cases with ADV mainly depends on the presence of associated anomalies. In isolated cases the prognosis is generally good, but neonates with a prenatally diagnosed portosystemic shunt should be followed until its occlusion. Portal venous system agenesis is rare but should be ruled out on prenatal ultrasound.

ZUSAMMENFASSUNG

Ziel Beschreibung der anatomischen Varianten, Begleitfehlbildungen und des postnatalen Outcomes von Feten mit einer pränatal diagnostizierten Ductus venosus-Agenesie (ADV).

Material und Methode Retrospektive Analyse von 119 Fällen mit pränataler sonografischer Diagnose einer Ductus venosus-Agenesie an zwei tertiären Pränatalzentren zwischen 2006 und 2014. Beschreibung von Art und Lokalisation der Drainage der Vena umbilicalis sowie begleitender struktureller oder chromosomaler Anomalien, Schwangerschaftsausgang und postnatalem Verlauf.

Ergebnisse In 24 Fällen (20,2 %) war die ADV isoliert und in 95 Fällen (79,8 %) zeigten sich weitere Auffälligkeiten. 84 Fälle (70,6 %) wiesen einen intrahepatischen und 35 Fälle (29,4 %) einen extrahepatischen Shunt der Vena umbilicalis auf. 58,8 % der Kinder lebten zum Zeitpunkt der Datenerhebung. Es zeigte sich kein statistisch signifikanter Zusammenhang zwischen Typ der Drainage, Begleitfehlbildungen und Out-

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come. Der postnatale Verlauf wurde von Vorhandensein und Schwere der Begleitfehlbildungen bestimmt, in der Gruppe mit isolierter ADV gab es keine direkten Todesfälle. Insgesamt gab es 6 persistierende portosystemische Shunts, 3 davon verschlossen sich spontan. Ein Kind verstarb an den Folgen einer totalen portalen Agenesie.

Schlussfolgerungen Der postnatale Verlauf wird bei ADV überwiegend vom Vorhandensein von assoziierten Anomalien bestimmt. In isolierten Fällen ist die Prognose gut, Neonaten mit pränatal diagnostiziertem portosystemischem Shunt sollten allerdings bis zu dessen Verschluss nachbeobachtet werden. Eine portale Agenesie ist selten, sollte aber beim pränatalen Ultraschall ausgeschlossen werden.

Introduction

The ductus venosus (DV) is an important shunt in the fetal blood circulation. It drains 20–30 % of the highly oxygenated blood from the umbilical vein (UV) directly to the fetal heart, bypassing the fetal liver. That way oxygenated blood preferably reaches the coronary circulation and the brain [1–4]. The prevalence and prognosis of agenesis of the ductus venosus (ADV) remain unclear. It has been reported in 1:500 to 1:2500 in a high-risk population referred for fetal echocardiography [5].

There are two types of UV drainage in ADV [6–9]:

- Intrahepatic drainage: the umbilical vein connects via the portal sinus to the portal venous system (PVS) without giving rise to the DV [3, 6, 10–12] (► **Fig. 1**). In some cases an intrahepatic shunt from a portal to a hepatic vein can be detected prenatally. This variant has been reported to have a favorable prognosis [3].
- Extrahepatic drainage with liver bypass. In these cases the UV does not connect to the PVS. The liver is bypassed and the UV drains into a systemic vein, e. g. the inferior vena cava (IVC) (► **Fig. 2**), right atrium (RA) (► **Fig. 3**) or rarely the left atrium, coronary sinus or iliac vein (IV) (► **Fig. 4**) [3, 10, 12–15]. This variant has been reported to have an unfavorable prognosis due to a presumed association with congestive heart failure and hydrops [3].

ADV has been reported to be highly associated with chromosomal, cardiac and extracardiac anomalies and also with agenesis of the portal venous system and persistent portosystemic shunts, all of which may have a severe impact on postnatal development. Prognosis in isolated ADV is less well known and counseling is currently based on small case series. We conducted a retrospective study in order to analyze the anatomical variants, the association with other anomalies and the correlation with postnatal outcome.

