10.5005/jp-journals-10009-1190

REVIEW ARTICLE

Ductus Venosus: A Love Story of 14 Years

Alexandra Matias, Nuno Montenegro

Ultrasound Unit, Department of Obstetrics and Gynecology, Hospital of S João, Medical Faculty, Porto University, Porto, Portugal

Correspondence: Alexandra Matias, Ultrasound Unit, Department of Obstetrics and Gynecology, Hospital of S João, Medical Faculty, Porto University, Porto, Portugal, e-mail: almatias@mail.telepac.pt

ABSTRACT

Ductus venosus is a tiny vessel with a central role in fetal circulation. Combining B-mode with color and pulsed Doppler is feasible to identify this vessel and evaluate the blood flow waveform at 11 to 13 weeks. The higher prevalence of abnormal A-wave in fetuses with abnormal karyotype and/or cardiac defects turned DV evaluation into a useful marker for chromosomal abnormalities and cardiopathies. Even when combined with nuchal translucency (NT) or biochemical markers, DV blood flow evaluation contributes to an increase in sensitivity and reduces false-positive rate. Abnormal ductal flow is also related to a worse fetal and perinatal outcome. In monochorionic twin pregnancies, in addition to NT measurement at 11 to 14 weeks, the Doppler assessment of DV blood flow increases relevantly the performance of screening for those at higher risk of developing twin-to-twin transfusion syndrome. This story of 14 years surely contributed to change the way first trimester screening is being implemented.

Keywords: Ductus venosus, Doppler blood flow, Chromosomal abnormalities, Cardiac defects, Pregnancy loss, Twin-to-twin transfusion syndrome.

INTRODUCTION

Almost 20 years ago screening for fetal chromosomal and structural defects moved from the second to the first trimester of pregnancy, based on the measurement of fetal nuchal translucency (NT) thickness. It was well-established from epidemiological studies that increased NT was more prevalent among fetuses with trisomy 21 but the reason why NT was increased specifically in those babies was not clear. Several causes were suggested, such as lymphatic immaturity, mediastinal compression with venous congestion, fetal immobility, altered composition of the subcutaneous connective tissue and cardiac failure/dysfunction. Further exploring this last hypothesis, our group began a pioneering work on venous return evaluation in the first trimester of pregnancy. We came across a very tiny vein with arterial behavior that showed a very characteristic Doppler wave, the ductus venosus. However, in certain fetuses this vessel presented an abnormal wave that changed the whole picture of first trimester screening and gave birth to a successful story of 14 years.

Ductus Venosus: A Window into the Fetal Heart

Ductus venosus (DV) is the main distributor of placental blood and directs preferentially well-oxygenated blood from UV to the cerebral and coronary circulations, across the foramen ovale towards the left atrium (Lind et al, 1949; Kiserud et al, 1992a,b). In fact, the venous return is arranged in a Y-shaped inferior vena cava—foramen ovale unit with two different pathways (Fig. 1):

- via *sinistra* (dorsal and left side stream): 30% (at mid-gestation) and 20% (at term) of umbilical blood is accelerated to the left atrium through the foramen ovale shunted from the DV and left hepatic veins (Kiserud 1992b; Bellotti et al, 2000).

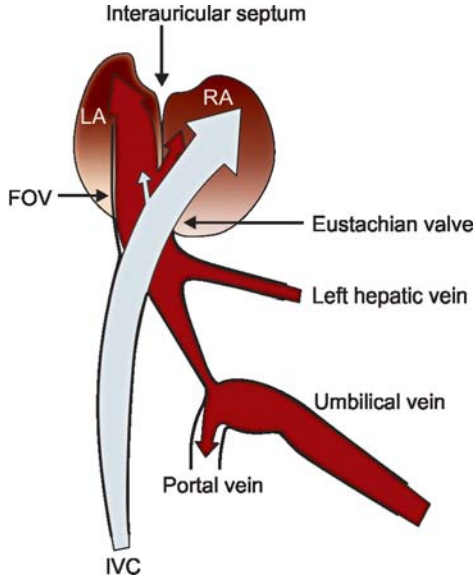

Fig. 1: Venous return is arranged in a Y-shaped inferior vena cava—foramen ovale unit with two different pathways (*Courtesy: Prof Torvid Kiserud*)

- via *dextra* (ventral and rightward stream): 70% of less oxygenated blood enters the right ventricle through tricuspid valve, originating from inferior vena cava.

The DV is located in the fetal abdomen, connecting the intra-abdominal ventral portion of umbilical sinus to the left side of the inferior vena cava, and streams caudocranially and ventrodorsally (Kiserud et al, 1991) (Fig. 2). It has a trumpet-like shape with the narrow portion (isthmus) measuring 0.5 mm at mid-gestation to about 2 mm in late-gestation; the outlet width increases from 1.25 to 3 mm and the length of the DV attains 20 mm at term (Kiserud et al, 1991, 1994a, 1998, 2000a; Mavrides et al, 2002) (Fig. 3).

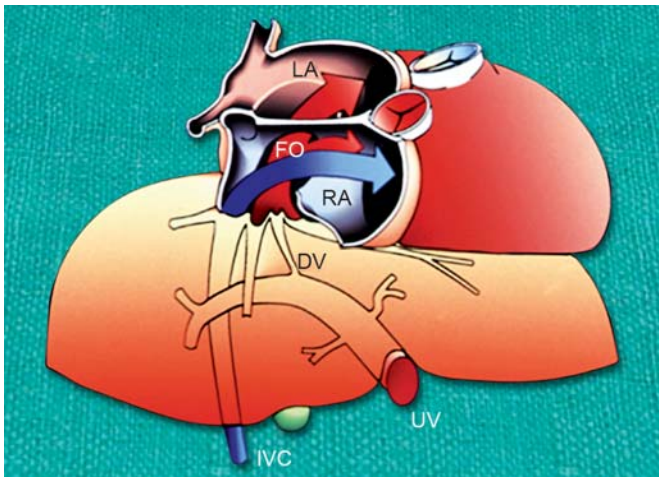

Fig. 2: Ductus venosus occupies a central position in the fetal circulation. Diagram representing venous return in the fetus (*Courtesy: Prof Torvid Kiserud*)

