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Current Cardiology Reviews, **2019**, *15*, 167-176

REVIEW ARTICLE

Clinical Significance of Ductus Venosus Waveform as Generated by Pressure-volume Changes in the Fetal Heart

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ARTICLE HISTORY

Received: July 13, 2018
Revised: January 02, 2019
Accepted: January 04, 2019

DOI:
10.2174/1573403X15666190115142303

Abstract: The ductus venosus is a vascular shunt situated within the fetal liver parenchyma, connecting the umbilical vein to the inferior vena cava. This vessel acts as a bypass of the liver microcirculation and plays a critical role in the fetal circulation. The ductus venosus allows oxygenated and nutrient-rich venous blood to flow from the placenta to the myocardium and brain. Increased impedance to flow in the fetal ductus venosus is associated with fetal aneuploidies, cardiac defects and other adverse pregnancy outcomes. This review serves to improve our understanding of the mechanisms that regulate the blood flow redistribution between the fetal liver circulation and fetal heart and the clinical significance of the ductus venosus waveform as generated by pressure-volume changes in the fetal heart.

Keywords: Ductus venosus, fetal venous circulation, ductus venosus shunting, ultrasound, doppler velocimetry, heart.

1. INTRODUCTION

The ductus venosus (DV) is a vascular shunt situated within the fetal liver parenchyma connecting the umbilical vein (UV) to the inferior vena cava (Fig. **1**). This vessel acts as a bypass of the liver microcirculation and plays a critical role in the fetal circulation. The DV allows oxygenated and nutrient-rich venous blood to flow from the placenta to the brain and myocardium, projecting a high-velocity jet flow posteriorly, from the umbilical vein to the foramen ovale [1]. The blood distribution through the DV is related to changes in umbilical venous pressure, blood viscosity, and an active regulation of the diameter of the entire DV [2]. Anatomically, the DV and the intrahepatic branches of the portal vein are arranged in parallel [3]. During pregnancy, the mean fraction of blood shunted through the ductus is not a constant [2, 3]. In human fetuses, the DV shunting rate is approximately 20-30%, and increases in the DV shunting rate are a mechanism of general adaptation to fetal distress [3] during extreme challenges of placental compromise or hypoxemia [2, 4, 5]. Additionally, the DV acts as a transmission line to the umbilical vein from pulse waves generated in the heart [2]. These waves, which may reflect cardiac function, are substantially influenced by the local variation of impedance and compliance [1].

An increased pulsatility index or impedance to flow in the fetal DV is associated with fetal aneuploidies, cardiac defects and other adverse pregnancy outcomes [6-9].

This review serves to improve our understanding of the mechanisms that regulate the blood flow redistribution between the fetal liver circulation and the DV and to analyze the clinical significance of the DV waveform as generated by pressure-volume changes in the fetal heart.

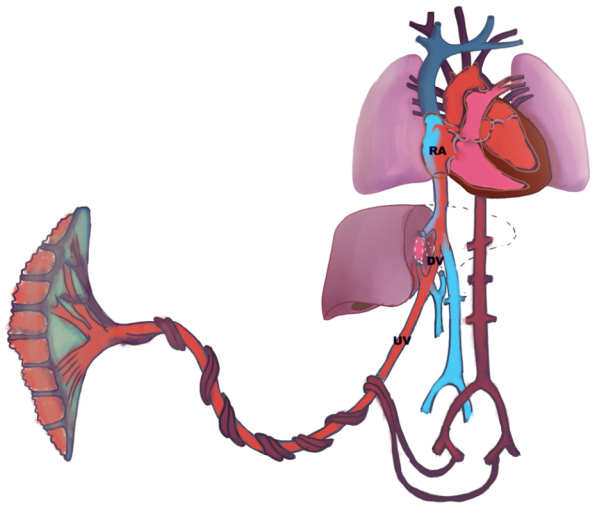

Fig. (1). Anatomy of the ductus venosus (DV). The DV is a vascular shunt situated within the fetal liver parenchyma connecting the umbilical vein (UV) to the inferior vena cava and right atrium (RA).

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1573-403X/19 $58.00+.00

2. METHODS

To compose this review, a thorough literature search was repeatedly performed in PubMed and Medline, with a limitation for articles written in the English language. Search terms used were DV, fetal venous circulation, DV shunting, ultrasound, and Doppler velocimetry.

