Ductus Venosus Agenesis: Ultrasound Diagnosis and Outcome

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ABSTRACT

Aim: The aim of the article was to enumerate the outcomes observed in fetuses with ductus venosus agenesis (DVA) in a tertiary care center.

Methodology: A retrospective observational study was conducted at the fetal medicine unit of a tertiary care center between July 2015 and July 2020. Outcomes were followed up for all fetuses diagnosed with DVA.

Results: A total of 14 patients were diagnosed with DVA in this study period. One patient was lost to follow-up and outcomes of 13 fetuses were studied. Nine patients presented with isolated DVA. Four patients had associated anomalies and underwent termination of pregnancy. Of the remaining nine fetuses with isolated DVA, eight survived with good neonatal outcomes.

Conclusion: Among eight fetuses with DVA without hepatic bypass (89%) and one fetus with intrahepatic umbilical venous drainage (IHD) (11%), seven of eight fetuses (88%) with isolated DVA had good neonatal outcomes. One fetus with intrahepatic drainage also had a good outcome. This leads to the impression that with close monitoring of the fetuses with DVA, particularly those without hepatic bypass, a good neonatal outcome can be expected.

Clinical significance: DVA is a rare anomaly. It is known to be associated with chromosomal abnormalities, structural defects, fetal growth restriction (FGR), and intrauterine fetal demise. Evaluation of ductus venosus (DV) at 11–13 weeks scan increases the diagnosis of DVA and its associated anomalies. This helps in the early detection of cardiac anomalies in these fetuses, and additionally, they benefit from close monitoring with serial Doppler evaluation.

Keywords: Congenital anomalies, Doppler ultrasound, Ductus venosus, Ductus venosus agenesis, Extrahepatic venous drainage, Intrahepatic venous drainage.

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INTRODUCTION

During the development of fetal circulation, right umbilical vein involutes and a direct channel develops between the left umbilical vein and the right hepatocardiac channel.¹ This direct channel is the ductus venosus (DV) and its agenesis is a rare congenital anomaly. DV is of great importance in the fetal circulation as it is essentially a physiological shunt that transports oxygenated blood from the placenta to the heart.² Ultrasound (USG) imaging of fetal venous system was introduced in the mid-1980s. Prior to USG, diagnosis of DVA was made only during fetal autopsy and the first published case report of prenatally diagnosed DVA was by Griess et al.³ DVA is diagnosed by the absence of connection between the portal vein and inferior venacava (IVC) using color Doppler taken in different planes.⁴⁻⁵ The venous flow via DV is related to the right atrial pressure and volume changes throughout the entire cardiac cycle and produces a characteristic triphasic pattern.⁵

• The first highest peak velocity coincides with the ventricular systole (S); during this phase, the pressure gradient between the umbilical vein and the atrium is the highest.
• The second peak with a forward flow corresponds to the early diastole (D), with the opening of the atroventricular valves and early passive filling of the ventricles.
• The third phase (lowest velocity) corresponds to the atrial contraction (a) during the late diastole, where the atrial pressure is high and there is a low-pressure gradient.⁷

In 1998, Gembruch et al. described the prenatal diagnosis of DVA by visualization of B-mode and color Doppler.⁵ The inclusion of assessment of DV flow in first-trimester screening increases trisomy 21 detection rates by 96% with a false-positive rate of 2.5%.⁸ Therefore, DV imaging has become an integral part of first-trimester scan to look for aneuploidies and structural defects and the early detection of this rare yet significant anomaly with the help of Doppler color flow mapping is the cornerstone to achieve sequential follow-up and management.

Major limitations of DV flow analysis are that it is time-consuming and requires experienced operators to detect changes as early as 11−13 weeks. A paper by Rao et al., focusing on the controversies and efficacy of 3D and 4D USG, stated that the usage of 3D/4D USG provides maximum prenatal diagnostic benefit to the couple in the detection of fetal malformations and treatment options.⁹ Recent advances have suggested the
use of 3D power Doppler for examination of DV as it provides a real-time depiction of complex anatomical structures in blood vessels of interest.\textsuperscript{10,11} This suggests that 3D reconstruction of DV can be utilized for a better understanding of the abnormal course of umbilical vein. Although this method requires specialist training, it has proved to be an invaluable diagnostic tool for DVA.