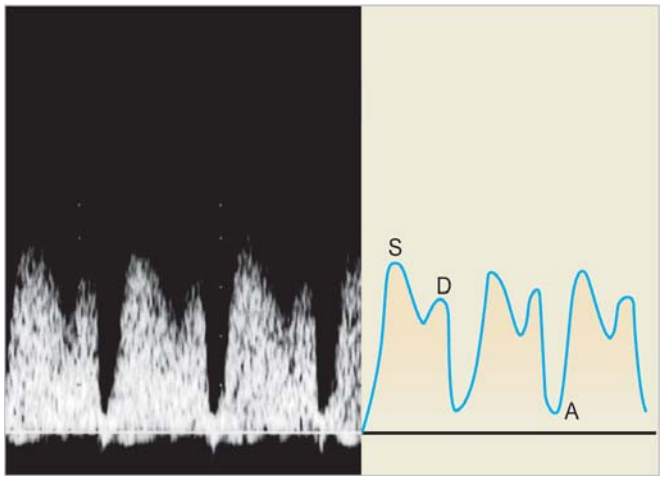

Fig. 4: Schematic representation of a typical waveform obtained by pulsed Doppler in the ductus venosus. S-wave: Ventricular systole; D-wave: Early distole; A-wave: Atrial contraction

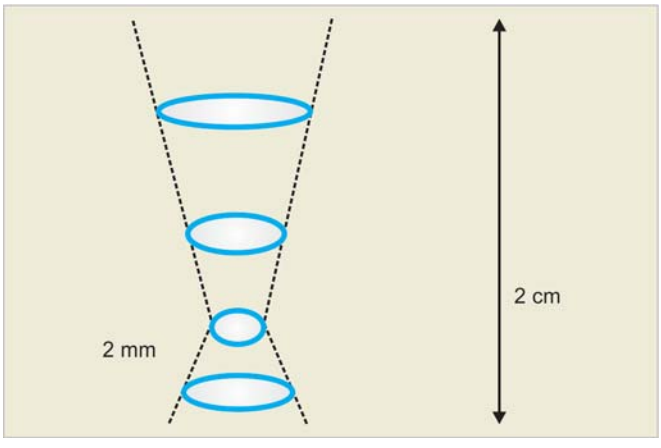

Fig. 3: Schematic representation of the architecture and dimensions of ductus venosus (*Adapted from Mavrides et al, 2002*)

Due to this architectural arrangement (sphincter-like), a pressure gradient is produced between the umbilical vein and the atrium, resulting in the acceleration of the blood flow in the DV and producing a triphasic high-velocity waveform (Kiserud et al, 1994). Still the existence of this "sphincter" remains controversial: some studies have shown the presence of smooth muscle fibers at the inlet of the DV (Chacko et al, 1953; Ehinger et al, 1968); others have interpreted these smooth muscle fibers as part of the muscular arrangement of the umbilical and portal veins (Lind, 1977; Meyer et al, 1966). More recently, Mavrides et al (2002) have shown the lack of an anatomical sphincter at the inlet that she described as narrow and rich in elastin. However, the presence of a single longitudinal layer of smooth muscle cells along the entire DV actively regulates the changes in diameter along the entire length of the vessel (Kiserud et al, 2000b). These fibers are sensitive to changes in oxygen saturation and viscosity of the blood, with a 60% increase of the inlet diameter and distension of the entire vessel in response to hypoxemia (Kiserud et al, 2000b).

Blood produces a very characteristic waveform through the DV when assessed by pulsed Doppler. An anterograde triphasic waveform is produced with a S-wave (ventricular systole), a D-wave (early diastole) and a A-wave (late diastole) (Fig. 4). This latter wave presents the lowest velocity but always with forward flow (Kiserud et al, 1991). The peak velocity attained in the A–wave is about 3 to 4 times the velocity in the umbilical vein. Unlike the second and third trimester, where the flow during the atrial contraction is always forward in normal pregnancies, one must take in consideration that in the early first trimester the A-wave can be null or reversed even in normal fetuses (Kiserud, 1999, 2003). However, after 11 weeks a reversed A-wave is considered abnormal (Fig. 5). Therefore, an easy qualitative assessment can be performed in routine clinical practice classifying the A-wave as positive, absent or reversed (Matias et al, 1998).

However, in order to quantify blood flow in the DV, several authors have suggested different indexes, such as pulsatility index for veins (PIV) (Hecher et al., 1994), S/D index (Huisman et al, 1992), the ductus venosus index (DVI) defined as (S-a)/S (DeVore et al, 1993) or (S-a)/D (Hecher et al, 1994), and the perfusion index (PFI) defined as Tamx/S (Kiserud et al, 1992a; Kessler et al, 2006).

Strict methodological principles should be adopted in order to obtain a reproducible and clinically relevant waveform. There is obviously a learning curve that implies the performance of 100 scans (Maiz et al, 2008a).The technique indicated for first trimester assessment of DV blood flow which was first described by our group in 1997 (Montenegro et al, 1997), assessing a right parasagittal plane by B-mode and taking care to avoid contamination by neighboring vessels (hepatic veins, inferior vena cava and umbilical vein) (Fig. 6). The identification of the DV is greatly aided by using color Doppler putting the gate directly on the aliasing zone (Fig. 7). Very comprehensive pictures can be obtained by tridimensional reconstruction (Fig. 8) and reviewed in necropsia specimens (Fig. 9). The DV is distinguishable from the UV by a distinctly higher velocity. Even so, reproducibility studies held contradictory results. Mavrides et al (2001) reported a good intraobserver

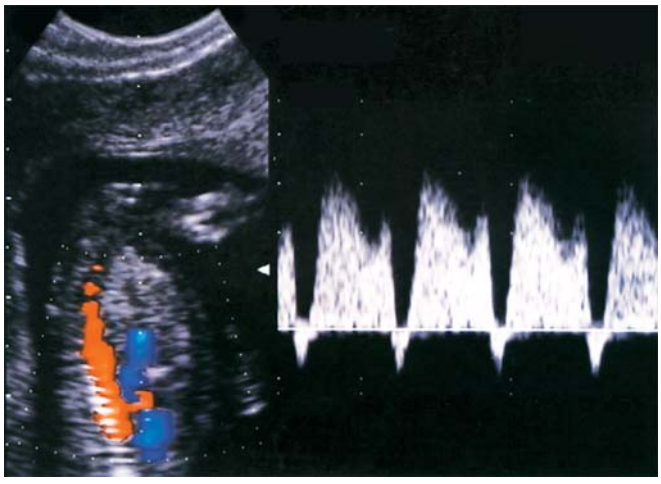

Fig. 5: Example of a reversed A-wave in the DV representing an abnormal waveform after 10 weeks of gestation

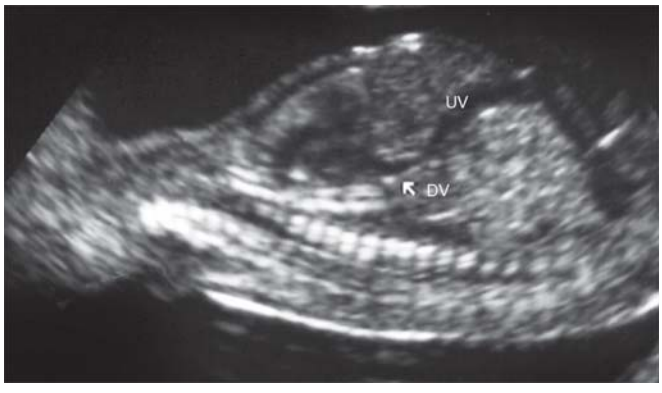

Fig. 6: Mode image of venous return in a fetus of 12 weeks of gestation. UV: Umbilical vein; DV: Ductus venosus

