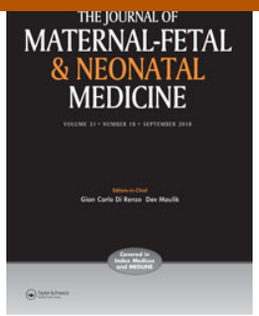

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REVIEW ARTICLE

Absent ductus venosus: case series from two tertiary centres

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ABSTRACT

Introduction: Congenital absence of the ductus venosus (ADV) is a rare vascular anomaly often associated with fetal cardiac and extracardiac anomalies, aneuploidies, and hydrops. The prognosis depends on the patterns of abnormal venous circulation, on the associated malformations and on chromosomal aberrations.

Methods: We performed a retrospective audit of all consecutive cases with ADV referred in our centres and analysed the outcomes.

Results: A total of six cases with prenatally diagnosed ADV were identified. The gestational age at diagnosis ranged from 15 to 35 weeks. Karyotyping was performed in all cases. Normal karyotype was found in five out of the six cases. Overall, four neonates survived at 28 days follow-up. The other two died 48 h after delivery: both of them had extrahepatic ADV.

Discussion: Absence of the ductus venosus may be compatible with normal fetal development without relevant disturbance of circulation and oxygenation independently from type of abnormal venous circulation.

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Ductus venosus agenesis; prenatal diagnosis; ultrasonography

Introduction

The ductus venosus (DV) connects the umbilical vein with the left portal system and the left hepatic vein, allowing proper oxygenation of the fetal organs. It courses superiorly from the transverse portion of the left portal vein to end in inferior vena cava near the confluence of the hepatic veins [1,2]. The DV plays a major role in the redistribution of fetal circulation. The volume of its flow depends on the pressure gradient between the umbilical vein and the heart. In cases of fetal hypoxia or reduced venous return from the placenta, the fraction of umbilical blood shunted through the DV increases significantly [3]. The normal embryologic development of the umbilical veins and their relationship to the liver and to the vitelline veins are known. The right umbilical vein normally obliterates and disappears by days 33–34, while the part of the left umbilical vein between the body wall and the liver normally persists throughout the fetal life, as the DV. After birth the left umbilical vein and the DV obliterate, and form the ligamentum teres and the ligamentum venosum, respectively.

Failure of the development of primitive veins of new vessels and anastomoses can produce abnormalities of umbilical-portal circulation that sometimes can be associated with DV agenesis, i.e. absence of the ductus venosus (ADV) [1,4]. Little is known about the incidence, and clinical implications of ADV.

Three main patterns of abnormal connection of the intraabdominal umbilical vein can be identified in case of ADV: the umbilical vein bypasses the liver and drains into the right atrium directly (46%); the umbilical vein bypasses the liver and connects to the inferior vena cava by one iliac or renal vein (25%); the umbilical vein connects to the portal circulation without giving rise to the DV (21%) [4].

We performed a retrospective audit off all recent cases with ADV seen in our centres.

Materials and methods

This is a retrospective multicentre case-series study performed at University of Naples "Federico II" (Naples, Italy), and at Thomas Jefferson University Hospital

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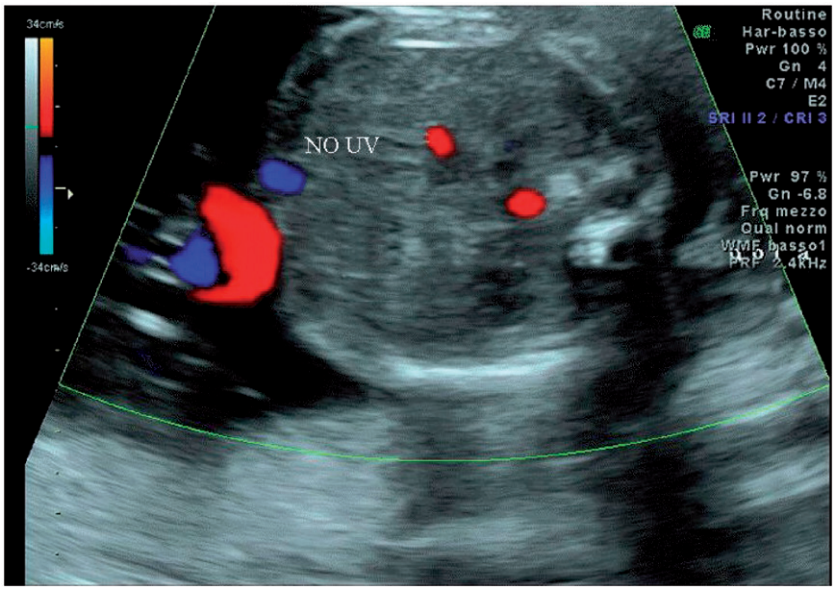