3. DUCTUS VENOSUS

3.1. Ductus Venosus Development and Anatomy

The arteries and veins are developed by a combination of vasculogenesis and angiogenesis [10]. This process involves a series of steps. Vasculogenesis (VS) is the process of blood vessel formation occurring by de novo production of endothelial cells and the construction of the primitive vascular plexus inside the embryo. Sometimes VS is treated as synonymous with angiogenesis, which is responsible for the remodeling and expansion of this network. VS is under the control of signaling molecules secreted from endoderm cells and begins first in the yolk sac at day 17, where Indian hedgehog, bone morphogenic protein, and transforming growth factor β (TGF-β) modulate the yolk sac's mesoderm to originate hemangioblastic aggregates [11]. These cellular hemangioblastic aggregates are composed for hematopoietic stem cells and endothelial cells that coalesce to form the extraembryonic umbilical vessels to act as a circulatory connection between the embryo and the maternal compartments. Much of this complex vascular network development is under the influence of vascular endothelial growth factor (VEGF) [10-13]. In addition, angiogenesis remodels this vascular system, promoting vascular intussusception that is facilitated by hypoxia. Oxygen depletion activates the expression of several genes, including those encoding VEGF, angiopoietin-2, and nitric oxide synthase [11]. These proteins are important modulators of cell proliferation induction, guided migration, differentiation and cell-to-cell communication [14].

At 4 weeks of gestation, a group of capillary networks begins to develop into the definitive veins of the embryo. At the same time, three paired venous systems form. The vitelline veins drain the yolk sac and the developing gastrointestinal tract, the umbilical veins return oxygenated blood from the placental tissue, and the cardinal veins drain the embryo [11]. Before the vitelline vein enters the venous end of the heart (sinus venosus), it forms the hepatic sinusoids in the developing liver [11]. The left vitelline vein regresses, and the enlarged right vitelline vein in the liver becomes the DV [10, 11]. The umbilical vein brings oxygenated blood from the placenta to the heart. Initially, the umbilical veins are paired, but as the embryo develops, the right umbilical vein degenerates, whereas the left persists [11]. The left umbilical vein forms a direct anastomosis with the DV, which delivers oxygen- and nutrient-rich blood from the placenta to the embryo-fetal heart. After birth, under normal conditions, the DV regresses and becomes the ligamentum venosum.

3.2. Ductus Venosus Shunting

The mechanism of redistribution of blood flow between the fetal liver and the DV is still a matter of debate [3]. DV shunting corresponds to the percentage of umbilical blood flow that enters the DV, which is arranged in parallel to the intrahepatic branches of the portal vein [3] (Fig. **1**). This aspect is of particular relevance because the amount of blood that is conducted by the DV is proportional to the resistance of the hepatic venous circulation [15, 16]. In other words, the flow regulation in the DV is a variable dependent on the degree of permissiveness to the flow through this blood channel.

DV shunting can be assessed during pregnancy using the indicator dye-dilution method, a radioactively labeled microsphere technique, and blood flow volume measurement using the Doppler ultrasound technique. In experimental situations in which the degree of blood flow through the DV is evaluated, the increase in the DV shunting rate is a defense mechanism. Therefore, theoretically, an increased DV/UV ratio is a sign of a potential hemodynamic compromise. The proportion of umbilical blood shunting through the DV has been evaluated in several animals, such as sheep [17-26], macaques [27], baboons [5-28], marmosets [5] and, finally, humans [15, 16, 25, 29-32].

Approximately 2 decades ago, Bellotti and colleagues [31] used color Doppler sonography to study umbilical, DV, and hepatic flows in 137 normal fetuses between 20 and 38 weeks of gestation. In all the venous segments examined, blood flow increased significantly with advancing gestational age [31]. The weight-specific amniotic umbilical flow did not change significantly during gestation (120 ± 44 ml. min-1 kg-1), whereas DV flow decreased significantly (from 60 to 17 ml min-1 kg-1). The percentage of umbilical blood flow shunted through the DV decreased significantly (from 40% to 15%); consequently, the percentage of flow to the liver increased during gestation. The right lobe flow changed from 20 to 45%, whereas the left lobe flow was approximately constant (40%) [31]. The authors suggested that these changes are related to different patterns of growth of the umbilical veins and DV diameters [31], and the findings support the hypothesis that the DV plays a less important role in shunting well-oxygenated blood to the brain and myocardium in late normal pregnancy than in early gestation, which leads to increased fetal liver perfusion [31].

The degree of shunting through the DV in the human fetus seems to be associated with fetal growth. In the study of Kiserud and colleagues, the average fraction shunted through the DV was 28% to 32% at 18 to 20 weeks, decreased to 22% at 25 weeks, and reached 18% at 31 weeks [30]. In this cross-sectional ultrasonographic study, fetuses at <10th percentile for birth weight had significantly more shunting (1.4%) than those at >90th percentile (95% confidence interval, 0.1%-2.7%; p =0.04) [30]. In fact, Doppler velocimetry of the DV is abnormal only when fetuses are severely compromised, whereas the ratio of DV to UV flow rates might be an indicator of the impaired fetal condition [33].