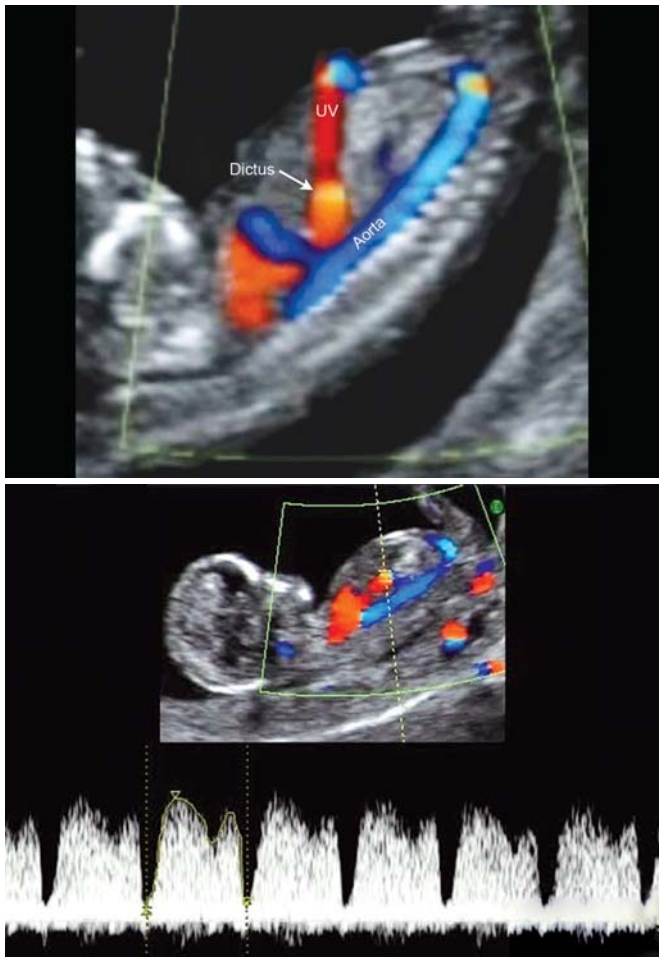

Fig. 7: Color Doppler with aliasing representing the turbulence due to the increased velocity in the inlet of the ductus venosus

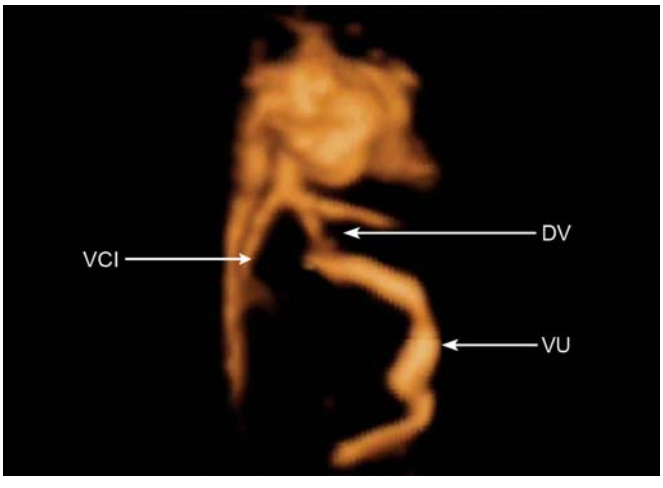

Fig. 8: Tridimensional reconstruction of venous return in a 12 weeks' fetus (*Courtesy: Dr Luiz Diaz Guerrero*)

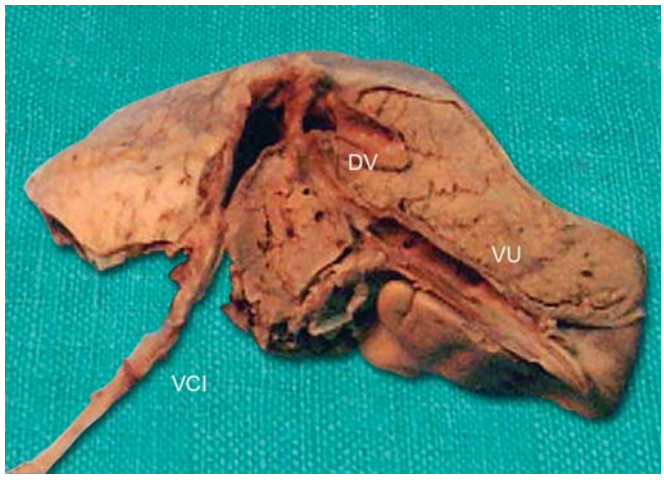

Fig. 9: Necropsia specimen showing the venous return in a fetus after enzymatic digestion (*Courtesy: Dr Luiz Diaz Guerrero*)

repeatability of PIV but poor interobserver reproducibility (Mavrides et al, 2001a) while in previous studies Huisman et al found acceptable reproducibility of DV velocities between 12 and 15 weeks (Huisman et al,1993). In 2007, Borrell et al selected a high-risk population and reported a good intra- and interobserver reliability for PIV but a moderate interobserver reliability for the A-wave (Borrell et al, 2007).

Most adequately, the bioeffects and safety of ultrasound in the first trimester of pregnancy were brought to discussion by Campbell and Platt (1999) with the outburst of Doppler studies early in pregnancy (Campbell and Platt, 1999). Some reassurance was provided by strict guidelines to ensure the ALARA principle. Equipment should display safety indices, such as thermal index (TI) < 1.5 and mechanical index (MI)

< 1.5. Bone should be avoided, maximum exposure time should not exceed 5 minutes with the ultrasonic beam used intermittently with a large Doppler window.

Ductus venosus and its Role in the First Trimester Screening

Ductus venosus behaves like an "arterialized" vessel with a high pulsatile flow and forward velocities throughout the whole cardiac cycle. Therefore, it appears as the most useful vessel in assessing indirectly disturbed cardiac function (Montenegro et al, 1997; Matias et al, 1998, 1999). Quoting Torvid Kiserud in 1993, "the physiological position of the DV in the circulation, and its extraordinary hemodynamic properties and regulatory mechanisms make the tiny DV different from all other venous sections, carrying the potential of unique diagnostic information".

Chromosomal Abnormalities

Each pregnant woman presents a background or a priori risk (which depends on maternal age and gestational age) for chromosomal abnormalities, correctable individually by the combination of ultrasound or biochemical screening tests carried out during the course of the pregnancy.