In the case of DVA, aberrant vessels develop to maintain fetal circulation, and the two alternative routes for umbilical venous return are:

- Extrahepatic umbilical venous drainage (EHD)—bypasses the liver by direct connections to the iliac veins, inferior vena cava, or the right atrium.\textsuperscript{4,12–14}
- Intrahepatic umbilical venous drainage (IHD)—via the portal system, namely the portal sinus connects to the hepatic sinusoids without giving rise to the DV.\textsuperscript{4,5,15,16}

High incidence of congestive cardiac failure, portal venous system agenesis, and hydrops fetalis has been observed in fetuses with EHD.\textsuperscript{4,13,14} IHD has shown better neonatal outcome as they are rarely associated with other malformations.\textsuperscript{17,18}

At present, it is known that 65% of patients with DVA are associated with congenital morphological defects.\textsuperscript{16,17} The major cardiac anomalies associated with DVA are atrial septal defect, ventral septal defect, double outlet right ventricle, pulmonic atresia, tricuspid atresia, and transposition of the great arteries. Multisystem anomalies involving the alimentary tract such as duodenal atresia and tracheoesophageal fistula (TEF), the urogenital system (bilateral hydronephrosis and ectopic kidney), and the skeletal system (hemivertebrae and structural defects of radius and ulna) have been noted.\textsuperscript{10,13,19} EHD is associated with agenesis of portal venous system, which postnatally can present with pulmonary edema, focal nodular hyperplasia, and hepatic tumors. Isolated DVA has shown to have 80 to 100% chance of normal neonatal outcome.\textsuperscript{20,21}

**Materials and Methodology**

This was a retrospective observational study conducted at the fetal medicine unit of a tertiary care center in South India, between July 2015 and July 2020. All patients with ultrasound diagnosis of DVA irrespective of gestational age, booked, or referred were included. Fourteen cases of DVA were seen and one patient was lost to follow-up. Hence, the outcomes of 13 patients were analyzed.

**Results and Outcome**

Thirteen patients with DVA were followed up. Nine of 13 patients presented with isolated DVA and four patients had associated anomalies (Flowchart 1).

Most fetuses with DVA (69%) were seen in mothers aged between 26 and 35 years. They were equally distributed between primigravidas (7 of 13) and multigravidas (6 of 13).

Among the six fetuses with first-trimester diagnosis, three had associated anomalies and underwent termination of pregnancy. These included one fetus with megacystis (bladder diameter—12 mm), DVA, and single umbilical artery (SUA) where the family declined direct testing and opted for termination (Table 1). The second fetus underwent target scan with fetal echo at 19 + 6 weeks which revealed additional findings of coarctation of aorta (COA), with hypoplastic left heart, bilateral superior venacava (SVC), and unilateral renal agenesis, and the patient opted for second-trimester termination of pregnancy (further testing was declined). Autopsy confirmed these findings, and additional facial dysmorphism, unilateral polydactyly (right upper-limb), and horseshoe kidney with hypoplastic left kidney suggesting possible vertebral defects, anal atresia, cardiac defects, renal abnormalities, limb abnormalities (VACTERL) association were found. The third patient with dichorionic diamniotic (DCDA) twins had fetus B showing DVA and unossified nasal bone at NT scan with otherwise normal cardiac imaging. Due to coexisting obstetric risk factors including Type I diabetes mellitus with uncontrolled sugars on insulin pump and chronic hypertension, the patient declined the option of further direct testing and fetal echo for fetus B and requested fetal reduction of the affected twin instead. After due counselling,