Tchirikov and colleagues have analyzed the blood flow rate through the liver as the difference between UV and DV blood flow [33]. The authors observed that the liver blood flow was significantly decreased in pregnancies with intrauterine growth retardation compared with normal pregnancies [33], and the normalized liver perfusion was significantly decreased only in intrauterine growth retardation pregnancies

[33]. The relative increase in DV blood flow in intrauterine growth retardation was attributed by the authors to an increase in hepatic vascular resistance and not to increases in the DV diameter. Later, the same group of authors hypothesized that changes in blood content of the liver evoked alterations to the vascular geometry of the DV, which would also affect its resistance to flow [33]. Consequently, these results suggest that the main factor responsible for the DV shunting regulation is the degree of resistance achieved by the portal circulation, the latter acting as a functional modulator of the flow through the DV.

Jensen and colleagues have examined the effect of graded reduction in uterine blood flow on distribution of cardiac output and oxygen delivery to fetal organs and venous blood flow patterns in 9 fetal sheep using the radionuclide-labeled microsphere technique [24]. The results of this experiment described a graded reduction in uterine blood flow that induced a redistribution of fetal oxygen delivery and in venous flow patterns [24], influencing the DV shunting. Approximately 15 years later, the umbilical venous flow, DV blood flow, and blood flow to the fetal liver in 56 severely intrauterine growth-restricted fetuses with an abnormal pulsatility index of the umbilical artery were compared with 137 normal control fetuses [16]. In severe intrauterine growth-restricted fetuses, Doppler examination of blood flow volume showed a significant increase in the shunting of umbilical vein blood flow through the DV and noted a relatively constant blood flow to the heart and brain at the expense of fetal hepatic perfusion [16]. These observations suggested that chronic hypoxia promotes the flow of more oxygenated blood from the DV towards the left heart, coronary circulation and fetal brain, which is a much more ancillary effect to achieve in acute situations or in cases of severe fetal UV compromise. This reasoning can be observed in one experimental study performed in 11 anesthetized pregnant sheep, in which the obliteration of one umbilical artery increases the DV/umbilical vein volume flow (mL/min/kg) ratio [26]. In addition, compression of the umbilical cord shifts down blood flow velocity profiles in the DV, increasing dramatically the pulsatility index of this vessel [26].

To study the regulation of the DV inlet in vivo, Kiserud and colleagues measured the effects of vasoactive substances and hypoxemia on its diameter in nine fetal sheep in utero at 0.9 gestation under ketamine-diazepam anesthesia [25]. Hypoxemia caused a 61% increase of the inlet diameter and a distension of the entire DV, suggesting that the DV inlet is under active regulation, demonstrated by its distension during infusion of a nitric oxide (NO) donor or hypoxemia [25]. This observation has never been demonstrated in humans, and therefore, the presence of a sphincter in the trajectory of the DV remains controversial.

3.3. Fetal Ductus Venosus Flow Assessment in Daily Clinical Practice

Doppler ultrasound is the technology of current use in daily clinical practice for the evaluation of the fetal DV waveform. In the recent years, as a result of the technological evolution in this area, especially in the quality and resolution of the ultrasound systems, Doppler ultrasound has proven to be an excellent technology for non-invasive evaluation of the fetal circulation. In particular, DV evaluation is a technique that requires training and should be used for clinical decisions when it is performed by trained and properly certified operators. In fact, competence in Doppler assessment of the DV is achieved only after extensive supervised training [34].

The evaluation of the DV flow can be made in the first [35-40] or second and third trimesters of pregnancy [41-49] (Figs. **2** and **3**). The DV can be visualized in a mid-sagittal longitudinal plane of the fetal trunk or in an oblique transverse plane through the upper abdomen [50].