Considering the trend to delayed childbearing with the consequent increase in the number of pregnant women ≥ 35 years (20-25%), it is not feasible to offer invasive testing to all of them. In fact about half of the affected babies with trisomy 21 would be detected but at the expenses of a greatly increased false-positive rate.

Therefore, maternal age per se proved to be useless and at that time a big step forward was made when nuchal translucency (NT) was introduced in daily practice at 11 to 14 weeks of gestation (Nicolaides et al, 1992) and later combined with PAPP-A and B-HCG (Nicolaides, 2004; Nicolaides et al, 2005).

In order to increase sensitivity (already set at 90%) and specificity, other complimentary tests were being searched. Our pioneering work in 1997 showed that a high proportion of fetuses with trisomy 21 and other chromosomal abnormalities had abnormal flow in the DV at 11 to 13 weeks of gestation (Montenegro et al, 1997). Combining data from nine posterior studies, abnormal blood flow in the DV was observed in 5.2% of euploid fetuses and 70.8, 89.3, 81.8 and 76.9% of fetuses with trisomies 21, 18 and 13 and Turner syndrome respectively (Table 2) (Matias et al, 1998; Murta et al, 2002; Zoppi et al, 2002; Borrell et al, 2003; Toyama et al, 2004; Prefumo et al, 2005, Maiz et al, 2009; Timmerman et al, 2010). Thus, nowadays it is generally accepted that the combined finding of an enlarged NT and abnormal DV flow patterns enhance the likelihood of an abnormal karyotype.

Several papers along these 14 years yielded strong evidence for the satisfactory performance of DV assessment in the 1st trimester of pregnancy: Among 6,653 women tested for DV blood flow between 10 to 13 weeks, the detection rate for aneuploidies was 88% (Comas et al, 2001). Zoppi et al (2002) showed that the probability of having a chromosomal abnormality in a fetus with enlarged NT was greater when an abnormal A-wave in the DV was found. Mavrides et al (2002) reported that an abnormal flow in the DV increased the risk of fetal aneuploidy by about 10 times. The pulsatility index of DV was 1.7× higher in fetuses with trisomy 21 (Borrell et al, 2005). The likelihood ratio for trisomy 21 was 7.05 in the case of abnormal DV and 6.42 for absent nasal bones (Prefumo et al, 2005). The finding of an abnormal A-wave in the DV was observed in 3.2% of euploid fetuses and 66.4% of fetuses with trisomy 21 (Maiz et al, 2009). More recently, in a cohort study, 80% of all chromosomal anomalies were identified by an increased DVPIV and 68% by an abnormal A-wave. The odds of chromosomal anomalies increased by a factor 4.2 per MoM increase in DVPIV (Timmerman et al, 2010).

Further to these populational studies, several case reports strengthen the same findings: Abnormal flow in the DV of a fetus with trisomy 10 (Brizot et al, 2001) or in a fetus with trisomy 18 but with normal NT (Campbell et al, 2001; Martinez-Crespo et al, 2003).

The exact reason for an abnormal A-wave in the DV in association with trisomy 21 is yet not entirely clear. However, it is likely that this abnormality is not a result of a change in the DV itself but rather due to a change in the fetal heart performance. The first trimester fetal heart has special structural and functional conditions that explain this reversal of A-wave only during this temporal window: Fetal myocardium is stiffer and less compliant; A-wave (atrial contraction) is preponderant over E-wave (passive filling) and there is high afterload (increased placental resistance).

Therefore, the mechanical explanation for the A-wave reversal may be that the atrial wall is contracting against a relatively stiffer wall with a consequent increased back pressure that would be sufficient to either stop or reverse the blood flow during atrial systole (absent or reversed A-wave).

Table 1: Methodological guidelines for Doppler assessment of blood flow in the DV (Montenegro et al, 1996)

- Pulsed Doppler
- Color Doppler (helpful)
- Right parasagittal plane
- Magnification: Fetal abdomen and thorax fill the majority of the image
- Pulsed Doppler gate 0.5-1 mm
- Caliper on DV isthmus (aliasing)
- Adjust PRF
- Adjust high-pass filter (50 MHz)
- Avoid contamination
- Set insonation angle below 30° (respect to the longitudinal axis of the DV)
- Obtain regular waves
- Increase sweep speed
- Maximum exposure time (30 seconds)

Table 2: Studies reporting on the incidence of abnormal flow in the DV in the first trimester in euploid fetuses and in those with trisomy 21, 18, 13 and Turner syndrome. Abnormal flow was defined as absent or reverse A-wave or pulsatility index for veins above the 95th percentile (adapted from Maiz and Nicolaides 2010).

Author	*N*	*Normal*	*Trisomy 21*	*Trisomy 18*	*Trisomy 13*	*Turner syndrome*
Matias et al 1998	486	13/423 (3.1%)	35/38 (92.1%)	12/12 (100%)	5/7 (71.4%)	2/3 (66.7%)
Antolin et al 2001	924	39/911 (4.3%)	5/7 (71.4%)	3/3 (100%)	—	1/1 (100%)
Murta et al 2002	372	7/343 (2.0%)	18/18 (100%)	1/1 (100%)	2/2 (100%)	2/2 (100%)
Zoppi et al 2002	325	38/292 (13.0%)	14/20 (70.0%)	6/7 (85.7%)	1/1 (100%)	1/3 (33.3%)
Borrell et al 2003	3,382	162/3,249 (5.0%)	36/48 (75.0%)	—	—	—
Toyama et al 2004	1,097	69/1,075 (6.4%)	5/7 (71.4%)	3/5 (60.0%)	1/1 (100%)	4/4 (100%)
Prefumo et al 2005	572	26/497 (5.2%)	18/47 (38.3%)	—	—	—
Maiz et al 2009	19,800	633/19,614 (3.2%)	81/122 (66.4%)	21/36 (58.3%)	11/20 (55.0%)	6/8 (75.0%)
Timmerman et al 2010	445	128/306 (41.6%)	57/72 (79%)	30/34 (88 %)	4/7 (57%)	6/8 (75%)
Total	27,403	1115/26,710 (4.1%)	269/379 (70.9%)	76/98 (77.5 %)	15/27 (55.5%)	22/29 (75.8%)

Table 3: Studies reporting on the relationship between DV waveforms and major cardiac defects in euploid fetuses with nuchal translucency thickness above the 95th percentile (adapted from Maiz and Nicolaides 2010)

Author	*Total*	*Cardiac defects*	*Abnormal ductus venosus flow*	
			No cardiac defects	*Cardiac defects*
Matias *et al* 1999	142	7 (4.9%)	4/135 (3.0%)	7/7 (100%)
Bilardo *et al* 2001	69	4 (6.8%)	19/65 (29.2%)	4/4 (100%
Murta *et al* 2002	16	1 (6.3%)	0/15 (0.0%)	1/1 (100%)
Zoppi *et al* 2002	115	2 (1.7%)	30/113 (26.5%)	2/2 (100%)
Haak *et al* 2003	22	2 (9.1%)	8/20 (40.0%)	2/2 (100%
Favre *et al* 2003	95	9 (9.5%)	20/86 (23.3%)	9/9 (100%)
Toyama *et al* 2004	141	4 (2.8%)	23/137 (16.8%)	3/4 (75%)
Maiz et al 2008	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%)