**Flowchart 1: Distribution of study population and the gestational age (GA) at diagnosis**

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>GA at diagnosis</th>
<th>Findings</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>12\textsuperscript{+3}</td>
<td>Megacystis, SUA</td>
<td>Termination of pregnancy</td>
<td></td>
</tr>
<tr>
<td>12\textsuperscript{+5}</td>
<td>DCDA twin, with Twin B-DVA, and unossified nasal bone</td>
<td>Twin B: Fetal reduction</td>
<td></td>
</tr>
<tr>
<td>12\textsuperscript{+6}</td>
<td>COA, unilateral renal agenesis, bilateral SVC, SUA</td>
<td>Twin A: normal karyotype</td>
<td></td>
</tr>
<tr>
<td>21\textsuperscript{+1}</td>
<td>TEF, interrupted IVC with azygous, left SVC, thymic hypoplasia</td>
<td>LSCS at 37 weeks (breech + PROM, BW—3.5 kg)</td>
<td></td>
</tr>
<tr>
<td>10,11</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SUA, single umbilical artery; DCDA, dichorionic diamniotic; COA, coarctation of aorta; TEF, tracheoesophageal fistula; IVC, inferior vena cava; SVC, superior vena cava; PROM, premature rupture of membranes; LSCS, lower segment Cesarean section
HbA1c was 9.5%. Serial Doppler was done fortnightly and patient was planned for repeat elective CS at 37 weeks due to uncontrolled diabetes mellitus (DM). Unfortunately, despite counselling, after two visits, she missed several reviews and reported at 38 weeks with intrauterine death (IUD). The macerated fetus (BW—2.65 kg) underwent autopsy which revealed isolated DVA with no additional anomalies (Fig. 2). The other fetus diagnosed at 31 weeks with DVA (extrahepatic type with drainage into IVC) and fetal growth restriction (FGR) at fourth centile with normal Doppler delivered vaginally at 32 weeks due to PPROM and did well postnatally (Table 2).

While analyzing the type of collaterals and outcomes, we discovered that among the nine fetuses with isolated DVA, majority (n = 8) were found to have extrahepatic venous drainage (six into the IVC and two into the RA) and only one was diagnosed with an IHD [Fig. 3(i)]. All fetuses irrespective of GA at diagnosis underwent Doppler examination at fortnightly/monthly intervals till term.

**Discussion**

The prognosis of DVA depends on the location and site of drainage and associated anomalies. In our study, 92% of fetuses were found to have an extrahepatic venous drainage and only one (8%) had an intrahepatic venous drainage. In a similar study by Bindiya et al., DVA detected at the second trimester alone was included. They presented with eight cases of DV agenesis in a period of 5 years, wherein two patients (25%) had an IHD and six (75%) were found to have an EHD. This study suggested that IHD may be a more common finding but is less frequently reported as it requires color flow mapping of the fetal portal.

![Multisystem anomaly detected at 21+1 weeks—interrupted IVC with azygous connection, TEF, thymic hypoplasia and DVA. (A) Sagittal section of fetal abdomen showing EHD of umbilical vein; (B and C) Color flow mapping of abnormal UV drainage bypassing liver and draining into IVC; (D) Autopsy confirming diagnosis of DVA with prehepatic drainage into IVC.](image-url)
Ductus Venosus Agenesis and Outcomes

