Review

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# Ductus venosus agenesis and fetal malformations: what can we expect? – a systematic review of the literature

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**Abstract**

**Background:** The ductus venosus agenesis (DVA) is a rare condition with a variable prognosis that relies partly on the presence of associated conditions. The purpose of our study was to analyze the literature regarding the postnatal outcome of fetuses with DVA associated with fetal malformations, in order to discuss the best management options for couples.

**Methods:** We performed a systematic review of the literature of MEDLINE and SCOPUS electronic databases in a 25-year period from 1992 to September 2017.

**Results:** We found 340 cases of DVA associated with fetal abnormalities. The most common chromosomal abnormalities were: monosomy X (12/48, 25%), trisomy 21 (11/48, 22.9%) and trisomy 18 (6/48, 12.5%). From the 340 cases with DVA, in 31 cases the umbilical venous shunt type was not reported. Of the fetuses, 60.8% (188/309) had an extrahepatic umbilical venous drainage while 39.2% (121/309) presented an intrahepatic connection. The DVA was associated in 71 cases (23.0%) with cardiac abnormalities, in 82 cases (26.5%) with extracardiac abnormalities and in 85 cases (27.5%) with both cardiac and extracardiac abnormalities.

**Conclusion:** DVA associated with both cardiac and extracardiac malformations may confer a poorer fetal outcome, a clinically relevant fact that should clarify what can be expected from this entity and help prenatal counseling.

**Keywords:** agenesis; ductus venosus; fetal malformations; outcome.

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## Background

The human fetal circulation relies on three physiological shunts: the ductus arteriosus, the foramen ovale and the ductus venosus (DV). The three shunts are essential distributional arrangements, making the fetal circulation a flexible and adaptive system throughout intrauterine life [1]. Although the first two are of great importance and have been extensively studied, less clinical value was attributed to the DV until the development of ultrasound techniques. Modern techniques, particularly ultrasound associated with Doppler, have opened a new era of clinical evaluation of the fetus, namely in the first trimester.

What about when one of these shunts, namely the DV, is absent? What can we expect when facing a ductus venosus agenesis (DVA)?

DVA is a rare anomaly which was first published in 1826 by Mende [2]. With the widespread use of ultrasonographic techniques and their improvement over the years, a more careful examination of the fetal circulation, particularly the umbilical and portal venous malformations, is now performed prenatally. A systematic DV evaluation in the late first trimester routine ultrasonography has become part of daily clinical practice which led to the increase number of DVA cases published in the literature. However, in spite of the new and better technologies, this is still a rare condition with a reported low prevalence ranging from one in 2532 [3] to one in 556 fetuses [4].

The DVA results from a failure of the “critical anastomosis” between the portal-umbilical venous system and the hepatic-systemic venous system. When the DV is absent, the umbilical blood flows from the umbilical

vein through an aberrant vessel that may be extrahepatic, bypassing the liver, or intrahepatic, via the portal venous system [5–7].

Regarding the extrahepatic shunt, there are different possible connections between the umbilical vein and the venous system: (1) the umbilical vein shows direct connection to the right atrium (RA), left atrium or through a dilated coronary sinus (CS). The connection to the RA was first diagnosed prenatally in 1992 [8] and is considered the most common as described by Moaddab and colleagues who reported a prevalence of 68:153 (44%) [9] (Figure 1); (2) the umbilical vein drains directly into the inferior vena cava. This is the second most common connection [9]; (3) the umbilical vein drains directly into the superior vena cava; (4) the umbilical vein drains into the left, right or internal iliac vein. The connection to the iliac vein was first described in 1996 [10]; (5) the umbilical vein shows a direct connection into the renal vein; (6) the umbilical vein shows direct connection into the right ventricle.

The intrahepatic umbilical venous drainage without liver bypass is another possible shunt. In this case, the umbilical vein connects to the portal sinus as usual but without giving rise to the DV [6].

The relevance of this entity has become even more pertinent now that DV blood flow evaluation is systematically performed in the first trimester screening for aneuploidies and has become part of the daily clinical practice. Previously it was easier for the DVA to go unnoticed. Figures 2 and 3 depict typically ultrasonographic images of the DVA.

