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REVIEW ARTICLE

Improving our Knowledge in Twins: The Role of Ductus Venosus in the First Trimester

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ABSTRACT

Ductus venosus (DV) is a tiny vessel with a central role in fetal circulation both in singletons and multiples. In the present review we detail the contribution of DV evaluation in twin pregnancies in the first trimeter of pregnancy. The higher prevalence of abnormal A-wave in fetuses with abnormal karyotype and/or cardiac defects made DV evaluation a useful marker for the screening of chromosomal abnormalities and fetal cardiac anomalies. In dichorionic (DC) pregnancies, DV blood flow assessment reproduces the role of NT in the screening for aneuploidies, just as in singleton pregnancies. In monochorionic (MC) twin pregnancies, the Doppler assessment of DV blood flow improves the detection of those at higher risk of developing twin-to-twin transfusion syndrome or growth discrepancy later in pregnancy. As for singletons, DV should be systematically evaluated in all first trimester scans for a more performant screening in multiples.

Keywords: Ductus venosus, Doppler, Monochorionic twins, Dichorionic twins, Screening, Twin-to-twin transfusion syndrome.

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THE TWINNING PROCESS MATTERS IN TWINS

An 'epidemic' of multiple pregnancies is being observed in the world, as a consequence of the increase in the reproductive age of pregnant women and the widespread use of ovulation induction and assisted reproduction techniques.[2] Though multiple pregnancies represent only 1 to 2% of the population, they heavily contribute to the perinatal morbidity and mortality. In the particular case of monochorionic (MC) twin pregnancies, the known perinatal morbidity and mortality are even more dramatic[25] (Hack et al 2008).

The first step toward prenatal diagnosis, screening and surveillance of multiple pregnancies is the establishment of chorionicity (around 100% correct chorionicity assignment is possible in the first trimester of pregnancy) (Figs 1 and 2). Zygosity can only be determined by DNA fingerprinting.

Zygosity refers to the type of conception, whereas chorionicity denotes the type of placentation, depending on the time of splitting of the fertilized ova. Eventually, it is chorionicity rather than zygosity that will determine several aspects of antenatal management and perinatal outcome.

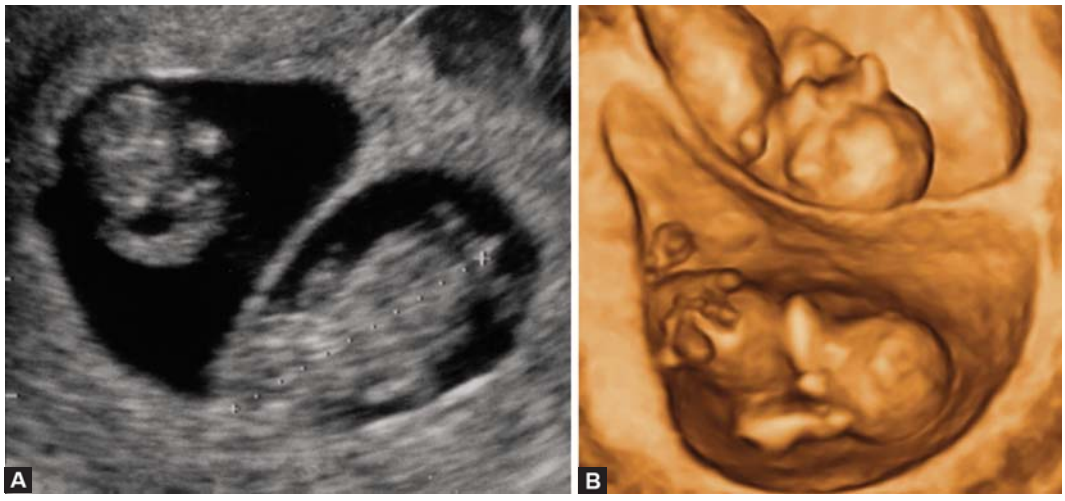
THE FETAL HEART SEEN THROUGH THE DUCTUS VENOSUS

Ductus venosus (DV) has a central role in the fetal hemodynamics both in singletons as in multiples.[9] The blood waveform is highly pulsatile flow with positive velocities throughout the whole cardiac cycle. It directs preferentially well oxigenated blood from the umbilical vein (UV) to the cerebral and coronary circulations, directly through the foramen ovale toward the left atrium. In fact, the venous return is arranged in a a Y-shaped inferior vena cava–foramen ovale unit with two different pathways (Fig. 3):