Figure 1. Transverse view of the abdomen. The Ductus Venosus cannot be visualized, even with color Doppler.

(Philadelphia, PA). All consecutive women with diagnosis of ADV from January 2008 to January 2016 were analysed. According to our protocol, the DV is assessed in all cases of suspected cardiac abnormalities or effusion/hydrops. The DV is insonated using colour or power Doppler in two planes during fetal quiescence. If the DV is not visualised connecting the portal sinus with the subphrenic confluence, ADV is diagnosed.

All ultrasound examinations were performed on GE Voluson E8 (GE Healthcare, Milwaukee, WI, USA) by Fetal Medicine Foundation (FMF) certified operators.

In both centres a retrospective search of the electronic database was made. The raw clinical data was extracted and organised to classify the ADV as isolated or associated with structural abnormality, chromosomal abnormality or with effusions/hydrops.

In both centres, women with ADV underwent fetal echocardiography and regular ultrasound follow-up every 2–4 weeks.

The pregnancy records of all the mothers who were diagnosed to have a fetus with ADV were reviewed and perinatal outcomes ascertained from the records. The perinatal outcomes were recorded.

In addition, a comprehensive literature review was performed. Electronic databases (i.e. MEDLINE, Scopus, ClinicalTrials.gov, EMBASE, Sciencedirect, the Cochrane Library at the CENTRAL Register of Controlled Trials, SciELO) were searched from their inception until January 2016. Search terms used were the following text words: "ductus", "agenesis", "prenatal diagnosis", "fetal Doppler" and "absent ductus venosus". No restrictions for language or geographical location were applied. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches. The electronic search and the eligibility of the studies were independently assessed by two authors (Andrea Ciardulli, Gabriele Saccone). Differences were discussed with a third reviewer (GMM).

Results

A total of six cases with prenatally diagnosed ADV were identified (Figure 1). Two cases were from University of Naples "Federico II", and four from Thomas Jefferson University. The gestational age at diagnosis ranged from 15 to 35 weeks (Table 1). Karyotyping was performed in all cases. Normal karyotype was found in five out of the six cases. Overall, four neonate survived at 28 days follow-up. The other two died 48 h after delivery: both of them had extrahepatic ADV' The systematic review found 19 studies (74 cases) of ADV [1,4–21]. Overall 10 (14%) induced terminations of pregnancy, 7 (9%) perinatal losses (either fetal or neonatal death), and 57 (77%) survivals were reported (Table 2).

In prior studies, gestational age at diagnosis ranged from 14 to 36 weeks (mean 25.8 weeks of gestations). The most common associated anomalies were cardiomegaly, portal vein abnormalities, and single umbilical artery. Hydrops was found in 10/74 (13.5%) foetuses..

Discussion

Absence of the ductus venosus is a rare fetal anomaly with an incidence of about 6/1000 cases in high risk

Table 1. Case from University of Naples "Federico II" and Thomas Jefferson University Hospital.