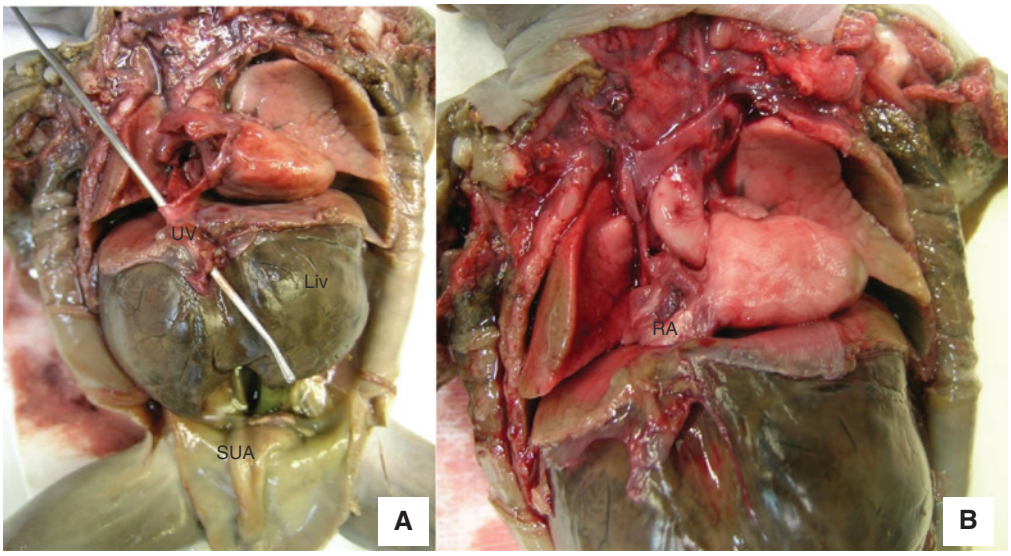


**Figure 1:** Macroscopic images [(A) general image; (B) closeup plan from the main thoracoabdominal organs] of the umbilical venous circulation from necropsy examination of a fetus with 25 weeks with a normal karyotype showing an aberrant course of the umbilical vein running anterior to the liver and leaving a marked groove in its surface until reaching the atrium (Liv = liver, UV = umbilical vein, RA = right atrium, SUA = single umbilical artery).

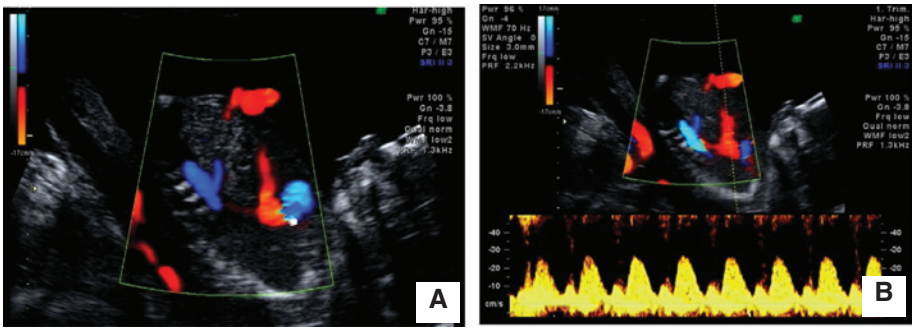


**Figure 2:** Ultrasonographic and Doppler blood flow evaluation in two cases of DV agenesis at 16 weeks of gestation.
Ultrasound images performed at 16 weeks + 2 days: (A) depiction of the umbilical venous circulation obtained by Color Doppler showing a large vascular structure with a discrete aliasing, establishing a continuum between the umbilical vein and the right atrium, (B) blood flow waveform obtained by pulsed Doppler showing a highly pulsatile flow without any retrograde waveform.

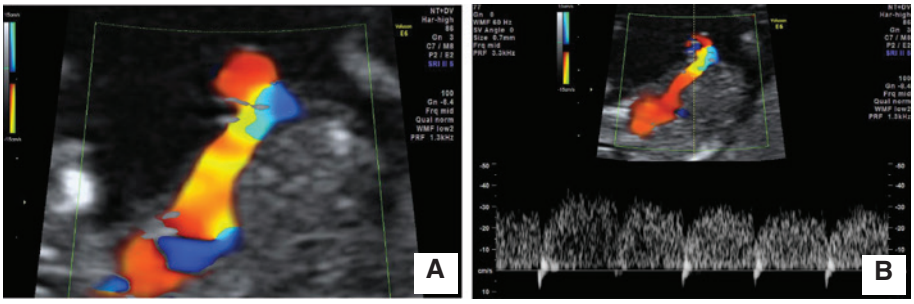


**Figure 3:** Ultrasound images performed at 16 weeks + 4 days: (A) depiction of a large vessel, without any funneling, connecting the umbilical vein to the right atrium, (B) blood flow waveform obtained by pulsed Doppler from a region with aliasing, showing higher velocities than those normally obtained from the umbilical vein and no retrograde flow.

The purpose of the present study was to analyze the published literature regarding the post-natal outcome of fetuses with DVA when associated with fetal malformations, in order to discuss the best management options for couples faced with this anomaly. We perform a systematic review of the literature comprising a 25-year period from 1992 to September 2017.

# Methods

## Data source

The review was planned and carried out according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* [11] and the PRISMA Statement [12] as guidelines for the description of the studies to ensure a transparent, complete and unbiased reporting of valuable data.

The MEDLINE and SCOPUS electronic databases were searched for studies published in a 25-year period from 1992 to September 2017 using the following relevant medical subject heading (MeSH) terms and keywords: ductus venosus, agenesis, absent, absence, missing and lack. The studies were restricted to the English language. The last search was performed on September 30, 2017.