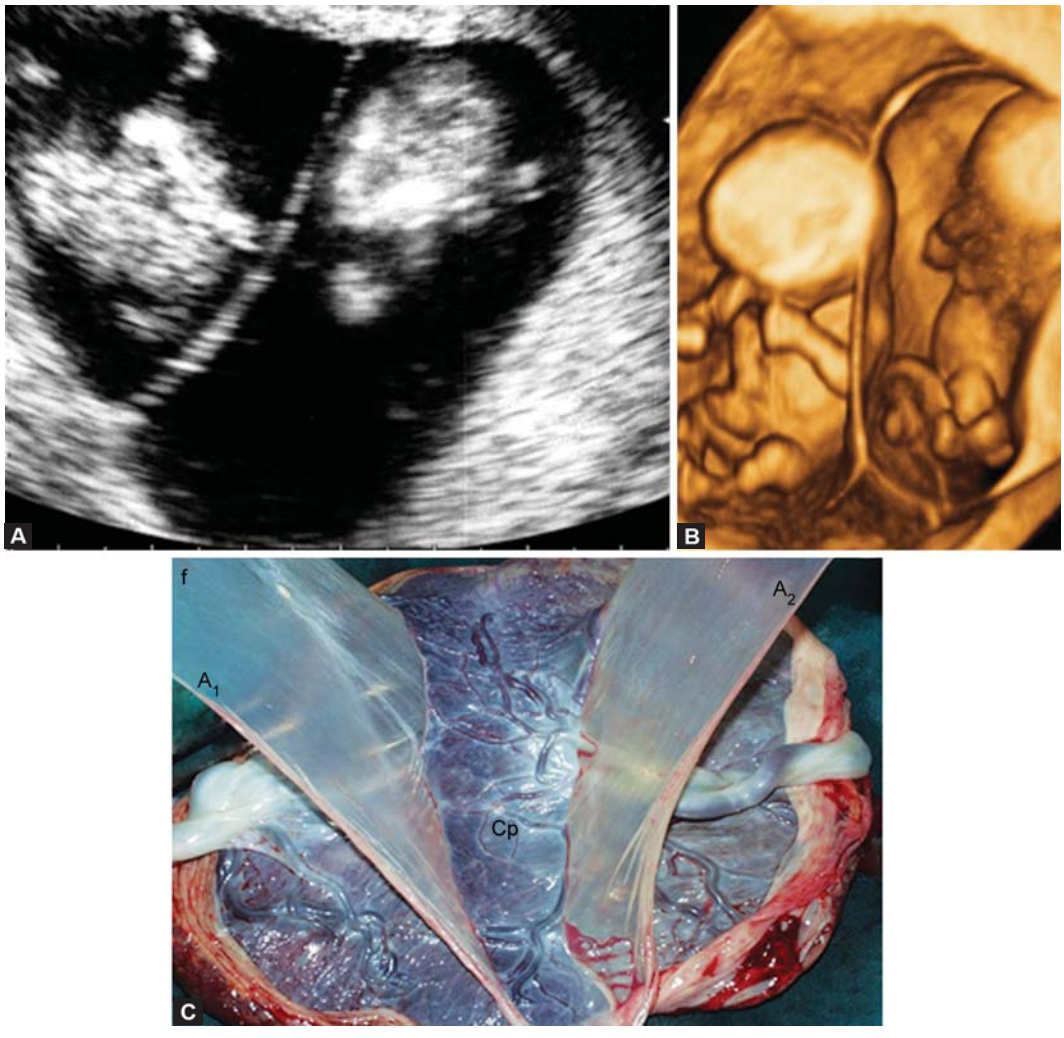
- *Via sinistra* (dorsal and left side stream): 30% (at mid-gestation) and 20% (at term) of umbilical blood is accelerated to the left atrium through the foramen ovale shunted from the DV and left hepatic veins.[9]
- *Via dextra* (ventral and rightward stream): 70% of less oxygenated blood enters the right ventreicle through tricuspid valve, originating from inferior vena cava.