Table 2: Isolated DVA and postnatal outcome

<table>
<thead>
<tr>
<th>GA at birth</th>
<th>Type of anastomosis</th>
<th>Mode of delivery</th>
<th>Outcome</th>
<th>Postnatal imaging</th>
<th>Present age</th>
</tr>
</thead>
<tbody>
<tr>
<td>37+6</td>
<td>EHD into IVC</td>
<td>LSCS-E (fetal distress)</td>
<td>Boy</td>
<td>2.47 kg NICU admission (TTN) was on cPAP for 2 days, discharged on D15</td>
<td>3 years (A&amp;H)</td>
</tr>
<tr>
<td>39+1</td>
<td>EHD into IVC</td>
<td>LSCS-E (FGR)</td>
<td>Boy</td>
<td>2.4 kg 2D echo normal</td>
<td>2 years (A&amp;H)</td>
</tr>
<tr>
<td>37+5</td>
<td>IHD</td>
<td>LSCS-E (breach with PROM)</td>
<td>Girl</td>
<td>2.5 kg USG abdomen—normal, discharged on D7</td>
<td>1 year (A&amp;H)</td>
</tr>
<tr>
<td>38 weeks</td>
<td>EHD into IVC</td>
<td>Elective repeat LSCS</td>
<td>Boy</td>
<td>2.7 kg USG abdomen—normal, discharged on D2</td>
<td>2 years (A&amp;H)</td>
</tr>
<tr>
<td>39+4</td>
<td>EHD into RA</td>
<td>NVD</td>
<td>Girl</td>
<td>3.1 kg USG abdomen—normal, discharged on D2</td>
<td>1 year (A&amp;H)</td>
</tr>
<tr>
<td>39+2</td>
<td>EHD into RA</td>
<td>LSCS-E (fetal distress)</td>
<td>Boy</td>
<td>2.96 kg USG abdomen—normal, discharged at D5</td>
<td>2 years (A&amp;H)</td>
</tr>
<tr>
<td>38 weeks</td>
<td>EHD into IVC</td>
<td>LSCS (maternal demand)</td>
<td>IUD at 38 weeks</td>
<td>Macerated, BW—2.65 kg</td>
<td>—</td>
</tr>
<tr>
<td>32 weeks</td>
<td>EHD into IVC</td>
<td>NVD (PPROM)</td>
<td>Boy</td>
<td>1.34 kg Postnatal USG abdomen—normal NICU admission for 12 days (sepsis) Discharged on D17</td>
<td>2 years (A&amp;H)</td>
</tr>
<tr>
<td>33 weeks</td>
<td>EHD into IVC</td>
<td>NVD (PPROM)</td>
<td>Girl</td>
<td>1.8 kg Postnatal USG abdomen—normal; NICU—7 days (RDS) Discharged on D8</td>
<td>2 years (A&amp;H)</td>
</tr>
</tbody>
</table>

EHD, extrahepatic drainage; IHD, intrahepatic drainage; A&H, alive and healthy; LSCS, lower segment Cesarean section, E, Emergency; TTN, transient tachypnea of newborn; NICU, neonatal intensive care unit; FGR, fetal growth restriction; PROM, premature rupture of membranes; PPROM, preterm premature rupture of membranes; NVD, normal vaginal delivery; D, day; IUD, intrauterine fetal demise; RDS, respiratory distress syndrome

In this study, only one fetus had isolated DVA (12.5%) and seven (87.5%) were associated with malformation syndromes Central nervous system and cardiovascular system anomalies and chromosomal anomalies. Five of eight fetuses were terminated due to these complex anomalies and the three fetuses who delivered had good outcomes. In our series, eight of nine fetuses with isolated DVA had a good neonatal outcome (Table 2). This probably indicates that although the incidence of DVA is rare and large case series may not be possible, a good neonatal outcome may be possible in those fetuses with isolated DVA.

Our series had one patient who was referred at 28 + 2 weeks in view of dilated IVC where we diagnosed DVA and an extrahepatic course of drainage that was the cause of the prominent IVC. Omer et al. in 2014 described a case report of a patient diagnosed with DVA at 20 weeks with no chromosomal or structural abnormalities, with features of dilated IVC as the only suspicious feature. They concluded that the presence of IVC dilatation can be a sign of DVA; in such patients, a color flow Doppler must be done, and these fetuses are more likely to have a favorable outcome. The dilated appearance of IVC should therefore prompt thorough the examination of the fetus for other features of DVA.

In this series, we had two fetuses with congenital heart disease (15%). Matsuoka et al. predicted an incidence of 0.6% of congenital heart defects in those fetuses with an interrupted IVC with azygos vein.24 We had one fetus with a similar presentation who also had associated persistent left SVC, TEF, and thymic hypoplasia, and hence, pregnancy was terminated.

In our study, none of the fetuses with DVA were found to have an increased nuchal translucency (NT). Increased NT is associated with a higher incidence of chromosomal or structural anomalies than fetuses with NT within the normal range. Raksha et al. studied the efficacy of NT in prenatal diagnosis and correlated NT with congenital anomalies and concluded that among 1,122 patients in their study population, detection rate of trisomy 21 was 90.9% using NT >95th centile and crown-rump length.25

We had one patient with DV showing “a” wave reversal at 11–13 weeks scan. Follow-up scan with echo at 18 weeks revealed DVA with EHD into the IVC [Fig. 3(ii)]. Maiz et al. emphasized that the precision and technique of measuring DV is of utmost importance to avoid IVC and hepatic vein artifact that can falsely appear as a reversed “a” wave. Conversely, if the sample gate is wide, the umbilical vein waveform might contaminate the image leading to missing the diagnosis of DVA in the “a” wave.5 In this instance, a repeat evaluation helped us to diagnose DVA and follow up.