	GA at diagnosis (weeks)	Sonographic findings/associated anomalies	Hydrops	GA at delivery (weeks)	Outcome
Federico II, 1 (Figure 1)	22	Liver bypass and direct connection to the right atrium. Normal karyotype	–	39	S
Federico II, 2	23	Polyhydramnios, scalp edema, cardiomegaly. Normal karyotype	+	33	PL (death after 24 h)
TJUH, 1	15	CAVC; absent left umbilical artery	–	35	S
TJUH, 2	32	Polyhydramnios, scalp edema, enlarged cisterna magna. Normal karyotype	+	32	PL (death after 24 h)
TJUH, 3	35	Porto-caval shunt, paradoxical IV septal motion with preserved ventricular function, dilated IVC	–	36	S
TJUH, 4	32	Cardiomegaly, polyhydramnios, LVNC, IUGR. Trisomy 13 mosaicism	–	39	S

N/A: not available; GA: gestational age; S: survivor; PL: perinatal loss; CAVC: complete atrioventricular canal defect; IVC: inferior vena cava; LVNC: left ventricular noncompaction; IUGR: intra uterine growth restriction; TJHU: Thomas Jefferson University Hospital.

populations [6–34]. Two major mechanisms seem to be involved in the genesis of fetal vein anomalies; in most cases primary maldevelopment of the venous system occurs, while in a minority of cases possible thromboembolic events or other systemic diseases may play a role [7].

The prognosis of ADV depends on the patterns of abnormal venous circulation, on the associated malformations and on chromosomal abnormalities. The overall mortality rate was 9% after review of the literature.

Agenesis of the ductus venosus might induce hydrops: in every case of hydrops the venous system should be evaluated by ultrasonography prenatally and/or immediately postnatal [23]. On the basis of the available data in literature, fetuses with ADV appear to be at risk of additional cardiac and extracardiac anomalies (Tables 1 and 2), including chromosomal abnormalities and a marked tendency towards the development of intrauterine heart failure. Cardiomegaly is a common sign in cases of ADV in which the umbilical vein bypasses the liver and drains into the right atrium directly [4,7–11]. The mechanism triggering in utero heart failure is not completely understood; it has been speculated that the umbilical vein bypassing the liver and draining directly into the heart may result in increased preload, increased cardiac work, progressive cardiac decompensation leading to high central venous pressure: this chronic volume overload may lead to increased demand on the fetal myocardium with the risk of high-output heart failure. In this cases polyhydramnios may appear early in gestation and became severe by the onset of the third trimester [4].

Anomalies which may occur in cases of ADV involve the cardiovascular system (atrial or ventricular septal defect, tricuspid regurgitation, interruption of vena cava, portal vein agenesis) [4,7–9,12], the central nervous system (CNS) (Dandy-Walker syndrome) [4], the gastrointestinal system (duodenal atresia, imperforate anus, tracheoesophageal fistula, intestinal malrotation) [9,10], the genitourinary system (ectopic kidney, unilateral renal agenesis, bilateral hydronephrosis, micropenis) [9,12], the placenta and umbilical cord (single umbilical artery) [9,12], the face (labial cleft) [9] and the musculoskeletal system (hemivertebrae) [12,24]. Abnormal karyotype may be also diagnosed [4,8]: according to data present in literature [25] the most frequent association of ADV is with Turner's syndrome and Noonan's syndrome. It has been suggested that Turner–Noonan phenotype could be a malformation sequence involving lymphatic drainage initiated by a defect in a putative lymphogenic gene located on the Xp chromosome [26,27].

In a recent multicentre retrospective study with systematic review of the literature [34], Moaddab et al. concluded that fetal hydrops, the presence of associated congenital anomalies and premature delivery are associated with poor prognosis in fetuses with ADV.

Fetuses with increased nuchal translucency at 11–14 weeks are at risk of heterogeneous fetal anomalies [28] and of unfavourable outcome. The association between cystic hygroma and the absence of the DV is known [25]. The increased nuchal translucency thickness in the first trimester should be carefully evaluated by ultrasonography prenatally.