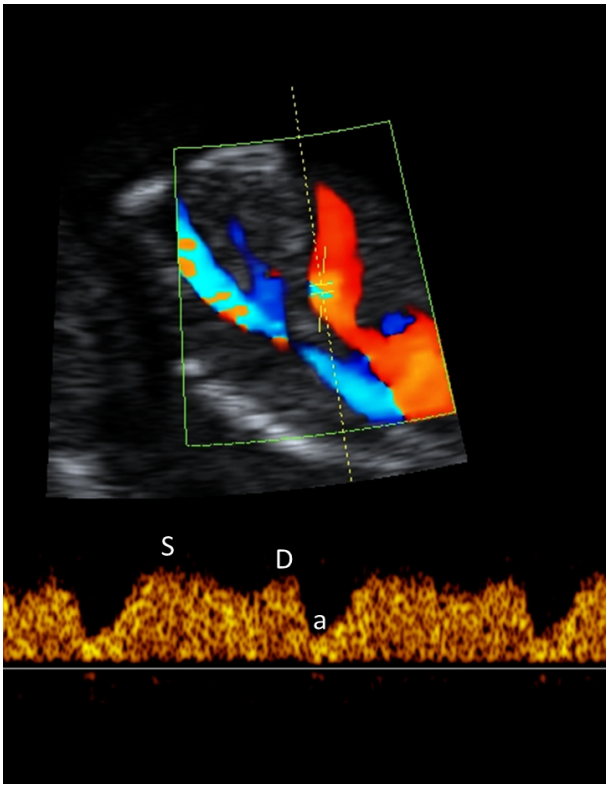

Fig. (2). Color Doppler imaging of the ductus venosus (DV) and a normal first-trimester DV waveform. *(The color version of the figure is available in the electronic copy of the article).*

According to the Fetal Medicine Foundation protocol [51], DV examination should be undertaken during fetal quiescence, in the absence of fetal movements. For an adequate observation of the DV, the magnification of the image should be such that the fetal thorax and abdomen occupy the whole image, and a right ventral mid-sagittal view of the fetal trunk should be obtained [51]. Color flow mapping should be undertaken to demonstrate the umbilical vein, DV and fetal heart [51]. This protocol suggests that the pulsed Doppler sample volume should be small (0.5-1.0 mm in the first trimester and 1.0-2.0 mm in the second and third trimesters) to avoid contamination from the adjacent veins, and it should be placed in the yellowish aliasing area. The insonation angle should be less than 30 degrees and the filter should be set at a low frequency (50-70 Hz) so that the a-wave is not obscured. The sweep speed should be high (2-3 cm/s) so that the waveforms are spread, allowing better as-

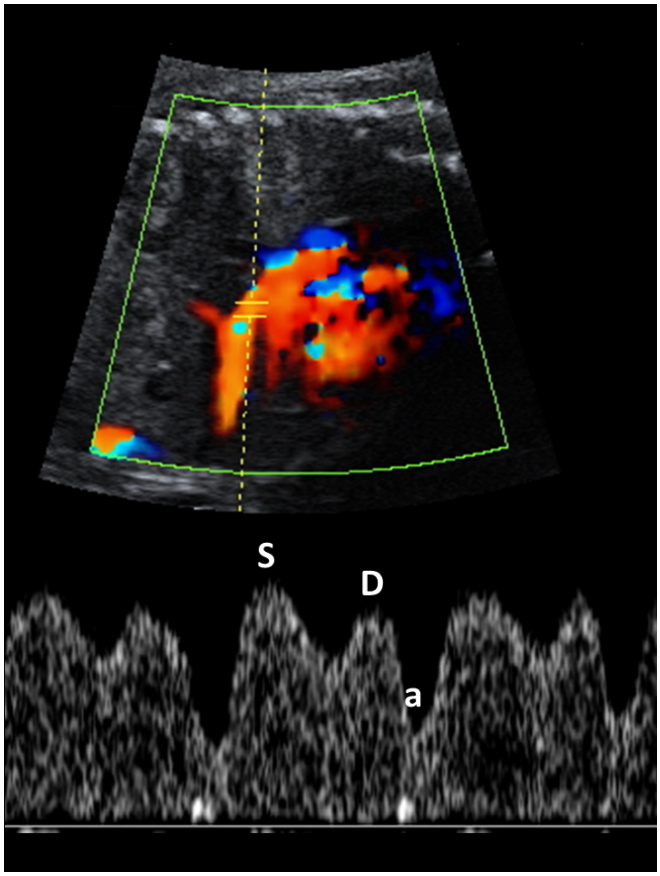

Fig. (3). Color Doppler imaging of the ductus venosus (DV) and a normal second-trimester DV waveform. *(The color version of the figure is available in the electronic copy of the article).*

sessment of the a-wave [51]. When these criteria are satisfied, it is possible to assess the a-wave and determine qualitatively whether the flow is positive, absent or reversed. The DV pulsatility index (DV-PIV), which is the Doppler ratio most utilized in daily clinical practice for impedance assessment of the DV, is measured by the machine after manual tracing of the outline of the waveform [51].

It is important to remember that the peak systolic velocity increases from 48 cm/s at 14 weeks to 71 cm/s at 41 weeks; therefore, the spectrum obtained by Doppler ultrasound should be in agreement with previously published reference curves [50, 52-55]. This is particularly relevant because of the similarity between DV waveforms and suprahepatic veins, which are in a satellite location to the DV and can be easily confused with the DV spectrum. The DV exhibits a normal flow-velocity profile that is typically antegrade throughout the entire cardiac cycle [56]. This feature is permissive to the semi-quantitative evaluation of its complex waveform.