The DV is located in the fetal abdomen (Fig. 3). Due to this architectural arrangement (sphincter-like), a pressure gradient is produced between the UV and the atrium, resulting in the acceleration of the blood flow in the DV and producing a triphasic high velocity waveform with forward flow through the whole cycle. The presence of a single longitudinal layer of smooth muscle cells along the entire DV is 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 hypoxemic situations.[9,10,21]

The typical blood waveform produced by the DV is an triphasic wave with a S-wave (ventricular systole), a D-wave (early diastole) and a A-wave (late diastole). This latter wave presents the lowest velocity but always with forward flow. The peak velocity attained in the S-wave is about 3 to 4 times the velocity in the UV. Unlike the second and third trimesters, in which the flow during the atrial contraction is always forward in normal pregnancies, one must take in consideration that in the early 1st trimester the A-wave can be null or reversed even in normal fetuses.[9] However, after 11 weeks the finding of a reverse A-wave is considered abnormal (Fig. 4). Therefore, a qualitative assessment can be easily performed in routine clinical practice classifying the A-wave as positive, absent or reverse.[16] In order to quantify blood flow in the DV, pulsatility index (PI) is the most commonly used parameter.



Figs 1A and B: (A) Ultrasound image of a Lambda sign in a DC diamniotic twin pregnancy at 12 weeks, (B) 3D image of a DC diamniotic twin pregnancy at 12 weeks



Figs 2A to C: (A) Ultrasound image of a T-sign in an MC diamniotic twin pregnancy at 12 weeks, (B) 3D image of an MC diamniotic twin pregnancy at 12 weeks, (C) placenta of an MC diamniotic twin pregnancy with two layers of amnion without chorion interspersed (*Courtsey*: Dr. Sousa Barros)

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 at least 100 scans.[12] The technique indicated for 1st trimester assessment of DV blood flow was first described by our group in 1997,[22] assessing a right

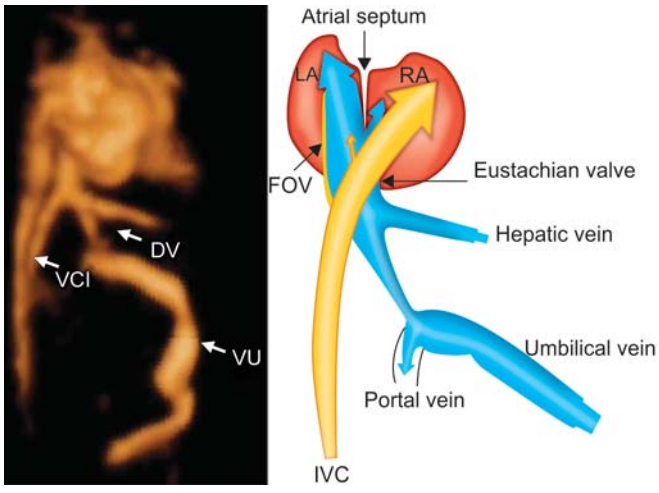


Fig. 3: Tridimensional reconstruction of venous return in a 12 weeks´ fetus (*Courtesy*: Dr Luiz Diaz Guerrero). Venous return is arranged in a a Y-shaped inferior vena cava–foramen ovale unit with two different pathways (*Courtesy*: Prof Torvid Kiserud)

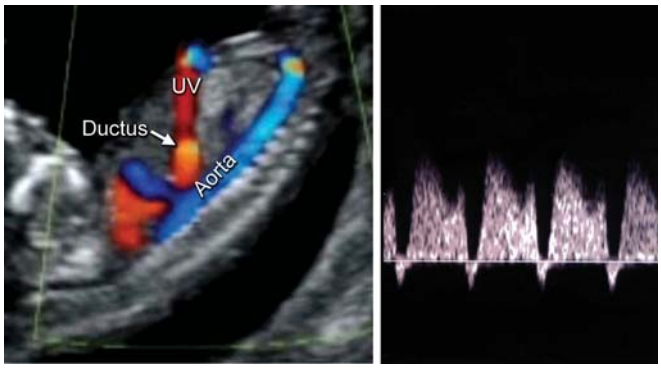


Fig. 4: Color Doppler with aliasing representing the turbulence due to the increased velocity in the inlet of the DV. Example of a reversed A-wave in the DV representing an abnormal waveform after 10 weeks of gestation

parasagittal plane by B-mode and taking care to avoid contamination by neighboring vessels (hepatic veins, inferior vena cava and UV). The identification of the DV is greatly aided by using color Doppler and putting the gate directly on the aliasing zone (area of turbulence) (Fig. 4).