Cardiac Defects

Congenital heart defects (CHD) are the most prevalent congenital defects, affecting 20% of spontaneous abortions, 10% of stillbirths and about 1% of term pregnancies (CEMACH report, 2008; EURO-PERISTAT Project, 2008). Moreover, they are responsible for over half the deaths from congenital malformations in childhood. Though a frequent finding, the overall detection rate of major CHD is disappointingly low (Hunter et al, 2000; Carvalho et al, 2002; Tegnander et al, 2006). Routine echocardiography is also not feasible considering this is a time consuming and technically differentiated diagnostic tool. It is common sense that detecting this kind of pathology prenatally allows the effective and timely planning of delivery in a tertiary center (Khoshnood et al, 2005). Therefore, the selection of a 'high-risk' group not only is based on maternal medical and obstetric history but also a family history of congenital heart disease would be dramatically useful.

In an attempt to address this issue, our group proposed in 1999 the evaluation of DV blood flow as one possible screening method for cardiac defects in the first trimester of pregnancy that could improve the role of increased NT in chromosomally normal fetuses (Matias et al, 1999). Combining data from eight studies that examined DV waveforms in chromosomally normal fetuses with increased NT thickness, a major cardiac defect was detected in 96.6% of those with abnormal Doppler waveforms in the DV (Table 3) (Borrell et al, 1998; Bilardo et al, 2001; Murta et al, 2002; Zoppi et al, 2002; Haak et al., 2003; Favre et al, 2003; Toyama et al, 2004, Maiz et al, 2008 in press).

Going into greater detail, Haak et al (2003) found abnormal ductal flow in 80% of the fetuses with increased NT that were chromosomally abnormal but with a normal heart, but in all fetuses with abnormal heart irrespective of the karyotype. In the same year, Favre et al reported that DV blood flow evaluation was as sensitive as NT in the detection of cardiac defects but far more specific (Favre et al, 2003). In a recent paper, Maiz referred that the risk of a cardiac defect is three-fold increased if DV presents an abnormal flow, but is halved if the ductal flow is normal (Maiz et al, 2008). More recently, Martinez et al (2011) scanned a low risk population and found

abnormal flow in 3.5% of the fetuses. Among those fetuses with reversed A-wave and normal karyotype, 11 CHD were diagnosed, yielding a sensitivity of 24.4% and an odds ratio of 9.4. In this study, the use of DV increased early detection of CHD by 11% with respect to the use of NT alone. Therefore, in experienced hands, the authors suggest that abnormal DV in the first trimester can be an independent predictor of CHD and should constitute an indication for early echocardiography (Martinez et al, in press).

Pregnancy Loss

It is well known that the risk of pregnancy loss increases with advanced gestational and maternal age, poor obstetric history, obesity, parity and smoking (Cnattingius et al, 2002. The risk of fetal death, mainly affecting fetuses before 24 weeks, also increases exponentially with the NT thickness (Souka et al, 2001; Michailidis et al, 2001; Goetzl et al, 2004; Dugoff et al, 2004).

Abnormal flow in the DV has also been associated with adverse perinatal outcome and fetal death. Toyama et al found a prevalence of fetal death of 22% in the abnormal DV flow group when compared to 6% in the normal outcome group (Toyama et al, 2004). A case-control study of fetuses with normal NT showed that in 23.8% of cases with abnormal flow in the DV an adverse outcome was recorded, including perinatal death and chromosomal, cardiac or non-cardiac abnormalities (Oh et al, 2007).

Major Fetal Abnormalities

A detailed fetal anatomy examination is part of the 11 to 13 weeks scan (Souka et al, 2004). Increased NT has been associated with a huge number of fetal abnormalities and syndromes (Souka et al, 2006). In the majority of the studies assessing the association of abnormal DV flow and chromosomal abnormalities or cardiac defects there is reference to non-cardiac structural abnormalities (Table 4).

Table 4: Noncardiac structural abnormalities reported in fetuses with abnormal DV flow

Author	*Abnormality*
Matias et al 1999	Chondrodysplasia punctata
Bilardo et al 2001	Multiple congenital abnormalities (Fryns syndrome) Adult polycystic kidney disease
Oh et al 2007	Omphalocele, dolicocephaly, bilateral club feet Omphalocele Multicystic renal dysplasia Unilateral renal agenesis
Ferreira et al 2004	Thanatophoric dysplasia
Machado et al 2010	Diaphragmatic hernia
Carraca et al 2011	Parvovirus infection

Twin-to-Twin Transfusion Syndrome (TTTS)

Monochorionic (MC) twin pregnancies frequency has been increasing in the last 20 years, placing a heavy burden in the twins' perinatal morbidity and mortality rates (Sebire et al, 1997a; Acosta-Rojas et al, 2007). Considering the shared placental territory and the nearly universal presence of intertwin anastomoses, we can understand TTTS as a rather common event that can endanger the course of those pregnancies. We also believe that the sooner the diagnosis of TTTS, the most efficacious the treatment is expected to be. It would be helpful for patients counseling and management if MC pregnancies at high risk for fetal complications could be predicted accurately in early pregnancy.

Therefore, several screening models have been proposed to predict the occurrence of TTTS prior to 18 weeks and anticipate the implicated hemodynamic imbalance as early as the first trimester of pregnancy, such as NT discrepancy (Sebire et al, 1997b, 2000; Kagan et al, 2007; Lewi et al, 2008) or crown-rump length discrepancy (Casabuenas et al, 2007) or intertwin membrane folding (Sebire et al, 1998). However, both sonographic markers have a high false-positive rate and none has provided a meaningful sensitivity with useful clinical application in the screening of TTTS. In fact, increased NT in at least one of the fetuses at 11 to 14 weeks has been associated with a 3.5 fold increased risk of TTTS, although the detection rate was only about 30% with a false-positive rate of 10% (Sebire et al, 2000). Similarly, intertwin discordance in NT thickness was proposed as a screening method to identify pregnancies at a higher risk of TTTS. If the discordance is > 20%, about one third of the pregnancies will eventually develop TTTS or end up in fetal death, while if the discordance is < 20% these occurrences decrease to 10% (Kagan et al, 2007).