Hand-searched references from included articles were also considered and included after considering the inclusion criteria. None of the publications had overlapping populations. Studies were eligible if they provided data on DVA.

## Inclusion and exclusion criteria

Regarding the inclusion criteria defined to decide about the eligibility of each paper in our pool, we include in the present study prospective and retrospective studies as well as case reports or case series as this is a rare anomaly. All published literature with reference to the prevalence, diagnosis, management or outcome of DVA was included. We did not apply any restriction to the trimester in which the screening of DVA was done, type of pregnancy (singleton or multiple) nor type of evaluation of the DVA.

The literature that comprised only reviews, systematic reviews, research or editorial letters or conference abstracts were excluded as well as studies published in a language other than English or experimental animal studies.

The criteria were applied in two phases: first, studies were screened by title and abstract for relevance. Secondly, full papers of studies, which appeared potentially relevant, were assessed for inclusion.

## Study selection

All the studies obtained from the electronic search were alphabetically ordered and the duplicates were excluded. Two reviewers examined the titles and abstracts of each article excluding those which did not apply to the present study. Potential articles were later forwarded to the full-text read, which was done independently by two reviewers to verify the inclusion and exclusion criteria.

The risk of bias of the included studies was assessed using Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). STROBE consists of a 22-item checklist that provides guidance on the reporting of observational studies to facilitate critical assessment and interpretation of results [13]. This checklist facilitates assessing the risk of potential bias in the title and abstract, introduction, methods, results and discussion sections of articles. Each item was classified as “Yes”

(low risk), "No" (high risk), or "Unclear". An item that was not relevant to an individual study was labeled as "Not Applicable (NA)". Total scores for each study were adjusted for the NA response. The results were reported as percentages. The application of this scale was carried out by two evaluators, independently. The case reports were assessed for the risk of bias using the CARE guidelines. The CARE guidelines, developed by an international group of experts, are designed to increase the accuracy, transparency and usefulness of case reports [14].

To improve the reliability of this analysis, any discrepancy or disagreement in the classification of the methodological quality was resolved through discussion or intervention of the leading investigator.

## Data extraction

For each study, we have recorded the name of the author, year, study design, gestational age, number of cases described with DVA, umbilical vein connection, pre-natal imaging findings, gestational age at delivery or pregnancy termination, fetal outcomes (intrauterine fetal death, neonatal death or survival), post-natal imaging findings, post-mortem findings, associated congenital anomalies and karyotype. All these variables were set before the review was started. No assumptions were made during the process of data collection and all collected variables were clearly stated in original reports.

The variables were extracted from included reports by the leading investigator who gathered the data into predesigned sheets. An independent reviewer verified the data grid for greater accuracy. Discrepancies or disagreements were also resolved by discussion.

## Synthesis and statistical analysis

Results were presented as means and standard deviations (SDs) for quantitative variables and by absolute frequencies and percentages for categorical variables.

# Results

## Eligible studies

Of the 653 items retrieved with the electronic database search, 604 were excluded when assessing the titles and abstracts. The remaining 49 papers were retrieved for screening in full text. Nineteen new studies were identified through scanning of bibliographic references of included papers, performing a total of 68 entries to review. We further excluded 10 studies for the reasons listed in the Figure 4. Hence, the final data included information from 58 reports, accounting for a total of 406 patients. An additional four patients who were diagnosed at our institution, were incorporated into the body of data and underwent the process of analysis (n = 410).

## Study characteristics

From the 58 studies included, 35 were case reports while 23 were retrospective or prospective studies. During the period used to perform this systematic review we could see an increasing trend in the number of studies published per year (Figure 5).

