Ductus Venosus in the First Trimester: Contribution to Screening of Chromosomal, Cardiac Defects and Monochorionic Twin Complications

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Abstract

In the first trimester the ductus venosus can be easily identified with color Doppler and a ductus venosus waveform can be obtained by pulsed Doppler. At 11–13 weeks the prevalence of abnormal a-wave in the ductus venosus is inversely related to fetal crown-rump length and maternal serum pregnancy-associated plasma protein-A (PAPP-A), increases with fetal nuchal translucency (NT) thickness and is more common in women of Black racial origin and in fetuses with abnormal karyotype or cardiac defects. Ductus venosus flow provides an independent contribution in the prediction of chromosomal abnormalities when combined with NT and the maternal serum markers of PAPP-A and free β-hCG, increasing the detection rate to 96% at a false-positive rate of 2.6%. Abnormal ductus venosus flow increases the risk of cardiac defects in fetuses with NT above the 95th centile, and it may increase the risk in fetuses with normal NT. In twin pregnancies, abnormal ductus venosus flow is associated with chromosomal abnormalities and cardiac defects. In monochorionic twins, abnormal flow in the ductus venosus in at least 1 of the fetuses increases the risk of developing twin-to-twin transfusion syndrome.

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Introduction

The 11- to 13-week scan is now widely accepted as an important component of early screening for fetal chromosomal and structural defects and for preeclampsia [1–3]. Assessment of the ductus venosus flow is an integral part of the 11- to 13-week scan because extensive studies have demonstrated that abnormal flow in this vessel is associated with an increased risk for chromosomal abnormalities, cardiac defects and other adverse pregnancy outcomes both in singletons and twin pregnancies [4–6].

Anatomically, the ductus venosus is strategically located as it has an important role directing the oxygenated blood towards the fetal heart and brain. About 30% of the oxygenated blood from the umbilical vein, which is distributed to the portal vein, is shunted through the ductus venosus [7, 8]. The degree of shunting will be determined by the diameter of the vessel, pressure gradient and blood viscosity [9]. The blood from the ductus venosus is then directed towards the left atrium as a consequence of the anatomical position of the fetal atrial septum, which is located further to the right than in the postnatal life, and the high volume and velocity of the blood flow from the ductus venosus that distends the foramen ovale flap like a spinnaker [10]. Different conditions affecting the cardiac pre- or afterload may produce pressure gradient changes and affect the ductus venosus waveform.

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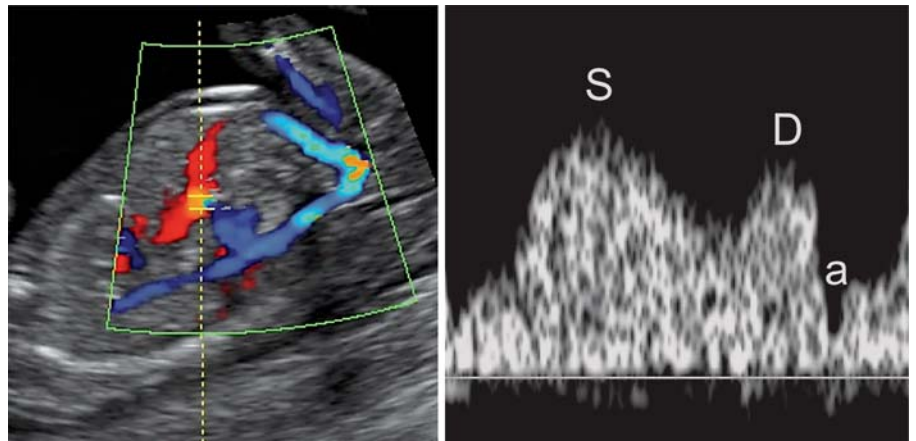Tel. +34 943 29 2499, Fax +34 943 29 1176, E-Mail nereamaiz@yahoo.es