Most adequately the bioeffects and safety of ultrasound in the 1st trimester of pregnancy were brought to discussion by Campbell and Platt (1999) with the outburst of Doppler studies early in pregnancy. 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 10 seconds at a time with the ultrasonic beam used intermittently with a large Doppler window. By the time the first trimester scan is carried out (>12 menstrual weeks), organogenesis is already completed and it has been demonstrated that lower energy outputs can be used without diminishing Doppler diagnostic capabilities.

THE ROLE OF DUCTUS VENOSUS IN THE 1ST TRIMESTER

DV appears to be the most useful vessel in assessing indirectly impaired cardiac function[1,3,8,16,17,22] 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

Down´s syndrome is the most prevalent autosomic chromosomal abnormality in human race (birth prevalence of about 1 in 800) and accounts for almost 50% of all aneuploidies.

The most important factor determining the incidence of trisomy 21 is maternal age. It has been used as a current screening method since it is very cheap, is universally available, has no intra- or interobserver variation, is noninvasive and is understandable by the women screened.

Twenty years have evolved and rules have changed in the screening of trisomy 21 for singleton pregnancies: detection rates have improved and invasive testing rate has decreased. Screening for trisomy 21 at 11 to 14 weeks of gestation is now optimized and combines the sonographic markers NT and nasal bone and the biochemical markers of free β-hCG and PAPP-A, yielding a detection rate of about 95% for a false-positive rate of 2%.

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.[16,22] 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[13,16,29] (Timmerman et al 2010). Thus, combining an enlarged NT and abnormal DV flow increases the likelihood of an abnormal karyotype.

Several papers along these 16 years yielded strong evidence for the satisfactory performance of DV assessment in the screening of aneuploidies in the 1st trimester of pregnancy. 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.[13] 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.[29]

Though first or second trimester screening in twin pregnancies is feasible and still effective, either by using the combination of ultrasound and maternal serum

biochemistry in the first trimester (80% detection rate), or maternal serum biochemistry in the second trimester (50-55% detection rate), its efficacy is decreased in comparison with singletons.[13,23,24]

Screening for chromosomal abnormalities in twin pregnancies arise unique clinical, ethical and moral problems. First, the possibility of deriving a risk for trisomy 21 from sonographic assessment in the first trimester of pregnancy shifted the consideration of a pregnancy-specific risk to a fetus-specific risk.

Second, the overall probability that a multiple gestation contains an aneuploid fetus is directly related to its zygosity. However, counseling based on chorionicity, is clinically more feasible than zygosity. The relative proportion of spontaneous dizygotic to monozygotic is about 2:1 and, therefore, the prevalence of chromosomal abnormalities affecting at least one fetus in a twin pregnancy would be expected to be about 1.6 times that in singletons. If zygosity is unknown the risk of at least one aneuploid fetus can be approximated as five-thirds that of the singleton risk. This is based on the assumption that a third of all twin pairs are monozygotic.[24]

We should take into consideration that unlike all MC pregnancies that are always monozygotic, only about 90% of dichorionic (DC) pregnancies are dizygotic. In dizygotic pregnancies, each fetus has an independent risk of aneuploidy given by sonographic markers, such as NT, NB and DV. Thus, the maternal age-related risk for chromosomal abnormalities for each twin may be the same as in singleton pregnancies, but the chance that at least one fetus is affected by a chromosomal defect is twice as high as in singleton pregnancies. In dizygotic twin pregnancies, the pregnancy-specific risk is calculated by summing the individual risk estimates for each fetus (summing method). The risk that both fetuses would be affected is a much rarer event, corresponding to the singleton risk squared. The 10% of DC twin pregnancies that are monozygotic will incorrectly have their risks calculated by the summing rather than the averaging method. However, the ultimate effect on screening performance will be a negligible one.

In a MC twin pregnancy, both will be affected or both will be unaffected. In monozygotic twins, the risk of an affected fetus approximates the maternal age risk of a singleton pregnancy and the risk for one fetus is, in expectation, the same as the risk for the other. It is therefore appropriate to take the average of the two NT measurements, so that a single risk estimate can be calculated (averaging method). The false-positive rate of NT screening is expectantly higher than in singletons. Nevertheless the calculated detection rates modelled using this method are still 10% lower than in singleton pregnancies.

