Doppler Sonography in Early Pregnancy

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Introduction

Since its introduction to obstetrical practice a few decades ago, Doppler sonography has revolutionized fetal and maternal investigations [1, 2]. Spectral and color Doppler ultrasound provides noninvasively relevant hemodynamic information [3], and its clinical applications have been widespread from high-risk fetal surveillance to fetal echocardiography [4, 5]. It is also useful as an adjunct to fetal ultrasound screening. Although these applications have been mostly limited to the second and third trimesters of pregnancy, Doppler ultrasound of fetal and maternal circulations has also been used during the first trimester. Over the years, various investigators have demonstrated the value and limitations for the first-trimester Doppler sonography for risk assessments in early pregnancy. The most prevalent first-trimester applications include Doppler assessment of the fetal ductus venosus and tricuspid flow, and the maternal uterine artery flow. This chapter reviews these applications, specifically addressing the following:

1. Ductus venosus Doppler during the first trimester and its applications in screening for aneuploidy and congenital heart disease.
2. Tricuspid Doppler flow assessment and its applications in screening for aneuploidy and congenital heart disease.
3. Doppler of the uterine artery in the prediction of subsequent development of preeclampsia.

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Doppler Sonography of the Ductus Venosus

Anatomy and Hemodynamics

The ductus venosus is a venous shunt preferentially streaming oxygenated blood from the placenta, via the umbilical vein, to the fetal heart and brain. Although it has been traditionally depicted as an anatomically contiguous vascular structure with the umbilical vein, more recent autopsy dissections in 14- to 19-week fetuses demonstrated that the umbilical vein ends in the portal sinus, a venous confluence that gives rise to ductus venosus and the right and left portal veins [6] (Fig. 12.1). The ductus venosus is a conical branchless structure with a narrower proximal inlet, called the isthmus, and a wider distal outlet that joins the portal sinus. This configuration increases the velocity of blood flow, propelling it to the foramen ovale and onto the left atrium. Interrelationship between the umbilical vein, ductus venosus and hepatic-portal circulations, in maintaining the perfusion of vital organs, is complex. Under pathological conditions, such as fetal growth restriction, oxygen and nutrient delivery to the heart and brain is maintained by increasing the ductus venosus blood flow, at the cost of perfusion of the liver [7].

Although its presence was recognized since the sixteenth century, the importance of the ductus venosus in fetal circulatory physiology and pathology has been appreciated only very recently, with the advent of Doppler sonography [8]. A detailed discussion of the ductus venosus is beyond the scope of this chapter, but Kiserud has comprehensively reviewed the topic elsewhere [9, 10]. Utilizing two dimensional, color Doppler and pulsed spectral Doppler sonography, Kiserud and colleagues studied longitudinally the ductus venosus flow in normal women from 18 weeks to term, and noted an increase in the mean peak velocity with the progression of gestation. They also reported reversed flow during atrial systole in two cases with fetal cardiac disease. Numerous investigators over the last two decades demonstrated the value of ductus venosus Doppler in understanding circulatory pathophysiology, as well as its prognostic utility in complicated pregnancies, especially with fetal growth restriction [11]. Subsequent studies have reported the potential of ductus venosus Doppler in prenatal risk assessment for aneuploidy and congenital cardiac disease in the first trimester of pregnancy, which is discussed in this review.

Doppler Imaging Technique for the Ductus Venosus

Optimal imaging technique for Doppler interrogation of the ductus venosus has been well described [12, 13]. The ultrasound modalities include two-dimensional, color flow Doppler, and spectral Doppler imaging. The essential guidelines are as follows.

The high-pass filter is set as low as permitted by the device and is usually set at about 50 Hz level. An adequate Doppler frequency range should be selected to accommodate peak velocities without aliasing. The acoustic power output (the mechanical and thermal indices) should be set at a level as low as practically achievable for adequate image quality following the ALARA principle [14]. Anterior sagittal fetal plane is optimal for imaging the ductus (Fig. 12.2). However, posterior sagittal plane may also be helpful. These approaches allow viewing the ductus venosus in a long axis, displaying aliased high velocity color flow at the isthmus and enabling optimal pulsed spectral Doppler interrogation with a minimal insonation angle. In difficult fetal positions, an oblique cross sectional view may be the only choice; however, this will limit imaging at an optimal angle. In early pregnancy, the fetal image should be large enough to include just abdomen and thorax. This minimizes measurement errors related to small size. The sample volume should be adjusted to include only the target vein in order to avoid collecting signals from other veins in proximity, such as the umbilical vein, the hepatic vein or the inferior vena cava. Imaging should be performed only when the fetus is at rest, without body movements, breathing or hiccups.