Materials and methods

We conducted a retrospective study of all consecutive cases with a prenatal diagnosis of ADV from 2006–2014. The electronic perinatal databases of two tertiary referral centers were searched for cases with a prenatal diagnosis of ADV. None of the cases have previously been published.

During the study period, anatomical survey and fetal echocardiography were performed in a standardized way [16, 17]. In both centers evaluation of the DV was performed in all patients as part of screening (in low-risk and high-risk patients) as well as targeted

anomaly scans. Fetal echocardiography was performed in all patients. Cardiomegaly was defined as a cardio-thoracic area ratio >0.30. 2 D color Doppler was used to identify the DV in an axial or sagittal plane and pulsed-wave Doppler was used to demonstrate typical high-velocity triphasic DV flow. ADV was diagnosed if there was no connection from the UV-PVS complex to the sub-diaphragmatic vestibulum separate from the IVC and hepatic veins. The site of connection of the UV with either the PVS or the systemic venous system was identified by color Doppler; type and drainage site were noted. We classified any connection of the UV to the systemic venous system as an extrahepatic drainage. Any connection with the PVS was classified as intrahepatic drainage. A systematic evaluation of the hepatic/UV/PVS circulation as previously described by Yagel et al. [7, 8, 18] was only performed after 2011.

Cases were classified as isolated or associated with other abnormalities. In the presence of minor vascular abnormalities (e. g. single umbilical artery, persistent right umbilical vein, aberrant right subclavian artery), cases were classified as isolated.

Invasive testing (conventional karyotype) was performed in cases with additional anomalies. Obstetric and pediatric charts were reviewed for type of ADV, obstetrical data, associated anomalies, chromosomal or genetic anomalies and postnatal outcome. Postnatal work-up was performed as clinically indicated by the neonatologist.

Outcomes were categorized as adverse (termination of pregnancy (TOP), intrauterine death (IUD), neonatal death (NND) in the first 7 days of life, infant or childhood death (ICD) during the first year of life) or survivors.

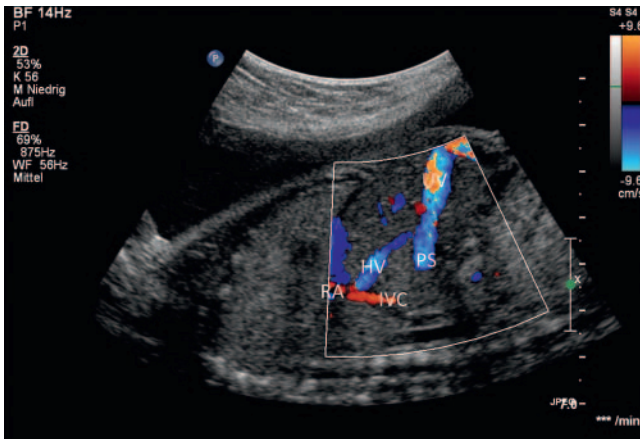
The institutional review boards of the two universities do not require formal ethical approval for retrospective archive studies.

Statistical analysis of the incidence of the associated conditions and the outcome was performed using the χ^2 and Fisher's exact test. $P < 0.05$ was considered statistically significant.

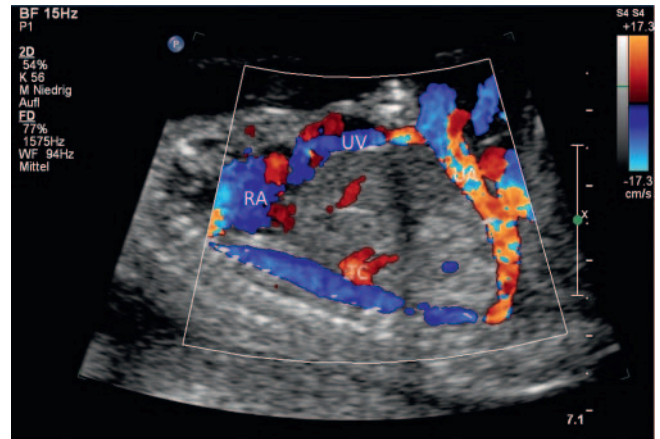
Results

During the study period, we identified 119 cases of ADV. Diagnosis was made at a median gestational age of 21 weeks (range 11 to 37 weeks).