Fig. 1. Ductus venosus color Doppler (left) and ductus venosus waveforms (right) showing the three phases: (S) systole, (D) diastole, and (a) atrial contraction.
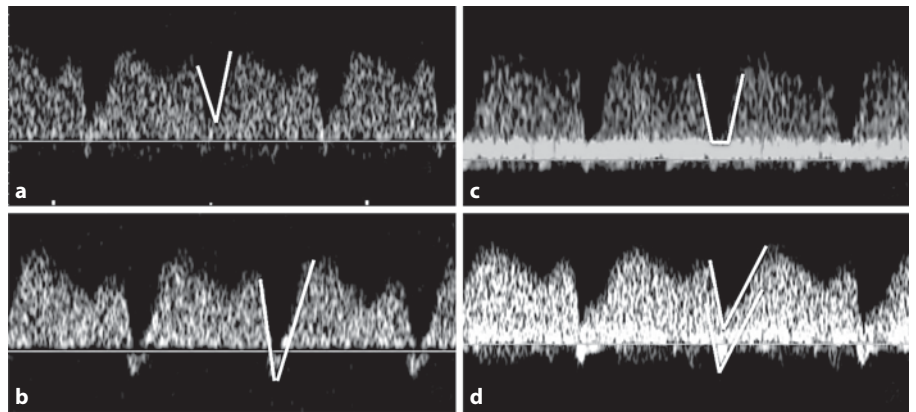

Fig. 2. Flow velocity waveforms showing a normal waveform (**a**), reversed a-wave (**b**), contamination by umbilical vein (**c**) showing a truncated V-shaped line and contamination by hepatic vein (**d**) showing two V-shaped lines [13].

Assessment of Ductus Venosus Flow

In the first trimester, the ductus venosus can be easily identified by color Doppler mapping as the portion with higher velocity following the umbilical vein. The ductus venosus has a typical waveform where three phases can be recognized. The highest velocity peak corresponds to the ventricular systole (S); during this phase the pressure gradient between the umbilical vein and the atrium is the highest. The next peak of forward flow corresponds to the early diastole (D), with the opening of the atrioventricular valves and early passive filling of the ventricles. The third phase, with the lowest velocity, corresponds to the atrial contraction (a) during late diastole; during this phase the atrial pressure is high and there is a low pressure gradient [11] (fig. 1).

Doppler assessment of the ductus venosus should fulfill the following criteria: (1) the examination should be taken under fetal quiescence; (2) the magnification of the image should be such that the fetal thorax and abdomen occupy the whole screen; (3) a right ventral mid-sagittal view of the fetal trunk should be obtained and color flow mapping used to demonstrate the umbilical vein, ductus venosus and fetal heart; (4) the pulsed Doppler sample should be small (0.5–1 mm) to avoid contamination from the adjacent veins, and it should be placed in the yellowish aliasing area, which is the portion immediately above the umbilical sinus; (5) the insonation angle should be <30°; (6) the filter should be set at a low frequency (50–70 Hz) so that the a-wave is not obscured, and (7) the sweep speed should be high (2–3 cm/s) so that the waveforms are spread allowing better assessment of the a-wave [12, 13].

Waveforms can be assessed quantitatively, the most frequently used parameter is the pulsatility index for veins [14], or qualitatively, classifying the a-wave as positive, absent or reversed according to the forward, absent or reversed flow, respectively, during the atrial contraction [15] (fig. 2).

A correct technique should be used to assess the ductus venosus waveform in order to avoid contamination from the adjacent veins, the main artifact in ductus venosus assessment. Contamination by the inferior vena cava

Table 1. Studies reporting on the incidence of abnormal flow in the ductus venosus in the first trimester in euploid fetuses and in those with trisomy 21, 18, 13, Turner syndrome and other chromosomal abnormalities

Author	Number	Normal	Trisomy 21	Trisomy 18	Trisomy 13	Turner syndrome	Other
Matias et al., 1998 [15]	486	13/423 (3.1%)	35/38 (92.1%)	12/12 (100%)	5/7 (71.4%)	2/3 (66.7%)	3/3 (100%)
Antolin et al., 2001 [23]	924	39/911 (4.3%)	5/7 (71.4%)	3/3 (100%)	–	1/1 (100%)	1/2 (50.0%)
Murta et al., 2002 [24]	372	7/343 (2.0%)	18/18 (100%)	1/1 (100%)	2/2 (100%)	2/2 (100%)	3/6 (50.0%)
Zoppi et al., 2002 [25]	325	38/292 (13.0%)	14/20 (70.0%)	6/7 (85.7%)	1/1 (100%)	1/3 (33.3%)	1/2 (50.0%)
Borrell et al., 2003 [26]	3,382	162/3,249 (5.0%)	36/48 (75.0%)	–	–	–	–
Toyama et al., 2004 [27]	1,097	69/1,075 (6.4%)	5/7 (71.4%)	3/5 (60.0%)	1/1 (100%)	4/4 (100%)	2/5 (40.0%)
Prefumo et al., 2005 [28]	572	26/497 (5.2%)	18/47 (38.3%)	–	–	–	–
Maiz et al., 2009 [17]	19,800	633/19,614 (3.2%)	81/122 (66.4%)	21/36 (58.3%)	11/20 (55.0%)	6/8 (75.0%)	
Total	26,958	987/26,404 (3.7%)	212/307 (69.1%)	46/64 (71.9%)	20/31 (64.5%)	16/21 (76.2%)	10/18 (55.6%)