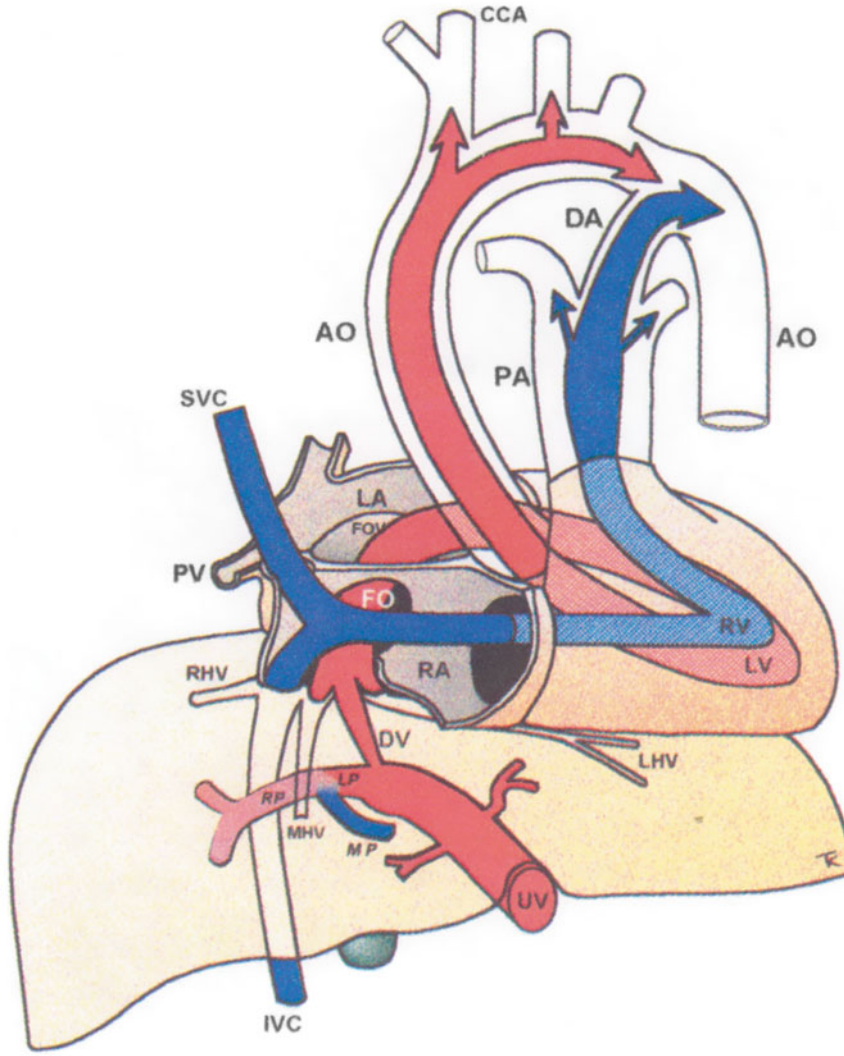

Fig. 12.1 Fetal circulatory pathways showing the three shunts, ductus arteriosus (DA), ductus venosus (DV), and the foramen ovale (FO). The via *sinistra* (*red*) directs blood from the umbilical vein (UV) through the DV and FO to reach the left atrium (LA), left ventricle (LV) and ascending aorta (AO) thus supplying the coronary and cerebral circuit with well oxygenated blood before joining with the via *dextra* (*blue*) in the descending AO. The via dextra receives deoxygenated blood from the abdominal inferior vena cava (IVC) and superior vena cava (SVC) directed to the right atrium (RA), right ventricle (RV), pulmonary trunk (PA) bypassing the pulmonary circuit through the DA. Splanchnic blood from the main portal stem (MP) is provided to the right liver lobe after blending with umbilical blood that reaches the right portal branch (RP) through the left branch (LP). *CCA* common carotid arteries, *FOV* foramen ovale valve, *LHV* left hepatic vein, *MHV* medial hepatic vein, *PV* pulmonary vein. With kind permission from Springer Science+Business Media: Ductus venosus, Kiserud T. In: Doppler ultrasound in obstetrics and gynecology, 2nd ed., Maulik D, Zalud I, editors, 2005