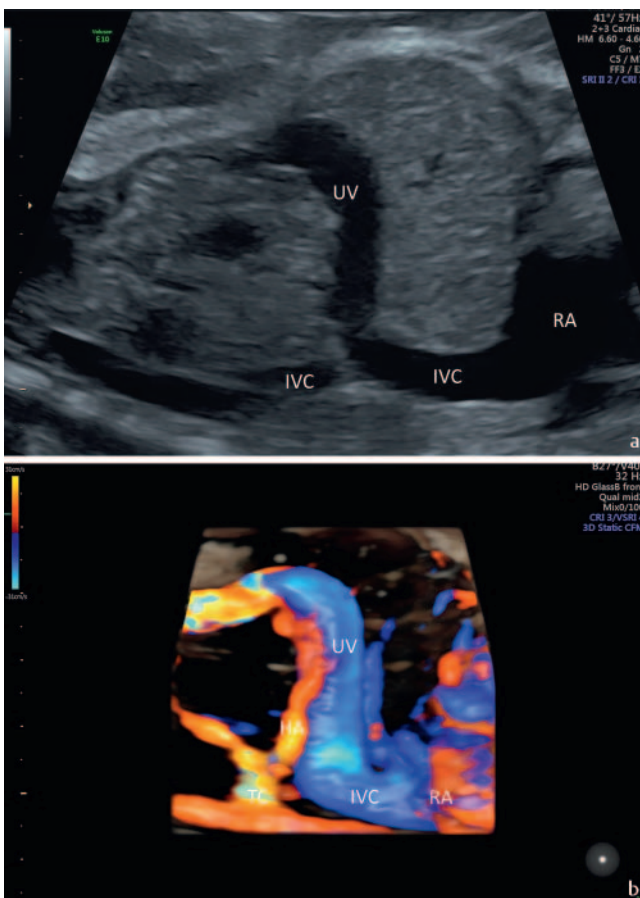
In 24 cases (20.2 %) ADV was isolated and 95 cases (79.8 %) had associated anomalies. Additional findings were congenital heart disease (25/119; 21 %), chromosomal anomalies (24/119; 20.2 %) and isolated extracardiac anomalies (14/119; 11.2 %). 27 fetuses showed multiple malformations or genetic syndromes (22.7 %). Additionally, ADV was found in two cases with cytomegalovirus



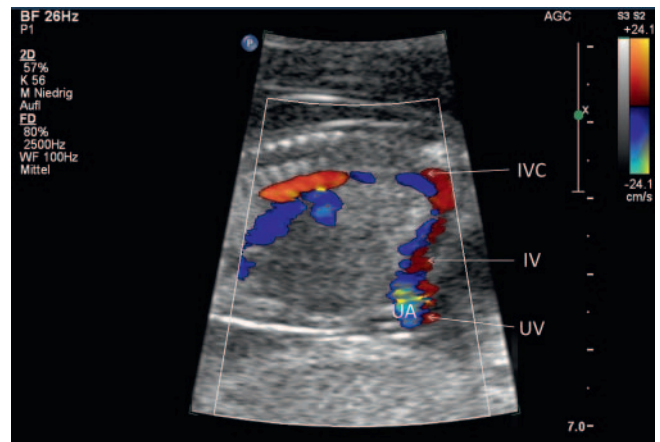
► **Fig. 1** Agenesis of ductus venosus with intrahepatic umbilical venous drainage to the portal venous system in a fetus at 19 weeks of gestation. In the median sagittal view no connection of the umbilical-portal venous complex to the subdiaphragmatic vestibulum can be demonstrated. IVC: inferior vena cava; HV: hepatic vein; PS: portal sinus; RA: right atrium; UV: umbilical vein