The denomination of the phases that make up the DV venous flow-velocity waveform is closely related to the respective period of the cardiac cycle. In normal conditions, the cardiac cycle involves five distinct phases: early diastole, atrial contraction, isovolumetric contraction, ejection phase, and isovolumetric relaxation.

During the isovolumetric contraction phase of the cardiac cycle, the ventricular pressure rises steeply with no change in ventricular volume as both the atrioventricular (AV) and semilunar valves are closed [57]. As the ventricular pressure continues to rise, it exceeds the pressure within the great arteries, and the semilunar valves open, resulting in rapid ejection of blood [57]. With ventricular ejection, myocardial deformation ensues, and this phase is associated with a drop in ventricular volume and pressure [57]. With the initiation of ventricular systole, the descent of the atrioventricular valve ring decreases atrial pressure and increases the amount of venous return that can be accommodated by the atria [56]. This produces the first increase in venous forward velocities, which peak at the S-wave [56] (Figs. **2** and **3**). As the ventricular pressure drops below the pressure within the great arteries, the semilunar valves close [57]. A period of isovolumetric relaxation ensues, which is associated with decreased ventricular pressure with no change in ventricular volume as the atrioventricular valves are closed [57]. At this time, the AV valve ring ascends towards its resting position, atrial pressures rise, and venous forward velocities fall to the first trough, designated the v-descent. As the ventricular pressure decreases below that of the atria, the AV valves open [57], and the higher pressures in the atria lead to an opening of the AV valves, allowing for an increase in venous forward velocities towards the second peak during passive diastolic ventricular filling (D-wave) [56] (Figs. **2** and **3**). The atrial contraction occurs in late diastole and results in complete filling of the ventricles, promoting a slight increase in ventricular pressure [57]. During the isovolumetric contraction phase of the cardiac cycle, ventricular pressure rises steeply with no change in ventricular volume as both the atrioventricular and semilunar valves are closed [57]. The fall in venous forward velocities produces the second trough, designated the a-wave [56] (Figs. **2** and **3**).

Although the correlation between the DV waveform and the phases of the cardiac cycle can be established temporally, there is no experimental evidence for a direct correlation between DV waveform and fetal heart function. Nevertheless, the continuity of venous forward flow fluctuates with the capacity of the heart to accommodate venous return, which depends on venous volume (preload), cardiac function (relaxation, compliance and contractility) and downstream arterial blood-flow resistance (afterload) [58]. In other words, DV blood velocity reflects the portocaval pressure gradient that drives this flow in addition to the portal liver perfusion, as assumed previously [53, 59]. However, this gradient must be modulated by adequate cardiac compliance, which varies according to the gestational age and in some fetal pathological conditions. Given that an umbilicocaval (portocaval) pressure gradient is the driving pressure for perfusing the liver and for causing the umbilical blood to reach the foramen ovale, it was assumed, in the construction of recent longitudinal reference ranges [53], that the peak systolic velocity or velocities close to this reflected the optimal perfusion pressure in the individual fetus [53].

In daily clinical practice, an abnormal flow in DV is easily identified, qualitatively, by observing the absence or inversion of the a-wave. In these cases, the pulsatility index increases significantly, translating a significant increase in the pressure gradient towards the right atrium. Nevertheless,

it is important to keep in mind that, during atrial systole, the venous blood column is in continuity with the right atrium, but this atrium is in continuity with the left atrium and right ventricle. For this reason, the identification of an abnormal DV waveform requires a careful examination of the fetal cardiovascular system, including the placental circulation, because multiple mechanisms of disease can coexist. The evaluation should be done in a systematic way and should be morphological and functional in order to rule out pathological conditions such as increased cardiac preload, abnormal cardiac structure and function, and increased cardiac afterload.

3.4. Ductus Venosus Doppler to Screening of Cardiac Defects

Congenital heart defects are the most commonly occurring congenital malformations that cause significant mortality and morbidity. For this reason, the interest in the early detection of this set of pathologies is a cause of concern for all those dedicated to prenatal diagnosis. In particular, visualization of the fetal heart with adequate echographic resolution is only possible from the end of the first trimester, and therefore, the identification of risk markers for the occurrence of congenital heart defects deserves the full commitment of the sonographers. Growing evidence suggests that assessment of DV flow improves the performance of nuchal translucency (NT) screening for cardiac defects.