Abnormal flow was defined as absent or reverse α-wave or pulsatility index for veins above the 95th centile.

or hepatic veins may mimic a reversed a-wave and, conversely, contamination by the umbilical vein may hide an absent ductus venosus a-wave. According to Borrell [13], in the contamination by inferior vena cava or hepatic veins, two V-shaped lines are seen, while in true reversed flow the line delineated by maximum velocity follows a single continuous V-shaped line, crossing zero. In contamination by the umbilical vein, a 'truncated' V line is seen (fig. 2). Competence in accurate assessment of the ductus venosus waveform requires extensive supervised training. Maiz et al. [12] showed that an experienced sonographer needs about 80 supervised scans in order to achieve this level of competence.

Ductus Venosus Flow in Normal Pregnancies

At 11–13 weeks, blood flow during atrial contraction is usually forward, although absent or reversed flow might be recorded in normal fetuses [16]. The prevalence of reversed a-wave is inversely related to the fetal crown-rump length and maternal serum pregnancy-associated plasma protein-A (PAPP-A) and is more common in women of Black racial origin [17]. There are three factors that may explain the crown-rump length-related decrease in the prevalence of reversed a-wave: (a) improved ventricular filling and decreased myocardial stiffness with advancing gestation, (b) decrease in placental resistance and therefore cardiac afterload, and (c) improvement in renal function to counteract any tendency to fluid retention [18–21]. The increased cardiac afterload due to impaired placentation and therefore increased placental resistance may explain the association between the reversed a-wave with low PAPP-A and Black racial origin [17].

Ductus Venosus Flow and Screening for Chromosomal Abnormalities

In fetuses with chromosomal abnormalities there is a higher prevalence of abnormal ductus venosus waveform [22]. In the combined data from eight studies, abnormal ductal blood flow was observed in 3.7% of euploid fetuses and in 69.1, 71.3, 64.5 and 76.2% of fetuses with trisomies 21, 18 and 13 and Turner syndrome, respectively (table 1) [15, 17, 23–28].

Different studies have assessed ductus venosus flow at 11–13 weeks together with other first-trimester markers. Several studies showed a significant correlation between ductus venosus flow and nuchal translucency (NT) thickness [5, 17, 26, 29]. This might be explained by the coincidence of cardiac defects or transient cardiac dysfunction [21]. One study examined the association between ductus venosus flow and nasal bone and found no significant interaction [28]. Two studies have found a significant association between ductus venosus flow and maternal serum PAPP-A MoM [17, 30]. A possible explanation for this association would be that low levels of PAPP-A are reflecting an early impaired placentation leading to an increased placental resistance and high cardiac afterload.

Logistic regression analysis has shown that ductus venosus flow provides independent contribution to the prediction of chromosomal abnormalities when it is combined with NT and maternal serum PAPP-A and free β-hCG [17, 30, 31].

Performance of first-trimester combined screening for trisomy 21 is improved by the addition of ductus venosus flow assessment at 11–13 weeks. Maiz et al. [17] found an increase in the detection rate from 94 to 97% and from 80

Table 2. Previous studies that examined the relationship between ductus venosus waveforms and major cardiac defects in chromosomally normal fetuses with NT thickness above the 95th centile

Author	Total	Cardiac defects	Abnormal ductus venosus flow	
			no cardiac defects	cardiac defects
Matias et al., 1999 [21]	142	7 (4.9%)	4/135 (3.0%)	7/7 (100%)
Bilardo et al., 2001 [29]	69	4 (5.8%)	19/65 (29.2%)	4/4 (100%
Murta et al., 2002 [24]	16	1 (6.3%)	0/15 (0.0%)	1/1 (100%)
Zoppi et al., 2002 [25]	115	2 (1.7%)	30/113 (26.5%)	2/2 (100%)
Haak et al., 2003 [33]	22	2 (9.1%)	8/20 (40.0%)	2/2 (100%)
Favre et al., 2003 [34]	95	9 (9.5%)	20/86 (23.3%)	9/9 (100%)
Toyama et al., 2004 [27]	141	4 (2.8%)	23/137 (16.8%)	3/4 (75%)
Maiz et al., 2008 [32]	191	16 (8.4%)	40/175 (22.9%)	11/16 (68.8%)
Total	791	45 (5.7%)	144/746 (19.3%)	39/45 (86.7%)

to 88% for fixed false-positive rates of 5 and 1%, respectively. Similarly, Borrell et al. [31] by addition of the ductus venosus to NT and serum markers found a detection rate of 92 and 88% for false-positive rates of 5 and 1%, respectively.