► **Fig. 3** Agenesis of ductus venosus with extrahepatic umbilical venous drainage to the right atrium in a fetus at 22 weeks of gestation. In the median sagittal view the broad insertion of the umbilical vein (UV) in the right atrium (RA) is demonstrated. TC: celiac trunk; UA: umbilical artery



► **Fig. 2** Agenesis of ductus venosus with extrahepatic umbilical venous drainage to the inferior vena cava 20 mm caudal to the typical insertion site in a fetus at 28 weeks of gestation. In the median sagittal view **a** the broad insertion of the umbilical vein (UV) in the inferior vena cava (IVC) is demonstrated. The 3D reconstruction **b** additionally shows the marked perfusion of the hepatic artery (HA). RA: right atrium; TC: celiac trunk



► **Fig. 4** Agenesis of ductus venosus with extrahepatic umbilical venous drainage to the iliac vein in a fetus at 17 weeks of gestation. In a paravesical sagittal view the umbilical artery (UA) is coded in blue while the umbilical vein (UV) connecting to the iliac vein (IV) is coded in red. IVC: inferior vena cava

infection and 3 complicated monochorionic pregnancies (two twin-twin-transfusion syndromes (TTTS) and one twin-reversed-arterial-perfusion syndrome (TAPS)) (► **Table 1**).

The majority of the group of fetuses with aneuploidies was affected by trisomy 21 (10/24; 41.6%). Turner syndrome (45, X0) was detected in 5 cases (20.8%), trisomy 18 in 2 cases (8.3%) and there was one case each of trisomy 13, trisomy 9, trisomy 22 and one microdeletion on chromosome 5. Three patients denied invasive procedures, but sonographic signs were highly suggestive of chromosomal abnormalities (one with holoprosencephaly and omphalocele at 12 weeks and two with cystic hygroma and generalized skin edema at 14 and 20 weeks, the latter also presenting with aortic coarctation).

► **Table 1** Associated anomalies and outcome in 119 prenatal cases with agenesis of the ductus venosus.

associated condition		total	TOP	IUFD	NND	ICD	alive
isolated		24	0	0	1	0	23
chromosomal anomalies		24					
	trisomy 21	10	8				2
	monosomy X	5	2		1		2
	trisomy 18	2	1		1		
	other	7	4	2			1
genetic syndromes		2	1				1
	achondroplasia	1					1
	Beckwith-Wiedemann	1	1				
multiple malformations		25	11	1	4	1	8
	VACTERL	4	1		1		2
	other	21	10	1	3	1	6
cardiac anomalies only		25	2			1	22
	VSD	5				1	4
	CoA	5					5
	other	15	2				13
single extracardiac anomalies only		14	1		3		10
	diaphragmatic hernia	6			1		5
	lower urinary tract obstruction	2					2
	omphalocele	3	1				2
	hydrothorax	2			1		1
	meconium peritonitis	1			1		
cytomegalovirus infection		2	1				1
twin to twin transfusion syndrome/TRAP		3		2		1	
total		119	31	5	10	3	70

ICD: death in infancy or childhood; IUFD: intrauterine fetal death; NND: neonatal death; TOP: termination of pregnancy; TRAP: twin reversed arterial perfusion.

Drainage site

Overall, we identified 84 cases (70.6%) with intrahepatic UV-PVS drainage and 35 cases (29.4%) with extrahepatic UV-systemic venous drainage (► **Fig. 5**). The majority of cases with extrahepatic drainage had an UV-IVC connection (22/35; 62.8%) or UV-RA connection (12/35; 34.3%) and in one case (2.9%) there was an UV-IV connection.

In the 24 cases with isolated ADV, there were 17 fetuses (70.8%) with intrahepatic UV-PVS drainage and 7 fetuses (29.2%) with extrahepatic drainage (6 UV-IVC, 1 UV-RA).