Addressing the issue of early fetal hemodynamic compromise, our group provided preliminary evidence that abnormal flow in the DV at 11 to 13+6 weeks of gestation in singletons is associated with increased risk of chromosomal abnormalities (Matias et al, 1998, Murta et al, 2002, Borrell et al, 2003, Prefumo et al, 2005, Maiz et al, 2009) and cardiac defects (Matias et al, 1999, Bilardo et al, 2001, Maiz et al, 2008a) as a translation of cardiac dysfunction/strain (Montenegro et al, 1997). It would clearly be a major advance if the sequence of events could be anticipated as early as the first trimester of pregnancy based on indirect signs of hemodynamic compromise. Thus, this rationale was applied with promising results to MC twins that eventually developed TTTS (Matias et al, 2000, 2005), considering that monochorionic pregnancies are not related to a higher prevalence of chromosomal abnormalities.

More recently, in a more inclusive study, we showed that discrepant values for NT over 0.6 mm had a sensitivity of 45.5% and a specificity of 86.9%. The presence of at least one abnormal blood flow waveform in the DV translated in a relative risk for developing TTTS of 11.86 (95% CI, 3.05-57.45) with a sensitivity of 72.7% and a specificity of 91.7% (Table 5). The

Table 5: Crude and adjusted relative risks (RR) and confidence intervals (CI 95%) were estimated by generalized regression model with Poisson distribution with log link for difference in NT and CRL, ratio NT and CRL and DV blood flow. (CRL–crown-rump length), nuchal translucency (NT), ductus venosus (DV) (adapted from Matias et al, 2010)

	Crude RR (CI 95%)	*Adjusted RR (CI 95%)*	*Adjusted RR (CI 95%)*
Difference in NT*	1.61 (1.19-2.08)	1.20 (0.84-1.62)	
Difference in CRL*	1.24 (0.71-2.05)	1.07 (0.65-1.67)	
NT ratio*	1.58 (1.16-2.03)		1.20 (0.82-1.63)
CRL ratio*	1.36 (0.81-2.15)		1.07 (0.67-1.60)
At least one abnormal DV	15.5 (4.64-70.14)	11.86 (3.05-57.45)	11.99 (3.12-58.00)

*The variable was standardized

combination of abnormal DV blood flow with discrepant NT > 0.6 mm, yielded a relative risk for the development of TTTS 21 times higher (95% CI, 5.47-98.33) (Matias et al, 2010).

Therefore, both increased nuchal translucency and abnormal flow in the DV in monochorionic twins may translate early manifestations of hemodynamic imbalance between donor and recipient. In these pregnancies, in addition to NT measurement at 11 to 14 weeks, the Doppler assessment of DV blood flow increases relevantly the performance of screening for those at risk of developing twin-to-twin transfusion syndrome.

CONCLUSION

Over the past 40 years, the use of ultrasound has been clearly established as an indispensable tool in obstetric management. The improvement in the quality of the ultrasound equipment and the more profound knowledge of fetal physiology moved the time of screening and diagnosis to an earlier point in pregnancy. The increased performance of ultrasonographic and biochemical markers improved the sensitivity and decreased the false-positive rates as well as the invasive testing rate, improving the capabilities of the first trimester scan.

The large contribution of DV flow assessment in the improvement of the performance of screening for chromosomal abnormalities is now well-established in more than 25,000 cases. It also proved useful in the early screening of cardiac defects, identifying a subgroup of higher risk with indication for a specialized echocardiography. Performing successfully in the prediction of twin-to-twin transfusion syndrome in monochorionic twin pregnancies, it helps to modify the intensity of fetal surveillance in those fetuses more prone to develop the syndrome. This story of 14 years surely contributed to change the way first trimester screening is being implemented.

REFERENCES

1. Acosta-Rojas R, Becker J, Munoz-Abellana B, Ruiz C, Carreras E, Gratacos E. Catalunya and Balears Monochorionic Network. Twin chorionicity and the risk of adverse perinatal outcome. Int J Gynaecol Obstet 2007;96(2):98-102.
2. Allan LD, Crawford DC, Chita SK, Anderson RH, Tynan MJ. Familial recurrence of congenital heart disease in a prospective series of mothers referred for fetal echocardiography. Am J Cardiol 1986;58:334-37.
3. Bellotti M, Pennati G, De Gasperi C, Battaglia FC, Ferrazzi E. Role of ductus venosus in distribution of umbilical flow in human fetuses during second half of pregnancy. Am J Physiol 2000;279:H1256-63.
4. Borrell A, Antolin E, Costa D, Farre MT, Martinez JM, Fortuny A. Abnormal ductus venosus blood flow in trisomy 21 fetuses during early pregnancy. Am J Obstet Gynecol 1998; 179:1612-17.
5. Borrell A, Gonce A, Martinez JM, Borobio V, Fortuny A, Coll O, Cuckle H. First-trimester screening for Down syndrome with ductus venosus Doppler studies in addition to nuchal translucency and serum markers. Prenat Diagn 2005;25: 901-05.
6. Borrell A, Martinez JM, Seres A, Borobio V, Cararach V, Fortuny A. Ductus venosus assessment at the time of nuchal translucency measurement in the detection of fetal aneuploidy. Prenat Diagn 2003;23:921-26.
7. Borrell A, Perez M, Figueras F, Meler E, Gonce A, Gratacos E. Reliability analysis on ductus venosus assessment at 11-14 weeks' gestation in a high-risk population. Prenat Diagn 2007;27:442-46.
8. Carraca T, Matias A, Brandão O, Montenegro N. Early signs of cardiac failure: A clue for Parvovirus infection screening in first trimester. Feb 16 2011 [Epub ahead of print].
9. Casabuenas A, Wong AE, Sepulveda W. Nuchal translucency thickness in monochorionic multiple pregnancies: Value in predicting pregnancy outcome. J Ultrasound Med 2008; 27(3):363-69.
10. CEMACH report. Perinatal mortality 2008.
11. Chacko AW, Reynolds SRM. Embryonic development in the human of the sphincter of the ductus venosus. Anat Rec 1953;115:151-73.
12. Campbell S, Platt L. The publishing of papers on first-trimester Doppler. Ultrasound Obstet Gynecol 1999;14:159-60.
13. Edelstone DI, Rudolph AM, Heymann MA. Liver and ductus venosus blood flow in fetal lambs in utero. Circ Res 1978;42:426-33.
14. Ehinger B, Gennser G, Owman C, Persson H, Sjoberg NO. Histochemical and pharmacological studies on amine mechanisms in the umbilical cord, umbilical vein and ductus venosus of the human fetus. Acta Physiol Scand 1968;72:15-24.
15. EURO-PERISTAT Project, with SCPE, EUROCAT, EURONEOSTAT. Data from 2004. European Perinatal Health Report 2008. www.europeristat.com.
16. Favre R, Cherif Y, Kohler M, Kohler A, Hunsinger MC, Bouffet N, Tanghe M, Cancellier M, Nisand I. The role of fetal