Cardiac Defects

Combining data from eight studies a major cardiac defect was detected in 96.6% of those fetuses with abnormal Doppler waveforms in the DV and increased NT thickness but normal karyotype.[17] 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, and in all fetuses with abnormal heart irrespective of the karyotype.[6] Maiz et al referred that the risk of a cardiac defect is 3-fold increased if DV presents an abnormal flow, but is halved if the ductal flow is normal.[12] Therefore, in experienced hands, abnormal DV in the first trimester can be an independent predictor of CHD either in singletons and in twins, and should constitute an indication for early echocardiography.[15]

Even in the first trimeter, DV blood flow assessment can be used to profile cardiac function in early twin-to-twin transfusion syndrome (TTTS), disclosing cardiac compromise in both the receptor (congestive heart failure) and the donor (high output cardiac failure), with the decrease in the velocity of the A-wave until null or reverse flow in one or both fetuses.[28]

Pregnancy Loss

Abnormal flow in the DV has also been associated with adverse perinatal outcome and fetal death. A prevalence of fetal death of 22% was found in the abnormal DV flow group when compared to 6% in the normal outcome group. 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 noncardiac abnormalities.

The ominous prognosis that can be associated with abnormal DV waveform in singletons can be similarly found in twins:[13] the prevalence of reversed A-wave in at least one of the fetuses was significantly higher in MC than in DC pregnancies (18.4% compared with 8.3%, $p < 0.001$) and in pregnancies complicated by miscarriage (28.6%, $p = 0.005$). However, we should bear in mind that in about 75% of DC twins and 40% of MC twins with reversed A-wave, the pregnancy outcome is normal.

Major Fetal Abnormalities

In the majority of the studies assessing the association of abnormal DV flow and chromosomal abnormalities or cardiac defects there is reference to noncardiac structural abnormalities (thanatophoric dysplasia, chondrodysplasia punctata, diaphragmatic hernia, parvovirus infection).[4,5] This finding can be confidently translated to twin pregnancies.

Twin-to-Twin Transfusion Syndrome

MC twin pregnancies frequency has been increasing in the last 20 years, with the consequent rise in twins' perinatal morbidity and mortality rates. 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 effective 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 earlier in 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[11,25-27] or crown-rump length discrepancy[11] or intertwin membrane folding. However, both sonographic markers (NT and CRL) 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 increase risk of TTTS although the detection rate was only about 30% with a false-positive rate of 10%.[25,26] Similarly, intertwin discordance in NT thickness was proposed as a screening method to identify pregnancies at a higher risk of TTTS. If the discordance was >20%, about a third of the pregnancies will eventually develop TTTS or end up in fetal death, while if the discordance was <20% TTTS occurrence decreased to 10%.[7]

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[14,16] and cardiac defects[14,17] as a translation of cardiac dysfunction/strain.[22] The underlying mechanism for the association of these conditions with abnormal DV flow is uncertain but it is likely to be the consequence of increased afterload in association with impaired placentation and/or increased preload due to impairment of cardiac diastolic function.[17] 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.

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,[18-20] considering that MC 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 1). The combination of abnormal DV blood flow with discrepant NT > 0.6 mm, yielded a relative risk for the development of TTTS 21 times higher.[19] It may well be that in MC twins with unequal placental sharing abnormal DV flow in the fetus with the smaller placenta may be a manifestation of increased cardiac afterload due to high resistance to flow in the placenta. In contrast, in cases of intertwin transfusion imbalance, abnormal DV flow in the recipient fetus could reflect an increased preload.

Discrepancy Growth in MC Twins

In MC twins there is an added value of DV flow in the prediction of discordance in birth weight later in pregnancy. Matias et al[20] (2011) demonstrated in a prospective study that in 237 MC twin pregnancies the median discordance in birth weight was 8.0%. There was no significant association between discordance in either CRL or NT and discordance in birth weight. However, in pregnancies with abnormal DV flow in at least one of the fetuses, the median discordance in birth weight was higher than in those with normal DV flow in both twins (13.2% *vs* 7.8%). Therefore, in uncomplicated MC twin pregnancies, abnormal DV flow in at least one of the fetuses is associated with a higher discordance in birth weight than in those with normal flow in both fetuses.[20] Again, the performance of this vessel in the screening of discrepancy in growth affecting MC twin pregnancies seems useful for a closer and more effective monitoring of MC twin pregnancies at risk.

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 deeper knowledge of fetal physiology shifted 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 TTTS in MC

twin pregnancies and anticipating discrepancy in growth later in pregnancy, it helps to modify the intensity of fetal surveillance in these fetuses with hemodynamic constraints.

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