Ductus Venosus Doppler Waveforms

In normal pregnancies, blood flow in the ductus venosus is directed toward the fetal heart. The Doppler waveform is triphasic with two peaks and a trough reflecting the phases of the fetal cardiac cycle (see Fig. 12.2). The first peak is the highest velocity during the ventricular systole and is designated as the S wave. The second peak, termed the D wave, is the highest velocity during

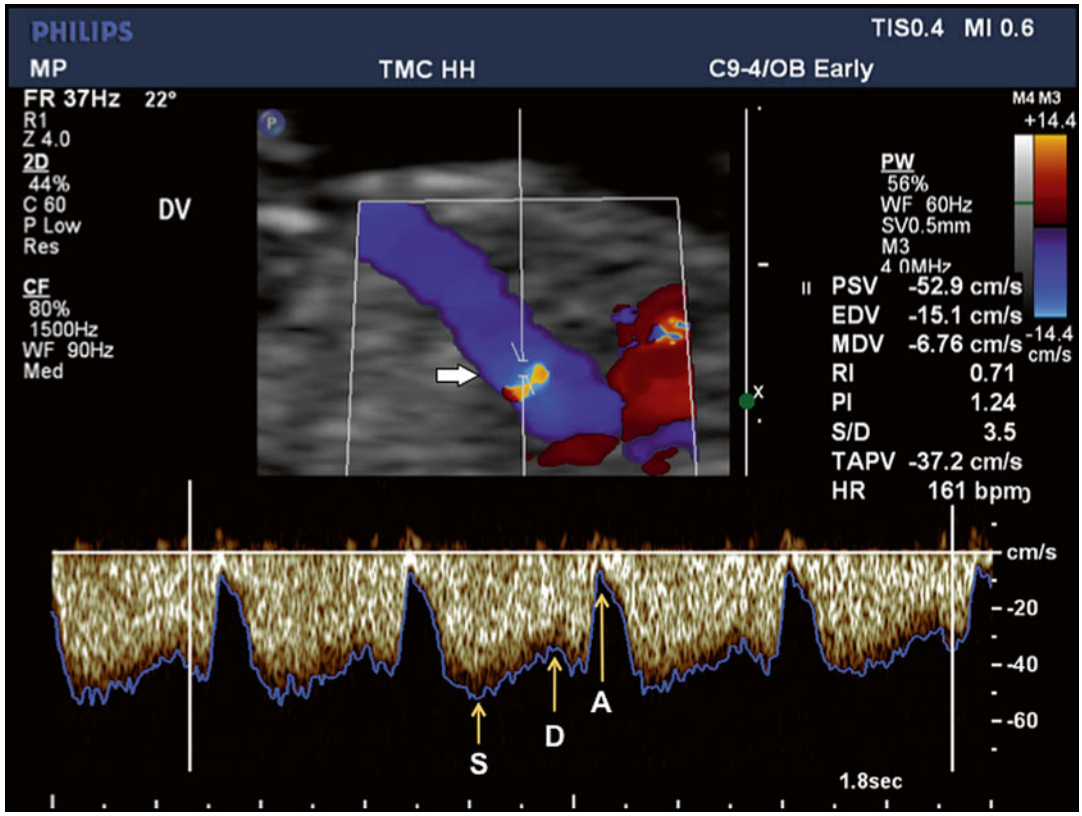

Fig. 12.2 Doppler ultrasound imaging of ductus venosus flow in the sagittal plane at 12 weeks' gestation is depicted in color Doppler and spectral Doppler modes. The *upper panel* shows color Doppler flow pattern with aliasing related to high velocity, which guides the placement of the Doppler sample volume (*horizontal arrow*). The flow is away from the transducer as indicated by the color map. The *lower panel* depicts the triphasic spectral waveforms from the ductus. In this display, the *blue line* corresponds to the peak velocity envelope through the cardiac cycle. S, peak systolic velocity; D, peak diastolic velocity; A, lowest peak velocity due to atrial contraction

the ventricular diastole and is lower than the S wave. The trough, called the a-wave, is the lowest velocity of the Doppler waveform corresponding to the minimum velocity during the atrial contraction. The Doppler waveforms from the ductus venosus can be analyzed in terms of the actual velocity values, which require an optimal insonation angle and angle correction. Alternatively, various indices of pulsatility have been described which obviates the need for angle correction. In all these measurements the maximum frequency shift envelope of the waveform is utilized (see Fig. 12.2).