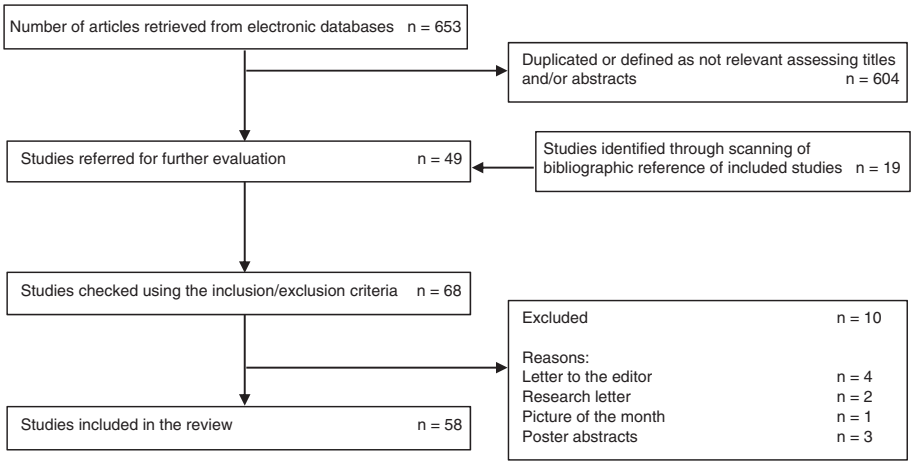


**Figure 4:** Schematic representation: from the search to the identification of articles.

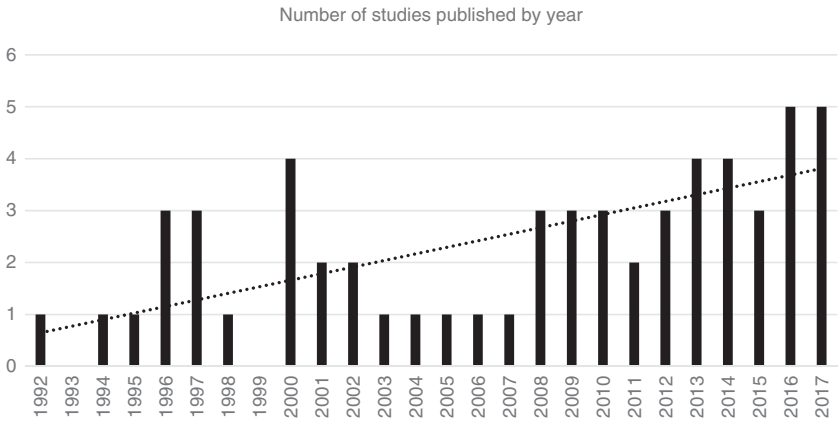


**Figure 5:** Number of studies published in the literature by year regarding the DVA.

All the studies presented the information case by case except one study [15] that presented grouped elements. However, the possible elements were extracted and added together with the additional data.

## Risk of bias in included studies

Overall study-level risk of bias is shown in Figure 6. As we can observe from this figure, we found a higher rate of low-risk comparing the number of items reported as high-risk of bias. Using both instruments to evaluate the risk of bias it was possible to recognize that, globally, the included studies were adequate in respect to the different sections and, in this sense, none of the studies was excluded.

For the CARE guidelines it was seen a higher proportion of high-risk of bias in the items 1 and 4. Regarding the item 1 "Title/Keywords/Abstract" most of the case reports did not include the words "case report" in the title and in the abstract section did not include a conclusion or "take away" message from the case. When looking to item 4 "Discussion/Patient Perspective/Informed consent" it was possible to see that although the authors present a careful discussion of the cases along with the medical literature, they did not discuss the strengths and limitations of the report. Furthermore, although informed consent is assumed when presenting a case report, the included studies did not provide that information. This is an item evaluated by the CARE guidelines and therefore contributed to the higher proportion of high risk of bias reported.

Concerning the STROBE statement, it was seen a higher proportion of high risk of bias in the items 2 and 4. For the item 2 "Methods" it was possible to see that from the 23 included studies, 17 did not describe any efforts to address potential sources of bias, 15 did not explain how quantitative variables were handled in the analysis

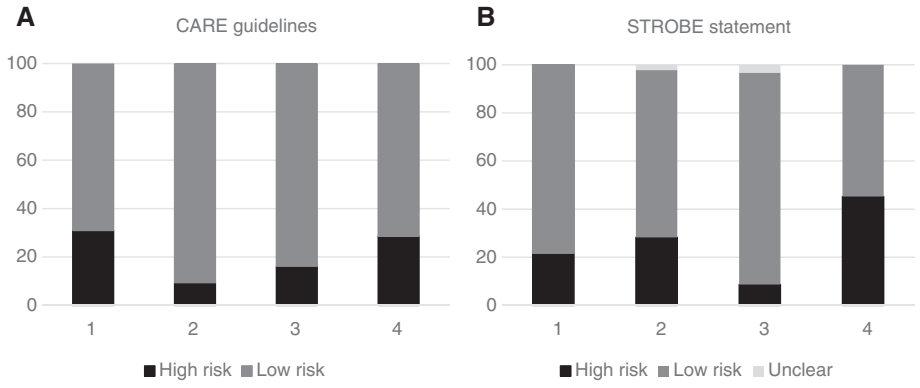


**Figure 6:** Results (in percentages) from the assessment of the risk of bias.
(A) CARE guidelines: (1) Title/Keywords/Abstract, (2) Introduction/Patient information/Clinical findings/Timeline, (3) Diagnostic Assessment/Therapeutic intervention, Follow-up and outcomes, (4) Discussion/Patient Perspective/Informed consent. (B) STROBE Statement: (1) Title/Abstract/Introduction, (2) Methods, (3) Results, (4) Discussion/Funding.

and 13 did not describe the statistical methods or explain how missing data were addressed. Regarding item 4 "Discussion/Funding" although the authors summarized key results with reference to study objectives and gave a cautious overall interpretation of results and considered the published literature, once more they did not discuss the study limitations or the generalizability of the study results.

## Study results

The present study includes 410 cases of DVA. From these 410 cases, in 70 cases the DVA was an isolated finding while in 340 cases it was associated with other abnormalities. As the purpose of this study was to analyze the cases with associated abnormalities, from this point will only be presenting the results referring to these cases.