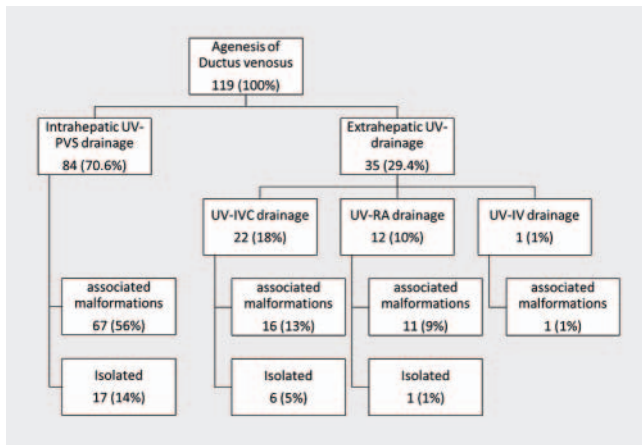
In the 95 cases with additional findings, there were 67 fetuses with intrahepatic UV-PVS drainage (70.5%) and 28 cases (29.5%) with extrahepatic drainage (16 UV-IVC, 11 UV-RA and 1 UV-IV). There was no statistically significant association between the type of drainage and associated anomalies ($p = 1$).

Pregnancy outcome

Overall adverse outcome was present in 41.2% (49/119). 26.1% of patients (31/119) opted for TOP due to additional malformations. There were 5 (4.2%) IUFDs, 10 NNDs (8.4%) and 3 (2.5%) ICDs. At latest follow-up, 70 infants (58.8%) were alive. After exclusion of TOP, outcome was favorable in 70 of 88 cases (79.5%).

In the group with isolated ADV, there were 23 survivors (95.8%) and 1 neonatal death (4.2%). In the group with associated findings, 31 (32.6%) patients opted for TOP, and there were 5 IUFDs (5.3%), 9 NNDs (9.5%), 3 ICDs (3.2%) and 47 survivors (49.4%).

Adverse outcome in isolated cases occurred in 4.2% (1/24) vs. 50.5% (48/95) in associated cases ($p = 0.0001$). After exclusion of TOP, the difference in rates of adverse outcome between isolated (4.2%) vs. non-isolated cases (26.6%) remained statistically significant ($p = 0.019$).



► **Fig. 5** Distribution of the different umbilical venous drainage sites in 119 cases with agenesis of the ductus venosus in cases with or without associated anomalies. RA: right atrium; IV: iliac vein; IVC: inferior vena cava; UV: umbilical vein

Overall, adverse outcome was significantly more common in cases with extrahepatic drainage (20/35; 57.1 %) compared to intrahepatic drainage (29/84; 34.5 %) ($p = 0.026$). This remained true when comparing rates of adverse outcome of non-isolated extrahepatic drainage (19/28; 67.8 %) vs. non-isolated intrahepatic drainage (29/67; 43.3 %) ($p = 0.042$), but not for isolated cases. However, after exclusion of TOP, adverse outcome was not significantly related to drainage location in non-isolated cases (extrahepatic (7/16; 43.8 %) vs. intrahepatic drainage (10/48; 20.8 %); $p = 0.103$).

Isolated vs. non-isolated intrahepatic drainage site

In the 17 cases with isolated intrahepatic UV-PVS drainage, there were 3 intrauterine growth restrictions (17.6 %) and 4 minor anomalies of the vascular system (single umbilical artery, persistent right umbilical vein, umbilical vein varix and aberrant right subclavian artery). All of these fetuses were born alive. One child had an atrial septal defect and one had a mild pulmonary stenosis after birth. Another child had a hemodynamically non-relevant persistent intrahepatic portosystemic shunt from the left portal vein to a hepatic vein. This child is currently 20 months old and is otherwise developing well.