In clinical practice, the most relevant and frequently used attribute is the a-wave, which is related to the atrial contraction. A zero or negative waveform indicates an increased end-diastolic filling pressure in the right heart (Fig. 12.3).

Factors Affecting the Ductus Venosus Waveform

In early pregnancy, the velocity of blood flow in the ductus venosus increases with gestational age. The increase is throughout the fetal cardiac cycle. In a cross-sectional study of 262 normal singleton fetuses between 8 and 20 weeks gestation, van Splunder and associates noted a significant nonlinear rise in S, D and time-averaged

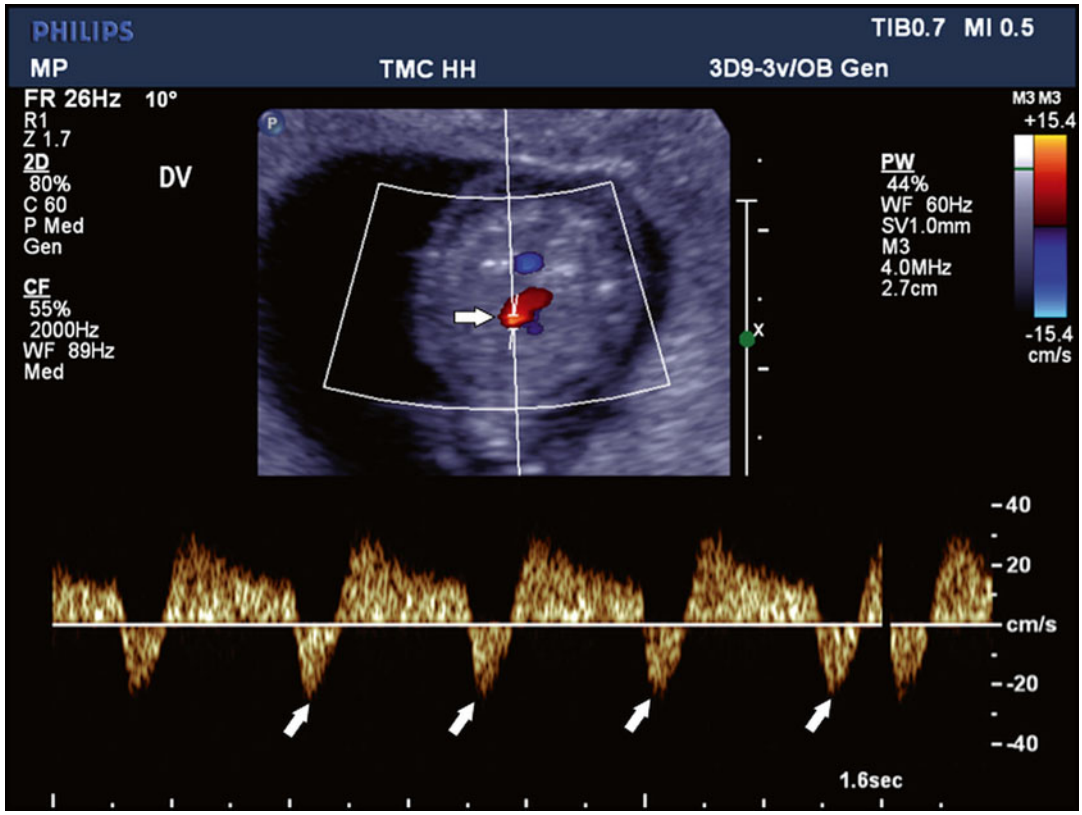

Fig. 12.3 Reversal of flow in the ductus venosus is depicted in color Doppler directed spectral Doppler display. The *upper panel*, in the oblique axial plane, shows the color Doppler flow in the ductus and the *lower panel* the spectral display. The oblique *arrows* indicate reversal of flow. The *horizontal arrow* shows the placement of the Doppler sample volume

peak velocity (Vta) but a significant decline in the pulsatility index for veins (PIV) [15]. The Vta increased almost fourfold. Prefumo and colleagues measured the ductus venosus velocity parameters between 10 and 14 weeks in 201 normal fetuses in a cross-sectional study [16]. During this period, the mean S wave increased from 27 to 33.6 cm/s, the mean a-wave from 5.9 to 7.8 cm/s, and the time-averaged peak velocity from 19.4 to 25.3 cm/s. These increases level off beyond the first half of pregnancy. The reference ranges for the ductus venosus Doppler velocity components from this study are depicted in Figs. 12.4, 12.5, 12.6, and 12.7.