The DVA was diagnosed in the first, second or third trimesters in 38 (11.2%), 114 (33.5%) and 76 (22.4%) cases, respectively. In 14 (4.1%) cases the DVA was detected postnatally. In 98 (28.8%) cases, it was not reported. From the cases included, 54 were female, 61 were male and in 225 the fetal sex was not stated in the reports.

Karyotype was performed in 141 cases (141/340, 41.4%) of which 48 were reported as an abnormal result. Among these 48 chromosomal abnormalities the most common were: Turner syndrome (12/48, 25%), trisomy 21 (11/48, 22.9%) and trisomy 18 (6/48, 12.5%), chromosomal deletions (5/48, 10.4%), chromosomal mosaicism (4/48, 8.3%), chromosomal derivations (2/48, 4.2%) and chromosomal duplications (2/48, 4.2%). In 199 cases it was not performed or not reported. We did not address microarray studies during the research as these studies are very recent in routine clinical practice and therefore no references are stated in a review of the last 25 years.

From the 340 cases with DVA, in 31 cases the umbilical venous drainage was not reported. In the remaining 309 cases, there were 60.8% (188/309) of the fetuses with an extrahepatic umbilical venous drainage while 39.2% (121/309) presented an intrahepatic umbilical venous drainage.

Regarding the extrahepatic shunt, the prevalence of the different structures to which the umbilical vein drained was as follows: RA (82/188, 43.6%), IVC (64/188, 34.0%), iliac vein (IV) (8/188, 4.3%), CS (7/188, 3.7%), right IV (5/188, 2.7%), left IV (4/188, 2.1%), internal IV (2/188, 1.1%), renal vein (2/188, 1.1%), left atrium (1/188, 0.5%), superior vena cava (SVC) (1/188, 0.5%), left internal IV (1/188, 0.5%), azygos vein and SVC (1/188, 0.5%), IVC-azygos shunt (1/188, 0.5%), caput medusae (1/188, 0.5%). In six (3.2%) cases the extrahepatic drainage was referred to only as "going to the heart", and two (1.1%) cases were only referred to as an "extrahepatic shunt" without characterization of the structure involved.

Concerning the intrahepatic umbilical venous drainage, 75 (62.0%) cases were reported only as "intrahepatic" and two (1.7%) cases as "hepatic". The prevalence of the different structures which the UV drained into an intrahepatic type in the remaining cases was as follows: portal vein (PV) (35/121, 28.9%), portal sinus (3/121, 2.5%), hepatic vein (2/121, 1.7%), right hepatic vein (2/121, 1.7%), left hepatic vein (1/121, 0.8%) and hepatic collaterals (1/121, 0.8%).

Cardiomegaly was observed in 82 fetuses (24.1%) as an isolated finding in fetuses with DVA or in combination with other findings. Some fetuses suffered from deteriorating cardiac function with advanced gestation and increased cardiac demands on the fetal heart. Some of them fully recovered while others did not survive. However, only 34 fetuses (10.0%) developed hydrops, while several cases demonstrated fluid accumulation in one fetal body space. A summary of the conditions diagnosed at prenatal or postnatal ultrasonographic evaluations or postmortem autopsies is shown in Table 1.

One report included in our analysis presented the results with grouped information, so it was only possible to collect the outcome of 64 cases out of 95 reported in this study [16]. Therefore, in 309 cases, the DVA was associated in 71 cases (23.0%) with cardiac abnormalities, in 82 cases (26.5%) with extracardiac abnormalities and in 85 cases (27.5%) with both cardiac and extracardiac abnormalities. In 71 cases (23.0%) ultrasonographic markers were found that occurred in isolation (such as, for example, cardiomegaly, increased nuchal translucency, tricuspid regurgitation or hydrops) and although these are not malformations, they may have implications in the fetal outcome.

As some of the malformations can be explained by chromosomal alterations we present, in Table 2, their prevalence for each type of malformation according to the respective fetal outcome.

# Discussion

The present study included a total of 410 cases of DVA: 70 occurred in isolation, 269 were associated with fetal malformations while 71 were associated with abnormal ultrasonographic markers of chromosomal aneuploidies and/or fetal malformations. It is possible that the isolated cases might be underreported compared with the cases