Absence of the ductus venosus may lead to significant long-term complications if this is associated with fetal anomalies such as portal vein agenesis, an anomaly which is present in approximately one-half – one-third of these infants. The major complications reported in the literature as associated with ADV include pulmonary edema, abnormal liver development with focal nodular hyperplasia and hepatic tumours and portosystaemic encephalopathy [29–32]. Our result and the review of literature suggest that

Table 2. Literature review: summary table.

References	GA at diagnosis (weeks)	Sonographic findings/associated anomalies	Hydrops	GA at delivery (weeks)	Outcome
Jouk 1991 [1]	23	No anomalies.	−	40	S
Greiss 1992 [12]	23	Single umbilical artery, interruption of the intrahepatic inferior vena cava, agenesis of right kidney, bifid right thumb, T12 hemivertebra.	−	39	S
Chaoui 1994 [14]	20	Tricuspid regurgitation.−	N/A	S	
Jorgensen 1994 [16]	20	No anomalies.	+	N/A	TOP
	21	No anomalies.	+	N/A	TOP
	36	No anomalies.	+	N/A	PL
	34	Microcephaly, arthrogryposis.	−	N/A	PL
Kinare 1996 [15]	28	Right hydronephrosis, hypertelorism, syndactyly, hemivertebra.	− N/AS		
Cohen 1997 [11]	23	Cardiomegaly.	−	N/A	TOP
Avni 1997 [17]	29	No anomalies; normal karyotype.	−	37	S
Hofstaetter 2000 [8]	37	Cardiomegaly, portal vein agenesis	−	38	S
	27	Portal vein agenesis	+	21	TOP
	19	DIV, portal vein agenesis, Turner.	+	36	S
	35	Portal vein agenesis.	+	36	S
Achiron (2000) [7]	21	Cardiomegaly.	−	N/A	TOP
	14	Portal agenesis of the left portal system.	−	33	S
Contratti. 2001 [4]	30	Cardiomegaly, severe hypertrophy, tricuspid regurgitation, portal vein agenesis.	−	38	S
	28	Cardiomegaly, portal vein agenesis. Polyhydramnios.	−	32	S
	28	Cardiomegaly, portal vein agenesis,	−	34	S
	21	Dandy-Walker syndrome, trisomy 18.	−	N/A	TOP
Langman 2001 [5]	N/A	TTTS; twin A: dilated UV draining into the right atrium, dysmorphic features: low set ear, depressed nasal bridge and a short nose; twin B: no malformation.	−32	PL	
Jaeggi 2002 [9]	30	ASD, cardiomegaly.	−	34	S
	30	ASD, cardiomegaly.	−	35	S
	24	Labial cleft, micropenis, cardiomegaly.	−	32	S
	29	Single umbilical artery, cardiomegaly.	−	32	S
	34	Portal vein to the right atrium, cardiomegaly.	−	35	S
	19	Portal vein hypoplasia, labial cleft, ASD.	−	N/A	S
	29	Cardiomegaly normal karyotype, intestinal malrotation, interrupted inferior vena cava.	+	33	S
Volpe 2002 [10]	20	Cardiomegaly.	−	N/A	TOP
	25	Cardiomegaly.	+	25	TOP
	26	Cardiomegaly, anorectal malformation	−	33	S
Sau 2004 [18]	21	Atrioventricular septal defect, double-outlet right ventricle, cardiomegaly.	−	30	PL
	21	Tracheoesophageal fistula, oesophageal atresia.	−	30	PL
	20	Ventricular septal defect, common arterial.	−	38	S
	24	Trunk from right ventricle, cardiomegaly, pericardial effusion, normal karyotype	−	39	S
	20	Bilateral superior cava, cardiomegaly.	−	34	PL
	27	Normal karyotype, tricuspid and mitral regurgitation, cardiomegaly.	−	38	S
	34	Hypoplastic left heart and left lung, double-outlet right ventricle, right ventricular hypertrophy coarctation of aorta.	−	39	PL
	29	Duodenal atresia, imperforate anus.	−	34	S
	31	Polyhydramnios, normal karyotype	−	37	S
Berg 2006 [13]	17	VACTERAL association, esophageal atresia, horseshoe kidney, hemivertebrae T4-9, single umbilical artery.	+39S		
Acherman 2007 [6]	30	Cardiomegaly, tricuspid regurgitation, pericardial effusion	+33	S	
Hajdù Nov 2007 [19]	22	Cardiomegaly, bradicardia, ventricular septal defects, transposition of the great arteries, normal karyotype	−N/A	TOP	
Hofmann 2012 [20]	25	No anomalies.	−	41	S
Corbacioglu 2012 [21]	28	Normal karyotype, brachycephaly, strawberry-shaped head, ventricular septal defect, pulmonary artery hypoplasia.	−	N/A	TOP
	26	Subaortic ventricular defect, overriding aorta, pulmonary hypoplasia.	−	N/A	S
	32	No anomalies.	−	N/A	PL