Fetal breathing movements produce intrathoracic pressure fluctuations, leading to changes in the venous pressure dynamics. Breathing induced pressure gradients of up to 22 mmHg across the ductus venosus have been estimated in fetuses during 18–40 weeks of pregnancy utilizing the Bernoulli equation [17]. This is the rationale for not assessing the ductus venosus Doppler hemodynamics during fetal breathing. Breathing movements in early gestation are not regular and become more frequent as the fetus approaches mid-gestation [18]. There is a dearth of information regarding the quantitative effects of breathing movements on precordial venous dynamic in early pregnancy. Fetal movements will also affect the Doppler shift.

Fetal heart rate affects ductus venosus Doppler waveform. Bradycardia allows an increased venous return and atrial filling, leading to an enhanced atrial contraction and, consequently, an enhanced a-wave. In a sheep model, Gudmundsson and coworkers noted changes in

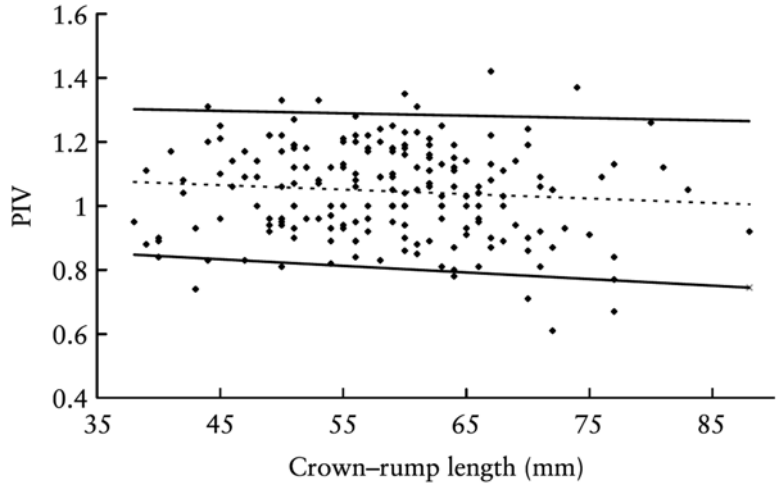

Fig. 12.4 Ductus venosus pulsatility index for veins (PIV) measurements according to crown-rump length in 198 fetuses presented with 5th, 50th, and 95th centiles. The equation for the 50th centile is $y = -0.0014x + 1.1279$ and for the standard deviation is $SD = 0.0004x + 0.1233$. Reprinted from Prefumo 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(1):42–6, with permission from John Wiley & Sons