Different screening strategies have been studied: (a) assessment of the ductus venosus at 11–13 weeks in all cases, (b) a two-stage strategy, with a first-stage screening using the combined test in all patients followed by a second-stage assessment of the a-wave only in those with an intermediate risk of 1 in 51 to 1 in 1,000 after the first stage, (c) an integrated test, with measurements of NT and PAPP-A in the first trimester and measurements of α-fetoprotein, unconjugated estriol, free β-hCG and inhibin-A in the second trimester (15–20 weeks). Maiz et al. [17] studied the first two strategies and found similar results with detection rates of 96 and 95.9% at a false-positive rate of 2.6%. Borrell et al. [30] investigated the integrated test and reported that the detection rates were 95 and 93% at false-positive rates of 5 and 3%, respectively.

Ductus Venosus Flow and Screening for Cardiac Defects

Abnormal flow in the ductus venosus is associated with increased risk for fetal cardiac defects. Early studies examining this association focused on fetuses with increased NT, but more recent studies have reported data on fetuses with normal NT.

In chromosomally normal fetuses with increased fetal NT, the finding of absent or reversed a-wave in the ductus venosus is associated with a threefold increase in the like-lihood of a major cardiac defect, whereas the finding of normal ductal flow is associated with a halving in the risk for such defects [32]. In the combined data from eight studies that examined ductus venosus waveforms in 791 chromosomally normal fetuses with increased NT thickness (above the 95th centile) a major cardiac defect was observed in 45 (5.7%) fetuses and 39 (86.7%) of these had abnormal Doppler waveforms in the ductus venosus (table 2) [21, 24, 25, 27, 29, 32–34]. However, there were wide variations between the individual studies in the number of cases examined (16–191), the prevalence of cardiac defects (1.7–9.5%), and the incidence of abnormal ductus venosus waveforms in those without cardiac defects (0–40%).

A more recent study assessed the performance of the ductus venosus in the prediction of cardiac defects in a screening population. This study involved 10,490 fetuses, including 20 (0.2%) with major cardiac defects, and found a higher prevalence of reversed a-wave in those fetuses with cardiac defects than in those without cardiac defects (25 vs. 3.7%). In a multiple logistic regression analysis, abnormal ductus venosus flow and NT measurement were the only contributors in the prediction of cardiac defects [5].

The results of the studies in euploid fetuses with normal NT are contradictory. In the study by Maiz et al. [5], none of the 12 fetuses with cardiac defect and normal NT had abnormal ductus venosus flow. Martinez et al. [35] found that 5 of 32 (15.6%) fetuses with a major cardiac defect and normal NT had a reversed a-wave in the ductus venosus. In a case-control study in fetuses with normal NT, Oh et al. [4] found that fetuses with abnormal flow in the ductus venosus had a higher prevalence of

cardiac defects than those with normal ductus venosus flow.

Martinez et al. [35] found no specific pattern of major cardiac defects in fetuses with increased NT and abnormal ductus venosus flow, but right heart abnormalities were predominant (4 out of 5, 80%) in fetuses with normal NT with abnormal flow in the ductus venosus. Some of the structural heart defects that are not associated with heart failure during the second and third trimesters but with heart failure after birth have a reversed a-wave in the ductus venosus in the first trimester [21, 36, 37]. The fetal heart has a lower compliance than an adult heart and this is more evident in the first trimester, where the predominance of the atrial contraction wave is greater than in later gestation. In addition, cardiac afterload is greater in the first trimester because of higher placental resistance. Thus, in the first trimester, only a small impairment of the cardiac diastolic function might be enough for cardiac dysfunction to become evident as a reversed a-wave in the ductus venosus [15, 21, 22].