With the objective to evaluate in a meta-analysis the screening performance of abnormal DV Doppler waveforms for detection of congenital heart disease (CHD) in chromosomally normal fetuses, a group of authors analyzed seven studies regardless of the NT status, nine studies with increased NT and seven studies with normal NT [60]. In populations including participants regardless of NT status, the summary sensitivity and specificity of DV for detecting CHD were 50 and 93%, respectively [60]. In participants with increased NT, the summary sensitivity and specificity were 83 and 80%, and in those with normal NT, the summary sensitivity and specificity were 19 and 96%, respectively [60]. The findings of this meta-analysis on chromosomally normal fetuses demonstrate that the DV waveform examination has moderate sensitivity for detecting CHD [60]. However, the authors concluded that DV assessment for the detection of CHD in chromosomally normal fetuses can be considered in evaluating the potential use and limitations of this screening test [60]. These results are consistent with more recent evidence suggesting that in chromosomally normal fetuses, the addition of an abnormal DV a-wave to increased NT does not improve the screening performance of NT in the detection of major hearts defects in the first trimester [61].

In conclusion, in fetuses with normal NT, the sensitivity of this marker is not strong enough to be used as a screening test for CHD [62]. Additionally, because there are some small differences in the DV flow of trisomy 21 (T21) fetuses with and without CHD, DV flow is not clinically useful in this group of patients [63]. Further investigations are needed to enhance the clinical utility of the DV in association with other markers of CHD in high-risk pregnancies [64, 65].

3.5. Ductus Venosus Doppler Contribution to Screen for Chromosomal Defects

NT screening combined with maternal age at early mid-trimester can identify approximately 75% of chromosomal abnormalities, with a false-positive rate of 5% [66, 67]. To improve the test performance, Doppler parameters have been included in the screening of fetal chromosomal abnormalities. In the first trimester, a reversed a-wave is associated with an increased risk for chromosomal abnormalities [68] and fetal death [69] in singleton and twin pregnancies [70]. However, in approximately 80% of cases with a reversed a-wave, the pregnancy outcome is normal [69]. Combining the DV-PIV and NT, overall sensitivity decreased to 55%, but specificity reached 99.3%, with a negative predictive value of 99.3% [71]. Because changes in the DV-PIV can be found in fetuses with chromosomal abnormalities, with or without cardiac defects, and in those with certain cardiac abnormalities with normal karyotypes, the DV-PIV should not be used as a first-line screening test at 10–16 weeks of gestation [71]. Although the DV-PIV does not increase the number of cases detected by NT, it can be useful as a second-line test in screen-positive cases with NT in order to increase the specificity, reducing the need for invasive testing [8, 71]. Additionally, because DV blood flow pattern is correlated with the nuchal translucency measurement, it cannot be used as an independent variable to reduce the indication for fetal karyotyping [72].

3.6. Ductus Venosus Doppler in the Management of Intrauterine Growth Restriction

Decreased, absent, or reversed flow in the a-wave of the DV may represent myocardial impairment and increased ventricular end-diastolic pressure resulting from an increase in right ventricular afterload. This abnormal DV waveform has been documented in fetuses with intrauterine growth restriction (IUGR) and linked to an increased neonatal acidemia and perinatal mortality [66].

Recently, in a sheep model of increased placental vascular resistance, a group of authors investigated whether hypoxemia without acidemia affects the DV blood velocity waveform pattern in sheep fetuses with an intact placenta and whether worsening acidemia and impending fetal death are related to changes in DV velocimetry in fetuses with increased placental vascular resistance [73]. The principal conclusion of this important experimental study was that fetal hypoxemia increases the pulsatility of the DV blood velocity waveform pattern [73]. However, in fetuses with elevated placental vascular resistance, DV pulsatility does not increase further in the presence of severe and worsening fetal acidemia and impending fetal death [73]. The authors state that fetal hypoxemia can increase pulsatility in the DV blood velocity waveform pattern [73]. However, it appears that it cannot recognize those ovine fetuses that will become acidic and even die within a short time period [73], suggesting that the development of an abnormal DV blood flow pattern requires additional pathophysiological events that lead to increased ventricular end-diastolic and systemic venous pressures [73]. In human fetuses, the duration of absent or reversed flow during atrial systole in the DV is a strong predictor of stillbirth that is independent of gestational age [74].

Although a progressive predictable sequence of placental and fetal Doppler changes has been described as an adaptive mechanism to a suboptimal intrauterine environment in pregnancies affected by IUGR, the optimal surveillance pattern and timing of delivery remain the focus of much debate and research, with no internationally accepted approach to management [75]. With the objective to assess whether changes in the fetal DV Doppler waveform could be used as indications for delivery instead of cardiotocography (CTG), an extensive randomized study (including women with singleton fetuses at 26-32 weeks of gestation who had very preterm fetal growth restriction) found that when the timing of delivery was based on the study protocol using late changes in the DV waveform, the results exhibited an improvement in the developmental outcomes at 2 years of age [76, 77]. Although assuming that the optimal management of early IUGR fetuses should integrate clinical, Doppler, and CTG parameters, the authors caution that severe anomalies in the DV, when they precede CTG abnormalities, are an indication for undertaking delivery [77].