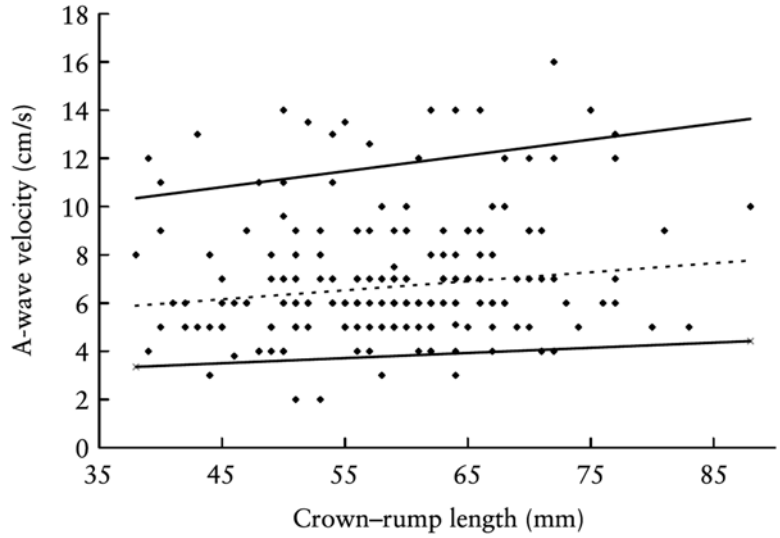

Fig. 12.5 Ductus venosus S-wave velocity measurements according to crown-rump length in 198 fetuses presented with 5th, 50th, and 95th centiles. The equation for the 50th centile is $y = 0.1304x + 22.083$ and for the standard deviation is $SD = 0.0448x + 4.862$. Reprinted from Prefumo F, Risso D, Venturini PL, De Biasio P. Reference values for ductus venosus Doppler flow measurements at 10–14 weeks of gestation. Ultrasound Obstet Gynecol. 2002;20(1):42–6, with permission from John Wiley & Sons

ductus venosus velocity waveform directly related to fetal bradycardia consequent to fetal hypoxemia, [19]. Any increase in the fetal myocardial compliance will lead to changes in the ductal waveform. Thus, hypoxia, acidosis or intra-thoracic lesions such as pleural effusion pressing on the heart lower cardiac compliance, leading to augmented a-waves [9, 13]. Blood viscosity also modifies venous Doppler waveforms, which is seen in fetal anemia. Lam and co-investigators reported significant increases in S, a-wave and Vta in nonhydropic fetuses between 12 and 13 weeks with homozygous alpha thalassemia-1 [20]. This was attributed to lower blood viscosity in anemia and also to hypoxia.

Ductus Venosus Doppler in First-Trimester Aneuploidy Screen

The most frequent and important utilization of ductus venosus Doppler in the first trimester of pregnancy is for aneuploidy screening. Various investigators have demonstrated its efficacy, with

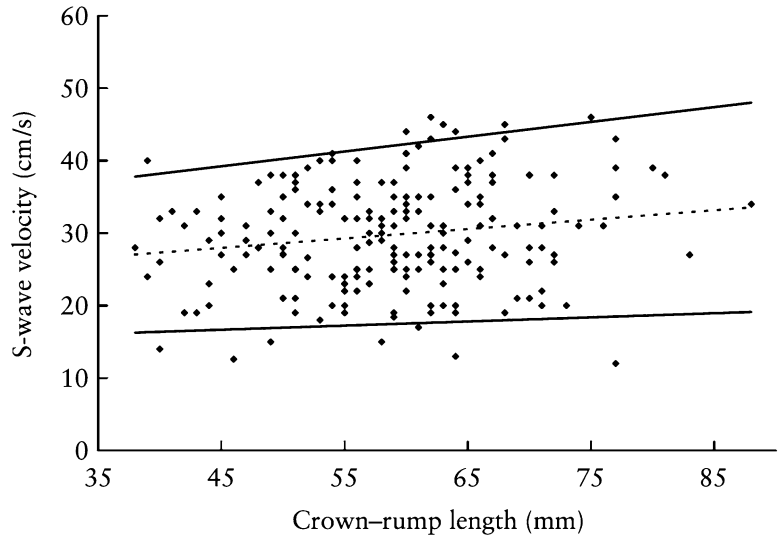

Fig. 12.6 Ductus venosus A-wave velocity measurements according to crown-rump length in 198 fetuses presented with 5th, 50th, and 95th centiles. Log_{10} transformation was performed for data analysis; data are displayed after antilog transformation. The equation for the 50th centile is $y = 10^{0.0024x+0.679}$ and the standard deviation is $SD = 10^{0.1492}$. Reprinted from 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(1):42–6, with permission from John Wiley & Sons