Ductus Venosus Flow and Screening for Monochorionic Twins Complications

Very few studies have analyzed ductus venosus flow at 11–13 weeks in twin pregnancies. The association of abnormal flow in the ductus venosus with fetal aneuploidies and cardiac defects is similar to that in singleton pregnancies. In a study with 695 twin pregnancies, 516 dichorionic and 179 monochorionic, there was a similarly high prevalence of reversed a-wave in aneuploid compared with euploid fetuses (70 vs. 7.7%, p < 0.001) as in singleton pregnancies, and assessment of the ductus venosus flow improved the prediction of aneuploidies provided by screening with fetal NT alone. In the same study, 3 of the 6 (50.0%) fetuses with a major cardiac defect had an abnormal flow in the ductus venosus [6].

A small study by Matias et al. [38] suggested that abnormal ductus venosus flow in the first trimester may be a predictor of twin-to-twin transfusion syndrome (TTTS). In a series of 11 monochorionic twin pregnancies, severe TTTS developed in the 2 cases with abnormal ductus venosus waveforms in the recipient fetus at 11–13 weeks of gestation and in none of the cases with normal ductus venosus flow patterns. Subsequently, two larger studies have analyzed this association. Maiz et al. [6], in a series of 179 monochorionic pregnancies, found a reversed a-wave in 10 of the 26 pregnancies (38.5%) that subsequently developed a TTTS. The rate of development

of TTTS was 15%, which was increased to 30% if there was a reversed a-wave in 1 of the fetuses and reduced to 10% if the ductus venosus flow was normal in both fetuses at 11–13 weeks. Matias et al. [39] have recently found abnormal flow in the ductus venosus in 9 of the 12 (75.0%) of the pregnancies that subsequently developed TTTS and 9 of the 16 (56.3%) pregnancies where 1 of the fetuses had an abnormal waveform developed TTTS. Despite the differences in the two studies, it seems clear that abnormal flow in the ductus venosus in at least 1 of the fetuses at 11–13 weeks increases the risk of developing TTTS and, therefore, the intensity of monitoring of such pregnancies should be increased.

The prevalence of reversed a-wave in fetuses from singleton pregnancies and dichorionic twins is similar, but in monochorionic twins it is substantially higher, even in those that do not develop TTTS [6]. It is possible that in pregnancies with abnormal Doppler and normal outcome there is spontaneous resolution of TTTS between the first and second trimesters and, in contrast, in those with normal Doppler and subsequent TTTS the hemodynamic abnormality develops during the second trimester. This is compatible with the hypothesis of 'asymmetric reduction in placental anastomoses' [40]. According to this hypothesis, in all monochorionic twins in early pregnancy, there is a large of number of bidirectional arteriovenous connections but with advancing gestation there is progressive spontaneous closure or disruption in these anastomoses, which occurs at random. Clinical features of TTTS occur when there is asymmetry in the arteriovenous anastomoses so that there is a net flow of blood in favor of one of the fetuses and at the expense of its co-twin. It is therefore possible that in some pregnancies with asymmetrical flow at 11–13 weeks, with advancing gestation, the random disruption of arteriovenous anastomoses restores symmetry in flow and therefore spontaneous resolution of the early sign of TTTS. In contrast, in some cases with symmetrical flow at 11–13 weeks the subsequent disruption of arteriovenous anastomoses is asymmetrical resulting in the development of TTTS during the second trimester. Previous studies reported that another early manifestation of TTTS is increased NT in at least 1 of the fetuses or a large discordance in NT between the 2 fetuses [41, 42]. Multiple regression analysis demonstrated that in the prediction of TTTS there was no significant improvement by the addition of NT discordance to the finding of reversed a-wave [6, 39].

Conclusions

Ductus venosus flow assessment at the 11- to 13-week scan has an important role in screening for chromosomal abnormalities and cardiac defects both in singleton and in twin pregnancies.

Ductus venosus flow assessment improves the performance of screening for chromosomal abnormalities provided by combined screening by NT thickness and serum PAPP-A and free β-hCG, and is also a useful tool in first-trimester screening for cardiac defects. Different strategies have been suggested. One option is to assess ductus venosus in all patients. Alternatively, since accurate assessment requires an extensive supervised training, it could be assessed by sonographers with this level of competence only in those patients that have an intermediate risk between 1 in 51 and 1 in 1,000 after the first-stage screening and in those fetuses with an increased NT thickness above the 95th centile. This way the number of patients requiring an assessment by a specifically trained sonographer would be reduced to no more than 20%. The detection rate of chromosomal abnormalities by the two approaches is the same. In twin pregnancies ductus venosus flow has similar applications as in singleton pregnancies, and in monochorionic twins it helps to modify the intensity of monitoring in search for TTTS.

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