**Table 1:** Type of associated abnormality and number of cases found in which category in the published cases of DVA.

| Abnormality | No. of cases (%) | Abnormality | No. of cases (%) |
|---|---|---|---|
| Cardiomegaly | 82 (24.1) | Duodenal atresia | 4 (1.2) |
| VSD | 37 (10.9) | Ebstein anomaly | 4 (1.2) |
| Facial anomalies | 35 (10.3) | Fetal edema | 4 (1.2) |
| Hydrops | 34 (10.0) | Hemivertebrae | 4 (1.2) |
| Cardiac valve anomalies (other than TR) | 31 (9.1) | Imperforate anus | 4 (1.2) |
| IUGR | 28 (8.2) | Interrupted IVC | 4 (1.2) |
| Polyhydramnios | 25 (7.4) | Microcephaly | 4 (1.2) |
| SUA | 24 (7.1) | Micropenis | 4 (1.2) |
| Limb anomalies | 23 (6.8) | Oligohydramnios | 4 (1.2) |
| Tricuspid regurgitation | 23 (6.8) | Right aortic arch | 4 (1.2) |
| Ascites | 21 (6.2) | TTTS/TRAP | 4 (1.2) |
| Increased NT | 21 (6.2) | Noonan syndrome | 3 (0.9) |
| Hydrothorax | 20 (5.9) | Placentomegaly | 3 (0.9) |
| Hygroma | 17 (5.0) | TGA | 3 (0.9) |
| Brain malformations | 16 (4.7) | ARSA | 2 (0.6) |
| Dilated IVC | 16 (4.7) | Absent IVC | 2 (0.6) |
| Pericardial effusion | 16 (4.7) | Absent spleen | 2 (0.6) |
| CoA | 13 (3.8) | Brachycephaly/plagiocephaly | 2 (0.6) |
| Diaphragmatic hernia | 13 (3.8) | Cryptorchidism | 2 (0.6) |
| LPSVC | 12 (3.5) | Hypoplastic left lung | 2 (0.6) |
| AVSD | 11 (3.2) | Horseshoe kidney | 2 (0.6) |
| Myocardial hypertrophy | 11 (3.2) | Intestinal malrotation | 2 (0.6) |
| Skin edema | 11 (3.2) | Patent foramen ovale | 2 (0.6) |
| DORV | 10 (2.9) | Placental edema | 2 (0.6) |
| TEF/tracheal/esophageal atresia | 10 (2.9) | Univentricular heart | 2 (0.6) |
| ASD | 9 (2.6) | Absent bladder | 1 (0.3) |
| Pleural effusion | 9 (2.6) | Absent UA flow | 1 (0.3) |
| PV agenesis | 9 (2.6) | Achondroplasia | 1 (0.3) |
| HLHS | 8 (2.4) | Ambiguous genitalia | 1 (0.3) |
| Pyelectasis | 8 (2.4) | Aortic hypoplasia | 1 (0.3) |
| PDA | 7 (2.1) | AMC | 1 (0.3) |
| VACTERL | 7 (2.1) | Beckwith-Wiedemann syndrome | 1 (0.3) |
| Bilateral SVC | 6 (1.8) | Bifid scrotum | 1 (0.3) |
| Dilated RA and RV | 6 (1.8) | Body-stalk syndrome | 1 (0.3) |
| Omphalocele | 6 (1.8) | Exencephaly | 1 (0.3) |
| Dextrocardia/partial situs inversus | 6 (1.8) | Extrophy of the bladder | 1 (0.3) |
| Hepatomegaly | 6 (1.8) | Fused adrenals | 1 (0.3) |
| Spinal deformities | 6 (1.8) | Heterotaxy syndrome | 1 (0.3) |
| Anal atresia | 5 (1.5) | Hypoplastic aortic arch | 1 (0.3) |
| Hydronephrosis | 5 (1.5) | Hypoplastic RV | 1 (0.3) |
| Persistent porto-systemic shunt | 5 (1.5) | Jacobsen syndrome | 1 (0.3) |
| Persistent right UV | 5 (1.5) | Meconium peritonitis | 1 (0.3) |
| Renal agenesis | 5 (1.5) | Nephroblastomatosis | 1 (0.3) |
| UV varix | 5 (1.5) | Pierre-Robin sequence | 1 (0.3) |
| Dandy-Walker malformation | 4 (1.2) | Smith-Lemli-Opitz syndrome | 1 (0.3) |
| Dilated RA | 4 (1.2) | Wolf-Hirschhom syndrome | 1 (0.3) |

ARSA, abnormal right subclavian artery; AMC, arthrogryposis multiplex congenita; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CoA, coarctation of the aorta; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; IUGR, intrauterine growth restriction; IVC, inferior vena cava; LA, left atrium; LPSVC, left persistent superior vena cava; NT, nuchal translucency; PDA, persistent ductus arteriosus; PV, portal vein; RA, right atrium; RV, right ventricle; SUA, single umbilical artery; SVC, superior vena cava; TGA, transposition of the great arteries; TR, tricuspid regurgitation; TEF, tracheoesophageal fistula; TTTS/TRAP, twin-twin transfusion syndrome/twin reversed arterial perfusion; UV, umbilical vein.

associated with fetal malformations. On the one hand because they can escape diagnosis if systematic evaluation of the DV is not routinely performed, and on the other hand, because the isolated cases with no associated malformations or significant conditions, are less likely to be published.