Among the 67 fetuses with non-isolated intrahepatic UV-PVS drainage, 11 (16.4 %) had hydrops and another 4 (6 %) showed cardiomegaly. There were 19 TOPs (28.3 %), 4 IUFDs (6 %), 5 NNDs (7.5 %), 1 ICD (1.5 %) and 38 survivors (56.7 %). Two IUFDs occurred in complicated monochorionic pregnancies: one in TOPS (twin oligohydramnios polyhydramnios sequence) after laser therapy and one in the pump twin in twin reversed arterial perfusion sequence. The other two intrauterine deaths and all other cases of neonatal or infant mortality occurred in fetuses with multiple anomalies. There was one intrahepatic portosystemic shunt in a neonate with omphalocele that closed spontaneously.

Isolated vs. non-isolated extrahepatic drainage site

In the group with isolated extrahepatic drainage, 4/7 (57.1 %) fetuses had cardiomegaly and 1/7 (14.3 %) had IUGR. There was one neonatal death (1/7) due to neonatal complications after delivery at 26 weeks of gestation following premature rupture of membranes at 16 weeks. In the remaining 6 cases, there were three persistent portosystemic shunts after birth, one of which required interventional occlusion. One child had an Abernethy II malformation with partial agenesis of the portal venous system but is developing well at 10 years of age. The third portosystemic shunt closed spontaneously within the first months of life.

In the group with non-isolated extrahepatic drainage, 3/28 (10.7 %) fetuses had cardiomegaly and 2/28 (7.1 %) had hydrops. There were 12 TOPs (42.9 %), 1 IUFD (3.6 %) due to trisomy 13, 4 NNDs (14.3 %), 2 ICDs (7.1 %) and 9 survivors (32.1 %). All 4 NNDs were due to associated malformations. One infant with a large ventricular septal defect died due to liver failure in association with total agenesis of the portal venous system while awaiting liver transplantation after cardiac repair. The second ICD occurred in a prematurely born child due to pulmonary hypertension at ten months of age.

In the 9 survivors, there was one persistent portosystemic shunt (UV-IVC extrahepatic shunt) that closed spontaneously after birth.

Discussion

In recent years the fetal venous circulation and ADV have become a topic of interest and several retrospective case studies have been published. Our study as well as other recent publications [3, 9] have demonstrated that intrahepatic drainage is more common (70 %) than extrahepatic drainage. This contradicts the majority of case series of ADV that reported a predominance of extrahepatic UV drainage [10, 12] resulting in over-representation of extrahepatic drainage in a recent meta-analysis [19].

The vast majority (> 79 %) of our cases were associated with congenital heart disease, chromosomal anomalies and multiple malformation syndromes, all contributing equally to these cases. We saw a predominance of multiple malformation syndromes compared to isolated (extracardiac) anomalies.

Overall, extrahepatic UV-drainage seems to carry a worse prognosis, but after exclusion of TOP there was no difference in outcome between intrahepatic and extrahepatic drainage.

An extrahepatic connection of the umbilical vein to the IVC caudal to the usual drainage site has been reported to be more common in trisomy 21 and 61.5 % of fetuses were reported to have chromosomal abnormalities [20, 21]. In our cohort 60 % of fetuses with trisomy 21 had intrahepatic drainage, but the IVC was indeed the only extrahepatic drainage site in fetuses with trisomy 21. The overall incidence of chromosomal anomalies in UV-IVC drainage in our study was slightly lower (42.1 %) than in other studies, which is probably due to the small numbers. All fetuses with UV-IVC drainage and aneuploidies showed additional ultrasound markers.

We detected cardiomegaly in > 50 % of isolated extrahepatic drainage to the IVC or RA. However, in cases with intrahepatic

drainage, cardiomegaly was only seen in the presence of associated anomalies. This might be due to a referral bias as cardiomegaly was the main reason for referral in isolated cases. In our study hydrops was only seen in association with aneuploidies or hydrothorax. Progressive heart failure or development of hydrops was never seen during prenatal follow-up. Therefore, we speculate that cardiomegaly in isolated ADV is not associated with adverse outcome and hydrops is rather causally related to the additional anomalies.