nuchal translucency and ductus venosus Doppler at 11-14 weeks of gestation in the detection of major congenital heart defects. Ultrasound Obstet Gynecol 2003;21:239-43.
17. Ferreira A, Matias A, Brandão O, Montenegro N. Nuchal translucency and ductus venosus blood flow as early sonographic markers of thanatophoric dysplasia: A case report. Fetal Diagn Ther 2004;19(3):241-45.
18. Fick AL, Feldstein VA, Norton ME, Wassel Fyr C, Caughey AB, Machin GA. Unequal placental sharing and birth weight discordance in monochorionic diamniotic twins. Am J Obstet Gynecol 2006;195:178-83.
19. Fries MH, Goldstein RB, Kilpatrick SJ, Golbus MS, Callen PW, Filly RA. The role of velamentous cord insertion in the etiology of twin-twin transfusion syndrome. Obstet Gynecol 1993;81:569-74.
20. Haak MC, Twisk JW, Bartelings MM, Gittenberger-de Groot AC, van Vugt JM. Ductus venosus flow velocities in relation to the cardiac defects in first-trimester fetuses with enlarged nuchal translucency. Am J Obstet Gynecol 2003;188:727-33.
21. Hecher K. Assessment of ductus venosus flow during the first and early second trimesters: What can we expect? Ultrasound Obstet Gynecol 2001a;17:285-87.
22. Huisman TWA, Stewart PA, Wladimiroff JW. Ductus venosus blood flow velocity waveforms in the human fetus. Ultrasound Med Biol 1992;18:33-37.
23. Kagan KO, Gazzoni A, Sepulveda-Gonzalez G, Sotiriadis A, Nicolaides KH. Discordance in nuchal translucency thickness in the prediction of severe twin-to-twin transfusion syndrome. Ultrasound Obstet Gynecol 2007;29:527-32.
24. Kessler J, Rasmussen S, Hanson M, Kiserud T. Longitudinal reference ranges for ductus venosus flow velocities and waveform indices. Ultrasound Obstet Gynecol 2006;28:890-98.
25. Kiserud T, Eik-Nes SH, Blaas HG, Hellevik LR. Ultrasonographic velocimetry of the fetal ductus venosus. Lancet 1991;338:1412-14.
26. Kiserud T, Eik-Nes SH, Hellevik LR, Blaas HG. Ductus venosus: A longitudinal Doppler velocimetric study of the human fetus. J Matern Fetal Invest 1992;2:5-11.
27. Kiserud T, Hellevik LR, Eik-Nes SH, Angelsen BAJ, Blaas HG. Estimation of the pressure gradient across the fetal ductus venosus based on Doppler velocimetry. Ultrasound Med Biol 1994A;20:225-32.
28. Kiserud T, Acharya G. The fetal circulation. Prenat Diagn 2004;24:1049-59.
29. Kiserud T, Eik-Nes SH, Blaas HG, Hellevik LR, Simensen B. Ductus venosus blood velocity and the umbilical circulation in the seriously growth-retarded fetus. Ultrasound Obstet Gynecol 1994b;4:109-14.
30. Kiserud T, Stratford L, Hanson MA. Umbilical flow distribution to the liver and the ductus venosus: An in vitro investigation of the fluid dynamic mechanisms in the fetal sheep. Am J Obstet Gynecol 1997;177:86-90.
31. Kiserud T. Hemodynamics of the ductus venosus. Eur J Obstet Gynecol Reprod Biol 1999;84:139-47.
32. Kiserud T, Rasmussen S, Skulstad SM. Blood flow and degree of shunting through the ductus venosus in the human fetus. Am J Obstet Gynecol 2000a;182:147-53.
33. Kiserud T, Ozaki T, Nishina H, Rodeck C, Hanson MA. Effect of NO, phenylephrine and hypoxemia on the ductus venosus diameter in the fetal sheep. Am J Physiol 2000b;279:H1166-71.
34. Lewi L, Lewi P, Diemert A, Jani J, Gucciardo L, Van Mieghem T, Doné E, Gratacós E, Huber A, Hecher K, Deprest J. The role of ultrasound examination in the first trimester and at 16 weeks' gestation to predict fetal complications in monochorionic diamniotic twin pregnancies. Am J Obstet Gynecol 2008;199(5):493.e1-7.
35. Lind J. Human fetal and neonatal circulation. Eur J Cardiol 1977;5:265-81.
36. Machado AP, Ramalho C, Portugal R, Brandão O, Carvalho B, Carvalho F, Matias A, Montenegro N. Concordance for bilateral congenital diaphragmatic hernia in a monozygotic dichorionic twin pair: First clinical report. Fetal Diagn Ther 2010;27(2): 106-09.
37. Maiz N, Kagan KO, Milovanovic Z, Celik E, Nicolaides KH. Learning curve for Doppler assessment of ductus venosus flow at 11 + 0 to 13 + 6 weeks' gestation. Ultrasound Obstet Gynecol 2008a;31:503-06.
38. Maiz N, Plasencia W, Dagklis T, Faros E, Nicolaides K. Ductus venosus Doppler in fetuses with cardiac defects and increased nuchal translucency thickness. Ultrasound Obstet Gynecol 2008b;31:256-60.
39. Maiz N, Valencia C, Emmanuel EE, Staboulidou I, Nicolaides KH. Screening for adverse pregnancy outcome by ductus venosus Doppler at 11-13 + 6 weeks of gestation. Obstet Gynecol 2008c;112:598-605.
40. Maiz N, Valencia C, Kagan KO, Wright D, Nicolaides KH. Ductus venosus Doppler in screening for trisomies 21, 18 and 13 and Turner syndrome at 11-13 weeks of gestation. Ultrasound Obstet Gynecol 2009a;33:512-17.
41. Maiz N, Staboulidou I, Leal AM, Minekawa R, Nicolaides KH. Ductus venosus Doppler at 11 to 13 weeks of gestation in the prediction of outcome in twin pregnancies. Obstet Gynecol 2009b;113:860-65.
42. Maiz N, Nicolaides KH. Ductus venosus in the first trimester: Contribution to screening of chromosomal, cardiac defects and monochorionic twin complications. Fetal Diagn Ther 2010;28:65-71.
43. Martinez J, Comas M, Borrell A, Benansar M, Gómez O, Puerto B, Gratacós E. Abnormal first trimester ductus venosus: A marker of cardiac defects in fetuses with normal karyotype and nuchal translucency. Ultrasound Obstet Gynecol 2011 (in press).
44. Martínez JM, Bermúdez C, Becerra C, López J, Morales WJ, Quintero RA. The role of Doppler studies in predicting individual intrauterine fetal demise after laser therapy for twin-twin transfusion syndrome. Ultrasound Obstet Gynecol 2003;22: 246-51.
45. Martínez JM, Comas M, Borrell A, Bennasar M, Gómez O, Puerto B, Gratacós E. Abnormal first-trimester ductus venosus blood flow: A marker of cardiac defects in fetuses with normal karyotype and nuchal translucency. Ultrasound Obstet Gynecol 2010;35(3):267-72.
46. Matias A, Gomes C, Flack N, Montenegro N, Nicolaides KH. Screening for chromosomal abnormalities at 10-14 weeks: The role of ductus venosus blood flow. Ultrasound Obstet Gynecol 1998;12:380-84.
47. Matias A, Huggon I, Areias JC, Montenegro N, Nicolaides KH. Cardiac defects in chromosomally normal fetuses with abnormal ductus venosus blood flow at 10-14 weeks. Ultrasound Obstet Gynecol 1999;14:307-10.
48. Matias A, Montenegro N, Areias JC. Anticipating twin-twin transfusion syndrome in monochorionic twin pregnancy. Is there a role for nuchal translucency and ductus venosus blood flow evaluation at 11-14 weeks? Twin Res 2000;3:65-70.
49. Matias A, Montenegro N, Loureiro T, Cunha M, Duarte S, Freitas D, et al. Screening for twin-twin transfusion syndrome at 11-14 weeks of pregnancy: The key role of ductus venosus blood flow assessment. Ultrasound Obstet Gynecol 2010;35: 142-48.