Once DVA is diagnosed, the exact site of collaterals must be established, and care must be taken to rule out associated venous system anomalies. Hofstetter et al. stated that the defects can include the umbilical, hepatic, portal, or caval venous systems alone, or a combination defect of any of the venous systems.26 Minor clinical implications were noted if the isolated abnormalities of the umbilical, hepatic, or portal system
were present. However, abnormalities involving the IVC and SVC were often associated with major cardiac and GIT anomalies as well as body dysmorphism. These malformations are of great clinical importance and are generally a poor prognostic marker.

Among 12 fetuses with extrahepatic drainage, 33% had associated anomalies (4 of 12). Contratti et al. suggested that those fetuses with EHD have a higher incidence of fetal malformations, aneuploidies, high-output cardiac failure due to chronic central venous system overload. No long-term sequelae of ductus venous absence were noted in 13 fetuses with isolated DVA with EHD in a study by Berg et al.17

Detailed pathological examination was performed, and USG diagnosis was confirmed for two fetuses terminated at the second trimester due to multisystem anomalies and one fetus with IUD at 38 weeks. However, both karyotyping and histopathological review did not reveal any additional information regarding etiology in these fetuses. In our study, among seven fetuses with isolated DVA diagnosed prior to 24 weeks, karyotyping was done for two fetuses and both were normal. Of the remaining four fetuses with associated anomalies, with the early detection, only one couple opted for karyotyping and was found to be normal. In our setting, the uptake of direct testing was limited (due to financial reasons) but all neonates who survived had no obvious anomalies and had good outcomes (Table 2).

In a large multicentric review of 259 fetuses with DVA by Amirhossein et al., in 116 cases fetal karyotyping was reported as normal; in 105 fetuses, it was not done, and in the remaining 38 fetuses, chromosomal abnormalities were detected, namely trisomy 21 (n = 10), monosomy X (n = 11), trisomy 22 (n = 1), chromosomal deletions (n = 7), trisomy 18 (n = 6 cases), Robertsonian translocations (n = 2 cases), and trisomy 13 (n = 1).27 As a dictum for all fetuses with prenatal diagnosis of DVA, fetal karyotyping must be done especially in those with associated anomalies.4,14,16

**Conclusion**

Agenesis of DV is a rare vascular anomaly, and the use of Doppler ultrasound has enabled us to diagnose the same as early as 11–13+6 weeks. Our study reveals that fetuses with isolated DVA have a near-normal prognosis. Association with additional anomalies including cardiac malformations was seen in our study. However, those fetuses without hepatic bypass had good neonatal outcomes. Early diagnosis is crucial for management. Further evaluation in a standardized manner with fetal echo, screening for anomalies, and karyotyping is essential.

**Limitations**

Fetuses with EHD are more prone to hydrops and cardiac failure. However, in our series, we did not have any fetuses with such complications. Due to the small number in our study, we do not have sufficient information that will be useful to change monitoring practices in DVA.
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Clinical Significance
Evaluation of DV at 11–13+6 week scan increases the diagnosis of DVA and its associated anomalies. This helps in the early detection of fetal cardiac anomalies in these fetuses, and additionally, they benefit from close monitoring with serial Doppler evaluation.

FGR, Fetal growth restriction
NT, Nuchal translucency
TTTS, Twin-twin transfusion syndrome

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References

Figs 3A to E: (i) Isolated DVA at 20+5 weeks. (A) Suspected “a” wave reversal of DV; (B) Confirmed as DVA with aberrant intrahepatic course of umbilical vein at 20+5 weeks; (ii) Suspected DVA at 13+6 weeks with “a” wave reversal; (C and D) Diagnosed as DVA with aberrant course of umbilical vein into IVC at 17+6 weeks; (E) Apparent “a” wave reversal seen in the hepatic vein.