The fetal portal and hepatic venous system and its malformations have been described in detail in the last decade [6–8, 18, 22, 23] and there is rising awareness of portal venous malformations that can present in the context of ADV, e. g. portosystemic shunts and agenesis of the portal venous system, that can have a severe impact on postnatal development. Achiron et al. [9] recently proposed a new classification of fetal umbilico-portal-systemic venous shunts resulting in a problem that has not yet been widely acknowledged: there is no universally accepted definition of the DV [24]. It can be defined either anatomically or functionally. The main novelty of the recently proposed classification is the concept of a *ductal systemic shunt*, describing an entity where the umbilical-portal system forms a small “ductus-like” vessel that drains either into the IVC caudally to its usual drainage site or into a hepatic vein and is interpreted as an ectopic DV. All of these cases have a good prognosis with regards to normal development of the portal system. As there is no normally located DV, these cases have been classified as ADV in all other publications, including our current one. Yagel et al. [25] have evaluated the diameter of the shunt in extrahepatic UV-drainage. If the diameter of the connecting vessel was smaller than the UV, the outcome was generally good with regards to the integrity of the portal venous system and liver function. In our cohort, the shunt diameter was not systematically assessed prior to 2012. Therefore, we cannot draw any conclusions regarding this parameter. Merging the existing evidence, ADV seems to be functionally relevant for the developing portal venous system in cases where adequate intra-vascular pressure within the liver cannot be maintained. Small shunting vessels might functionally replace the DV, even if their drainage site is ectopic.

We could demonstrate that the prognosis depends mainly on the associated malformations, but there was a persistence of a portosystemic shunt after the immediate neonatal period in 4/15 (26.6%) of the survivors with extrahepatic drainage and one case of total portal agenesis, whereas there were only two portosystemic shunts (2.3%) in the intrahepatic group. In our opinion, evaluation of the presence of an anatomically normal DV should be an integral part of a detailed anomaly scan and in its absence a thorough evaluation of the portal and hepatic veins is mandatory. However, clinically relevant anomalies of the portal venous system (e. g. portosystemic shunts, partial portal agenesis) can occur even if the DV is present [9, 18].

Our study, although representing the largest cohort of prenatally diagnosed ADV, has a number of limitations. Most cases were referred in the second trimester for suspected anomalies. Therefore, first trimester DVA is underrepresented in our cohort and the natural history of first trimester DVA might differ from cases detected later in pregnancy. In addition, due to the long study

period, a detailed prenatal evaluation of the hepatic/UV/PVS circulation was only carried out in the second half of the study period. Neonates with intrahepatic UV-PVS drainage, especially if there was not sign of cardiomegaly, had a neonatal follow-up in our centers but were followed elsewhere afterwards. The follow-up duration in our cohort was variable. Therefore, cases with prenatally missed partial agenesis of the PVS or portosystemic shunts that were clinically unapparent in the postnatal period might have been missed. A further drawback of our study is the absence of histopathological examinations of the PVS in cases of TOP and IUFD as postmortem examinations were often denied by the parents.

In conclusion, in cases of isolated ADV with intrahepatic UV-drainage, the prognosis is excellent and counseling can be reassuring. In cases with intrahepatic shunts between portal and hepatic veins on prenatal ultrasound, neonates should be monitored for hyperammonia and elevated liver enzymes after birth and follow-up should be performed until closure of the shunt is demonstrated [26]. In cases with extrahepatic UV-drainage, follow-up until closure of the portosystemic shunt is mandatory. Agenesis of the portal system should be ruled out in all cases, bearing in mind that cases with postnatal recovery of prenatally suspected agenesis have been reported [9]. Smaller diameter and location of the UV-drainage might be prognostic markers with regards to the persistence of a portosystemic shunt or agenesis of the portal venous system that need to be prospectively evaluated in the future. Our study underlines the impact of associated anomalies on prenatal and postnatal outcome in prenatal ADV. In cases of isolated agenesis of the ductus venosus, the postnatal outcome depends on the persistence of a portosystemic shunt or agenesis of the portal venous system.

Conflict of Interest

The authors declare that they have no conflict of interest.

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