50. Mavrides E, Holden D, Bland JM, Tekay A, Thilaganathan B. Intraobserver and interobserver variability of transabdominal Doppler velocimetry measurements of the fetal ductus venosus between 10 and 14 weeks of gestation. Ultrasound Obstet Gynecol 2001;17:306-10.
51. Mavrides E, Moscoso G, Carvalho JS, Campbell S, Thilaganathan B. The human ductus venosus between 13 and 17 weeks of gestation: Histological and morphometric studies. Ultrasound Obstet Gynecol 2002;19:39-46.
52. Montenegro N, Matias A, Areias JC, Castedo S, Barros H. Increased fetal nuchal translucency: Possible involvement of early cardiac failure. Ultrasound Obstet Gynecol 1997;10: 265-68.
53. Murta CG, Moron AF, Avila MA, Weiner CP. Application of ductus venosus Doppler velocimetry for the detection of fetal aneuploidy in the first trimester of pregnancy. Fetal Diagn Ther 2002;17:308-14.
54. Nicolaides KH. Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. Am J Obstet Gynecol 2004;191:45-67.
55. Oh C, Harman C, Baschat AA. Abnormal first-trimester ductus venosus blood flow: A risk factor for adverse outcome in fetuses with normal nuchal translucency. Ultrasound Obstet Gynecol 2007;30:192-96.
56. Prefumo F, De Biasio P, Venturini PL. Reproducibility of ductus venosus Doppler flow measurements at 11-14 weeks of gestation. Ultrasound Obstet Gynecol 2001;17:301-05.
57. Prefumo F, Risso D, Venturini PL, De Biasio P. Reference values for ductus venosus Doppler flow measurements at 10-14 weeks of gestation. Ultrasound Obstet Gynecol 2002;20:42-46.
58. Prefumo F, Sethna F, Sairam S, Bhide A, Thilaganathan B. First-trimester ductus venosus, nasal bones and Down syndrome in a high-risk population. Obstet Gynecol 2005;105:1348-54.
59. Sebire NJ, Snijders RJ, Hughes K, Sepulveda W, Nicolaides KH. The hidden mortality of monochorionic twin pregnancies. Br J Obstet Gynaecol 1997a;104:1203-07.
60. Sebire NJ, D'Ercole C, Hughes K, Carvalho M, Nicolaides KH. Increased nuchal translucency thickness at 10-14 weeks of gestation as a predictor of severe twin-to-twin transfusion syndrome. Ultrasound Obstet Gynecol 1997b;10:86-89.
61. Sebire NJ, D'Ercole C, Carvalho M, Sepulveda W, Nicolaides KH. Inter twin membrane folding in monochorionic pregnancies. Ultrasound Obstet Gynecol 1998;11:324-27.
62. Sebire NJ, Souka A, Skentou H, Geerts L, Nicolaides KH. Early prediction of severe twin-to-twin transfusion syndrome. Hum Reprod 2000;15:2008-10.
63. Sebire NJ, Talbert D, Fisk NM. Twin-to-twin transfusion syndrome results from dynamic asymmetrical reduction in placental anastomoses: A hypothesis. Placenta 2001;22:383-91.
64. Souka AP, Pilalis A, Kavalakis Y, Kosmas Y, Antsaklis P, Antsaklis A. Assessment of fetal anatomy at the 11-14 weeks ultrasound examination. Ultrasound Obstet Gynecol 2004;24:730-34.
65. Souka AP, Pilalis A, Kavalakis I, Antsaklis P, Papantoniou N, Mesogitis S, Antsaklis A. Screening for major structural abnormalities at the 11- to 14-week ultrasound scan. Am J Obstet Gynecol 2006;194:393-96.
66. Tegnander E, Eik-Nes SH, Johansen OJ, Linker DT. Prenatal detection of heart defects at the routine fetal examination at 18 weeks in a non-selected population. Ultrasound Obstet Gynecol 1995;5:372-80.
67. Tegnander E, Williams W, Johansen OJ, Blaas HG, Eik-Nes SH. Prenatal detection of heart defects in a non-selected population of 30,149 fetuses: Detection rates and outcome. Ultrasound Obstet Gynecol 2006;27:252-65.
68. Teixeira LS, Leite J, Viegas MJ, Faria MM, Chaves AS, Teixeira RC, Pires MC, Pettersen H. Ductus venosus Doppler velocimetry in the first trimester: A new finding. Ultrasound Obstet Gynecol 2008;31:261-65.
69. Timmerman E, Rengerink KO, Pajkrt E, Opmeer BC, van der Post JA, Bilardo CM. Ductus venosus pulsatility index measurement reduces the false-positive rate in first-trimester screening. Ultrasound Obstet Gynecol 2010;36(6):661-67.
70. Timmerman E, Clur SA, Pajkrt E, Bilardo CM. First-trimester measurement of the ductus venosus pulsatility index and the prediction of congenital heart defects. Ultrasound Obstet Gynecol 2010;36(6):668-75.
71. Toyama JM, Brizot ML, Liao AW, Lopes LM, Nomura RM, Saldanha FA, Zugaib M. Ductus venosus blood flow assessment at 11 to 14 weeks of gestation and fetal outcome. Ultrasound Obstet Gynecol 2004;23:341-45.
72. van Splunder P, Huisman TWA, de Ridder MAJ, Wladimiroff JW. Fetal venous and arterial flow velocity waveforms between eight and twenty weeks of gestation. Pediatr Res 1996;40:158-62.
73. Zoppi MA, Putzolu M, Ibba RM, Floris M, Monni G. First-trimester ductus venosus velocimetry in relation to nuchal translucency thickness and fetal karyotype. Fetal Diagn Ther 2002;17:52-57.