**Table 2:** DVA and associated malformations with the respective fetal outcome (n = 309).

| | | TOP | IUFD | NND | Child death | Alive | NA |
|---|---|---|---|---|---|---|---|
| Cardiac anomalies only | 71 | 15 | 4 | 4 | 3 | 44 | 1 |
| Normal karyotype | | 4 | 3 | 2 | | 10 | |
| Turner syndrome | | 5 | | | | | |
| Trisomy 21 | | 2 | | | | 1 | |
| Other chromosomal abnormalities | | | | | | 3 | |
| Karyotype not available | | 4 | 1 | 2 | 3 | 30 | 1 |
| Extracardiac anomalies only | 82 | 12 | 7 | 12 | 2 | 48 | 1 |
| Normal karyotype | | 5 | 2 | 5 | | 12 | |
| Trisomy 18 | | 1 | | | | | |
| Trisomy 21 | | | | | | | 1 |
| Other chromosomal abnormalities | | 3 | 1 | 1 | | 6 | |
| Karyotype not available | | 3 | 4 | 6 | 2 | 30 | |
| Both cardiac and extracardiac anomalies | 85 | 40 | 4 | 13 | 3 | 25 | 0 |
| Normal karyotype | | 13 | | 2 | 2 | 9 | |
| Turner syndrome | | 4 | | | | | |
| Trisomy 18 | | 2 | 2 | 1 | | | |
| Trisomy 21 | | 2 | | | | 1 | |
| Other chromosomal abnormalities | | 4 | | | | | |
| Karyotype not available | | 15 | 2 | 10 | 1 | 15 | |
| Ultrasound markers only | 71 | 16 | 10 | 8 | 0 | 35 | 2 |
| Normal karyotype | | 5 | 2 | 5 | | 14 | |
| Turner syndrome | | 1 | 1 | | | | |
| Trisomy 21 | | 3 | | | | 1 | |
| Other chromosomal abnormalities | | | 1 | | | | |
| Karyotype not available | | 7 | 6 | 3 | | 20 | 2 |

TOP, termination of pregnancy; IUFD, intrauterine fetal demise; NND, neonatal death; NA, not available.

Regarding the time of diagnosis, we found that the lowest percentage of cases were diagnosed in the first trimester (11.2%) while most of the cases were diagnosed in the second trimester (33.5%). Iliescu et al. proved the ability of an early scan during first trimester to accurately detect the DVA. The main finding of their study was that all but one case with DVA were detected during first trimester evaluation and confirmed at follow-up [4]. This demonstrates the need for a careful and effective evaluation in early pregnancy as the detection of DVA is possible and may have an impact on the follow-up and care needed during pregnancy.

As regards the umbilical venous drainage, Gembruch and colleagues reported, in 1998, the first two cases of intrahepatic drainage diagnosed prenatally [16]. Since then, the intrahepatic umbilical venous drainage was less often reported in comparison to the extrahepatic drainage. In another study, were reported 19 fetuses with DVA and an intrahepatic shunt and only four with extrahepatic venous drainage. The authors explain their high proportion of intrahepatic connection without liver bypass by the different sonographic methods required to diagnose the two different shunts. For the extrahepatic connection, the umbilical venous drainage can be detected by the abnormal course of the intra-abdominal umbilical vein on gray-scale sonography, while the intrahepatic connection requires color flow mapping of the fetal portal circulation in various planes of evaluation [17].

In addition, Berg and colleagues point out that although the extrahepatic connection is much rarer its assessment is easier, while the intrahepatic shunt may occur more frequently, but often the diagnosis is missed [18]. In our study we found an extrahepatic shunt in 60.8% of the cases in contrast to the intrahepatic shunt that accounted for 39.2% of the cases.

The assessment of DV blood flow is an integral part of the first trimester screening since it was demonstrated that the abnormal flow in this vessel is associated with an increased risk for chromosomal abnormalities, cardiac defects and adverse perinatal outcome both in singletons and twin pregnancies [18–23]. In good accordance, the DVA has also been related to congenital cardiac, genitourinary and/or gastrointestinal anomalies with or without associated chromosomal abnormalities. The study of Wiechec and colleagues was able to analyze both the abnormal DV flow and DVA and its relation with markers of aneuploidies and fetal abnormalities in a population of 5810 singleton pregnancies. This study described a higher

prevalence of cardiac and extracardiac anomalies in cases of abnormal DV flow and DVA when compared to normal DV flow [23].

Although the malformations found in our study occurred in association with the DVA we cannot conclude that they are disease-specific. Gastrointestinal malformations included among others, tracheoesophageal fistula, tracheal atresia, esophageal atresia, duodenal atresia, anal atresia, imperforate anus and intestinal malrotation. Cardiovascular malformations comprised simple atrial septal defects, ventricular septal defects, hypertrophic cardiomyopathy, Ebstein's anomaly, or more complex cardiac malformation such as double outlet right ventricle, hypoplastic left heart syndrome and transposition of the great arteries. The most commonly associated genitourinary tract anomalies include pyelectasis, hydronephrosis and renal agenesis, but we also found micropenis, cryptorchidism, absent bladder and ambiguous genitalia. Musculoskeletal malformations included facial anomalies, limb anomalies, spinal deformities and hemivertebra. Concerning the nervous system, we found 16 cases with brain malformations such as vermis agenesis, corpus callosum agenesis, Dandy-Walker malformation and microcephaly.