3.7. Ductus Venosus Doppler Contribution to Screening of Monochorionic Twin Complications

Ultrasonography is central to the proper diagnosis of the type of twinning. Monochorionic twin pregnancies are at increased risk for adverse outcomes compared to dichorionic twin pregnancies and singletons, including twin-twin transfusion syndrome (TTTS), twin anemia-polycythemia sequence, single intrauterine fetal demise and its consequences on the co-twin, and selective intrauterine growth restriction [78]. In particular, TTTS is associated with significant mortality and morbidity [79].

Several studies have assessed the role of first- and early second-trimester markers in the prediction of TTTS in monochorionic twin pregnancies [80] because DV flow profiles and the timing of waveform events are already altered in preTTTS and in the early-stage disease [81]. As a corollary of an extensive meta-analysis that included approximately 2000 pregnancies, of which 323 developed TTTS, an increased risk of TTTS was associated with intertwin NT discrepancy (positive likelihood ratio (LR+), 1.92 (95% CI, 1.25-2.96); a negative likelihood ratio (LR-), 0.65 (95% CI, 0.50-0.84)); NT > 95th percentile (LR+, 2.63 (95% CI, 1.51-4.58); LR-, 0.85 (95% CI, 0.75-0.96)); CRL discrepancy > 10% (LR+, 1.80 (95% CI, 1.05-3.07); LR-, 0.92 (95% CI, 0.81-1.05)); and abnormal DV flow (LR+, 4.77 (95% CI, 1.33-17.04; LR-, 0.49 (95% CI, 0.17-1.41)) [80]. The highest sensitivities were observed for intertwin NT discrepancy >10% (52.8% (95% CI, 43.8-61.7%)) and abnormal DV flow (50.0% (95% CI, 33.4-66.6%)) [80]. Additionally, unbalanced blood volume in TTTS led to alterations in the time intervals of DV, suggesting that the assessment of DV Doppler velocimetry will provide detailed information on fetal cardiac function before and after laser therapy [82].

3.8. Agenesis of the Ductus Venosus

Congenital absence of the DV (ADV) is a rare vascular anomaly with a controversial prevalence. Prognosis largely depends on other fetal cardiac and extra-cardiac anomalies, chromosomopathies, the presence of effusions/hydrops fetalis and the pattern of umbilical venous drainage associated.

There are three main patterns of drainage. If the umbilical vein bypasses the liver, it leads to an increased and unregulated flow into the right atrium (46%), putting this fetus at risk of developing cardiomegaly; this can result in high-output cardiac failure and hydrops. The umbilical vein can also bypass the liver and connect to the inferior vena cava by one iliac or renal vein (26%), causing hyperperfusion of the liver sinusoids and portal hypertension and hydrops. Lastly, the umbilical vein may connect to the portal circulation without giving rise to the DV (21%) [83, 84]. Therefore, when ADV is detected, a more detailed fetal examination and the detection of other anomalies is often necessary.

The exact etiology of ADV is unclear, and it may result from primary agenesis and/or functional or structural closure. Usually, ADV can be detected during the early scan of the first trimester evaluation [85], but in some cases, the ultrasound scan is reported as normal in early pregnancy; there can be a missed diagnosis, but another explanation is the formation of a secondary closure due to an unknown gradual condition [86]. ADV can appear associated with varying comorbidities, some of which are incompatible with life: cardiomegaly, chromosomopathies, altered fetal growth and hepatic calcifications [87]. It was reported [84] that the overall survival rate was 60% and only 50% when the ADV was associated with effusions/hydrops. However, if there was no evidence of hydrops and cardiac overload associated with the ADV, the survival rate was 100%, regardless of the type of ADV [84]. In fact, many studies report a good outcome when there is no further pathological finding, as chromosomopathy or hydrops [84, 85, 88]. Fetuses with ADV and restrictive alternative umbilical venous pathways may have a more benign clinical course because the "small shunt" is unlikely to induce cardiac failure [88]. Not only the caliber of the shunt but also the NT thickness, seems to be important in the evaluation of the prognosis unless ADV appears isolated [85, 88].

Postnatally, cessation of umbilical venous flow occurs, and the short-term impact does not appear to be significant [84], with a regression of the anomaly [88]. However, ADV may lead to significant long-term complications if associated with particular fetal anomalies, such as portal vein agenesis with extrahepatic umbilical vein drainage or congenital absence of the portal venous system. Although ADV with intrahepatic drainage is associated with better chances of survival, infants with congenital absence of the portal venous system, complicated with intrahepatic drainage, have a potentially serious condition [86].