GA: gestational age; S: survivor; TOP: termination of pregnancy; PL: pregnancy loss; N/A: not available; UV: umbilical vein; TTTS: twin to twin transfusion syndrome; ASD: atrial septal defect.

the perinatal outcome depends on the patterns of abnormal venous circulation and on the presence of other cardiac, extracardiac and chromosomal abnormalities. ADV without liver bypass may represent a subgroup with a more favourable outcome, if it is not associated with other malformations and the karyotype is normal. ADV and liver bypass, with an additional risk of developing congestive heart failure that significantly affects outcome, represent a subgroup with a more unfavourable outcome even if the fetal cardiovascular anatomy is otherwise normal.

Absence of the ductus venosus with liver bypass [2,4,25], may be detected more reliably by the visualization of the aberrant course of the intra-abdominal umbilical vein during the US examination; ADV without liver bypass often escapes diagnosis because it requires a meticulous colour flow mapping of the portal circulation in various planes [13].

The ultrasonographic diagnosis of portal vein agenesis is more difficult and is often associated with ADV [4,7–9]; during the prenatal counselling session the couple must be informed of the type of malformation, of its variants and its possible complications considering that also without other fetal detected anomalies, in cases of portal vein agenesis, the long-term sequel can't be well predicted.

In normal fetuses the umbilical venous blood shunted through the DV to the right heart decreases from 30% to less than 20% during the second half of the pregnancy; this results in an increased flow of well-oxygenated blood in the liver compared to the brain at this stage. These data support the hypothesis that the DV plays a less important role in supplying well-oxygenated blood to the brain and the myocardium in late gestation [2,33]. In cases of ADV the entire oxygenated blood from the placenta returns directly into the heart via the umbilical vein, so that fetal arterial blood oxygen concentration may not be affected [9]. However, ADV may also be associated with other complications [34–38].

A careful assessment of the DV and the umbilical vein should be part of the routine evaluation of every fetus with unexplained cardiomegaly, atrioventricular valve insufficiency, increased nuchal translucency or nonimmune hydrops; the fetus should undergo a careful clinical and ultrasonographic assessment prenatally and postnatally to exclude any cardiac and extracardiac abnormality.

We observed that isolated ADV may be compatible in many cases with normal fetal development without relevant disturbance of circulation and oxygenation independently from type of abnormal venous circulation (Table 2). Dependent on the other associated anomalies and on the possible surgical correction of these, the prognosis of babies with absence of the DV and umbilical vein connected to the right atrium is good in 62% of the prenatally diagnosed cases (Table 2) [4,5,7–12,14–17]; poor outcome of the pregnancy is often best correlated with the severity of fetal congestive heart failure [4,5,7,8,10,11,17] and the presence or absence of an abnormal karyotype [4,8] (Table 2).

However, limited follow-up prevents any definitive conclusions concerning the long-term outcome of this rare anomaly; further studies and longer follow up are needed to improve the counselling and the management of the fetuses with the in utero diagnosis of ADV.

Disclosure statement

No potential conflict of interest was reported by the authors.

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