The DVA has also been associated with syndromic diseases such as Turner or Noonan syndromes [3, 24]. In our study we found different syndromic diseases associated or not with chromosomal abnormalities. When the DVA is associated with other findings it is much easier to diagnose the DVA as the fetus needs a more accurate evaluation.

If the DVA is associated with other abnormalities or if the venous drainage is extrahepatic the likelihood of a poorer outcome is much higher while if isolated or in the presence of an intrahepatic shunt a more favorable postnatal outcome is expected [9, 23]. In our study, we searched for the outcome of the DVA associated with fetal malformations and we were able to see a trend of a poorer outcome when the malformations comprised both cardiac and extracardiac malformations with a higher proportion of no survivors (70.6%) compared to the survivors (29.4%) (Table 2).

The fetus with DVA could have a vulnerability when facing hypoxemic states and it can be also the primary cause of fetal hypoxia as the obstruction of the placental venous flow return can result in placental edema and impaired gas exchange. This edema reduces maternofetal transfer of proteins which in turn may contribute to a decrease in fetal plasma protein levels, one of the causes of the development of hydrops fetalis [5]. It is important to highlight that the role of DV is relevant in early pregnancy as it has been demonstrated in experimental investigation in fetal lamb that the obstruction of the DV late in pregnancy does not affect cerebral or regional organ oxygen delivery [25]. In addition, it is possible that the developing liver may have a greater adaptive potential to compensate for the hemodynamic defects of DVA [16].

The umbilical venous drainage with liver bypass is often associated with fetal cardiac compromise, a characteristic that typically is not found in the intrahepatic pattern [24, 26, 27]. However, the trigger is not yet fully understood. It has been suggested that the probable mechanism responsible for triggering heart failure might be the increased cardiac preload, increased cardiac work and progressive cardiac decompensation [26].

The direct drainage of the umbilical blood flow into the heart can lead to high central venous pressure [27, 28]. This increase in central venous pressure is most likely due to the volume overload as a result of the DV regulatory mechanism loss [27]. This chronic volume overload may lead to an increased stress on the fetal myocardium with the risk of high-output heart failure, leading to fetal hydrops [24, 28]. Hydrops was one of the most prevalent prenatal findings in our study. We also have found a high percentage of cases of edema restricted only to one body compartment, such as pleural and pericardial spaces or subcutaneous tissue.

In our study the most prevalent prenatal finding was cardiomegaly. As described earlier, cardiomegaly and polyhydramnios may appear as early as mid-gestation and usually become more severe by the onset of the third trimester [26]. The cardiomegaly can be one of the first findings in the ultrasonographic evaluation of the fetus affected by DVA and thus be an important marker that can raise the suspicion of a DVA.

In this sense, careful serial sonographic evaluation proves to be of crucial importance as the presence of progressive heart failure and consequently the evidence of severe fetal compromise are plausible reasons to anticipate the delivery [24, 28].

Regarding the strengths of our study we can highlight the longest period of assessment covered to date (25 years) that allowed the gathering of a high number of fetuses with DVA. Our study also demonstrates an increasing trend in the number of studies published in this area reflecting on the one hand, the increasing interest in a tiny structure with a vast impact in fetal development and, on the other hand, that a more careful examination of the fetal circulation is being performed with the support of modern and improved ultrasonographic technologies. Furthermore, this paper adds value in oriented clinical information specifically addressing what to expect when faced with DVA in association with fetal malformations. Until now the papers did not properly address this issue

and most of the papers are short reports or case reports with a simple literature review.

The lack of randomized controlled studies (RCTs) in this area required the inclusion of retrospective, non-randomized prospective studies and a large number of case reports or case series in our systematic review. However, to overcome this possible limitation and despite the heterogeneity of the included studies, we used two different and validated methods for a critical assessment of the risk of bias. Furthermore, we have followed the main guidelines regarding the conduction of a systematic review in order to limit the outcome bias as the correctly conducted comprehensive reviews have the most probability of all forms of reviews to become an important source of evidence. Another limitation of our study was the limited information retrieved from some studies that made the data extraction difficult and led to the non-inclusion of some DVA cases.

The DVA pathophysiology and its repercussions in fetal development and ultimately in the fetal outcome is not yet fully understood, and as a rare condition it is difficult to perform studies with a large number of cases. In this basis, we suggest a multicenter based study for future research.

In conclusion, the clinicians should be aware of different and important findings during the fetal examination according to the different steps in developmental biology, which can be indicative, although not disease-specific, of a DVA, and, when suspected, serial revaluations should be scheduled in order to identify any malformation. The DVA when associated with both cardiac and extracardiac malformations may confer a poorer fetal outcome, a clinically relevant fact that should clarify what can be expected from this entity and help in prenatal counseling.

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