Fetal echocardiography, with access to detailed anatomy, and fetal karyotyping are recommended actions when ADV is noticed [84]. The ultrasound plays an important role not only in detecting abnormalities that can help dictate the prognosis but also allowing parental counseling.

3.9. Patent Ductus Venosus

Patent DV (PDV) is a rare congenital condition where the DV persists as a portosystemic shunt connecting the portal system and inferior vena cava [89-91]. A DV flow effect in

neonatal liver and its persistence after birth remain an unclear subject [90-92]. Few cases have been described so far, and diagnoses occurred not only in early childhood but also in adulthood or even on autopsy studies [93-96]. The majority appear sporadic, but a recessive genetic heritage has been hypothesized since the description of PDV in three brothers [89].

DV blood flow influences important liver functions in early neonates, such as ammonia detoxification, coagulation and serum bile acid concentration [97]. When this portosystemic communication persists, hepatic atrophy and hepatic failure will develop, and biochemical markers include hypergalactosemia, hyperbilirubinemia, hyperammonemia, an increased coagulation time and an augmented serum bile acid concentration. Thereafter, presentation of PDV includes systemic manifestations, representing hepatic, pulmonary and cardiac dysfunction [97-99]. Manifestations reported include cholestatic jaundice [93-100], hepatic encephalopathy [91, 94, 95, 99], massive gastrointestinal bleeding [98]; acute liver failure [99, 101]; respiratory distress [102] and pulmonary arteriovenous fistulae [103, 104], and tumor-like hepatic lesions [92, 105]. A child with a single ventricle, who presented with spontaneous microbubbles on echocardiography, was found to have a PDV [106]. Other peculiar associations have been reported. Yamaguchi *et al*. presented a girl with T21 who was diagnosed with PDV after neonatal cholestasis and a transient abnormal myeloproliferative disorder [100]. Sagiv-Friedgut et al. questioned a genetically linked association of PDV and immunoglobulin E syndrome after their description of these conditions in a pair of siblings [107]. An association between PDV and autoimmune disorders was noted by Yashimoto *et al*. [102]. Acute liver failure has been associated not only with PDV but also with Enterovirus infection and neonatal hemochromatosis [99, 101]. One case of Budd-Chiari syndrome has been associated with PDV and confirmed only in autopsy [96].

Given these pleiotropic presentations, diagnosis may be challenging. Usually, biochemical alterations suggest a hepatic disorder, and a liver ultrasound or abdominal computed tomography (with or without angiographic study) is performed. This may reveal or at least raise the suspicion of a portosystemic shunt [91, 94, 95, 97, 99, 102, 103, 105, 106]. Magnetic resonance angiography has also been suggested as an important diagnostic tool, specifically for infants [108].

Most cases improve substantially with anomalous shunt closure by surgical ligation (*via* laparotomy or laparoscopy) or embolization using a vascular plug through interventional radiology [90, 91, 93-95, 98, 99, 101-104].

In summary, the DV acts as a bypass of the liver microcirculation and plays a critical role in the fetal circulation. The DV allows oxygenated and nutrient-rich venous blood to flow from the placenta to the myocardium and brain. Increased impedance to flow in the fetal DV is associated with fetal aneuploidies, cardiac defects and other adverse pregnancy outcomes. Further research is necessary to determine the importance of the DV Doppler assessment in improving perinatal outcomes.

CONCLUSION

In conclusion, the DV acts as a bypass of the liver microcirculation and plays a critical role in the fetal circulation. The DV allows oxygenated and nutrient-rich venous blood to flow from the placenta to the myocardium and brain. Increased impedance to flow in the fetal DV is associated with fetal aneuploidies, cardiac defects and other adverse pregnancy outcomes. Further research is necessary to determine the importance of the DV Doppler assessment in improving perinatal outcomes.

LIST OF ABBREVIATIONS

ADV	=	Congenital Absence of the Ductus Venosus
AV	=	Atrioventricular
CHD	=	Congenital Heart Disease
CTG	=	Cardiotocography
DV	=	Ductus Venosus
DV-PIV	=	Ductus Venosus Pulsatility Index
IUGR	=	Intrauterine Growth Restriction
LR	=	Likelihood Ratio
NO	=	Nitric Oxide
NT	=	Nuchal Translucency
PDV	=	Patent Ductus Venosus
T21	=	Trisomy 21
TGF-β	=	Transforming Growth Factor β
TTTS	=	Twin-Twin Transfusion Syndrome
UV	=	Umbilical Vein
VEGF	=	Vascular Endothelial Growth Factor
VS	=	Vasculogenesis

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The staff of the Department of Obstetrics of Centro Hospitalar do Porto is acknowledged.

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