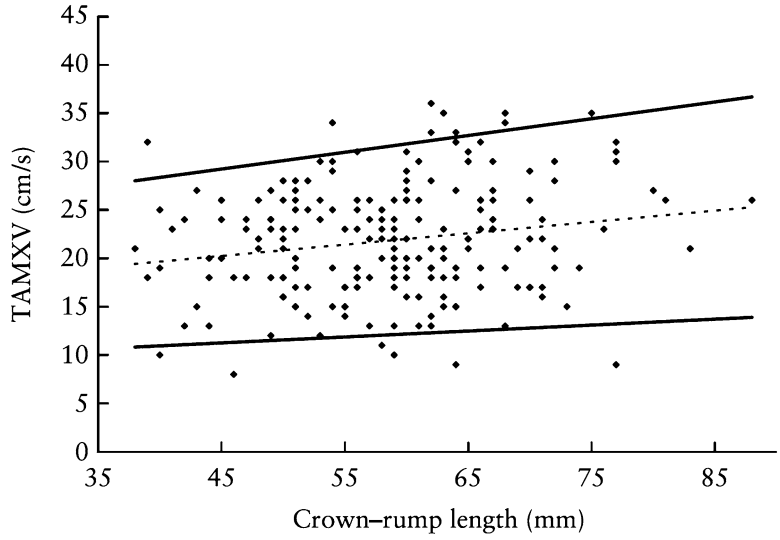

Fig. 12.7 Ductus venosus time-averaged maximum velocity (TAMXV) measurements according to crown-rump length in 198 fetuses presented with 5th, 50th and 95th centiles. The equation for the 50th centile is $y = 0.1174x + 14.95$ and for the standard deviation is $SD = 0.0342x + 3.9375$. Reprinted from Prefumo 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(1):42–6, with permission from John Wiley & Sons

or without the nuchal translucency and various biomarkers. Selected reports are discussed below and summarized in Table 12.1 [21–30].

Borrell and colleagues reported Doppler velocimetry of the ductus venosus, prior to performing invasive diagnostic procedures for trisomy 21, in

Table 12.1 Reported abnormal ductus venosus doppler in fetal aneuploidy in the first trimester of pregnancy

First author (reference)	Date	Total patients	Euploid cases	Aneuploid cases	Abnormal DVD aneuploid cases (%)	Abnormal DVD in euploid fetuses (%)
Matias [22]	1998	486	423	63	90.5	3.07
Antolin [23]	2001	924	911	13	77.0	4.28
Murta [24]	2002	372	343	29	89.7	2.04
Zoppi [25]	2002	325	292	33	69.7	13.0
Borrell [26][a]	2003	3382	3289	93	64.5	4.93
Toyama [27]	2004	1097	1075	22	68.2	6.42
Prefumo [28]	2005	572	497	47[b]	[c]	5.23
Maiz [29]	2009	19,800	19,614	186	64.0	3.17
Florjański [30]	2013	1526	1480	46	63.0	7.43
Totals		28,484	27,924	532	69.9	3.89

DVD ductus venosus Doppler
[a]Forty cases were defined as euploid cases due to being either placental mosaicism or a balanced translocation
[b]Only trisomy 21 cases
[c]Data not reported given that not all aneuploid cases in this study had DVD findings reported

534 consecutive fetuses of 10–18 weeks of gestation [21]. Trisomy 21 was present in 11 fetuses, eight of whom had venous pulsatility index >95th centile, and three had the a-wave below 5th centile. Matias and coworkers performed Doppler velocimetry of the ductus venosus, just before fetal karyotyping, in 486 consecutive singleton pregnancies between 10 and 14 weeks [22]. Of the 63 fetuses with chromosomal anomaly, 57 (90.5 %) had reverse or absent a-wave. Abnormal ductus venosus Doppler was also observed, however, in 13 (3.1 %) of the 423 euploid fetuses. Multivariate regression analysis demonstrated that only the abnormal a-wave offered a significant independent discrimination between the euploid and the aneuploid cases.

In a cohort of about 20,000 singleton pregnancies, Maiz and colleagues performed a combined first-trimester screening test, comprising maternal age, fetal nuchal translucency thickness, fetal heart rate, serum free beta-human chorionic gonadotropin, pregnancy-associated plasma protein-A (PAPP-A), and the ductus venosus Doppler [29]. The a-wave was reversed in 66–75 % of aneuploid, but in only 3.2 % of euploid fetuses. Universal inclusion of the first-trimester ductus venosus Doppler would detect 96 %, 92 %, 100 % and 100 % of trisomies 21, 18 and 13 and Turner syndrome, respectively, at a false-positive rate of 3 %. Similar detection rates were achieved in a two-step strategy with a false-positive rate of 2.6 %, necessitating ductus venosus Doppler in only 15 % of the total population.

It should be appreciated that most fetuses with abnormal ductus venosus Doppler are euploid and not all fetus with aneuploidy will have abnormal findings. As shown in Table 12.1, which summarizes several studies on first-trimester ductus venosus Doppler, abnormal Doppler findings were present in 70 % of aneuploid fetuses, but only in 4 % of the euploid fetuses (see Table 12.1).

Obviously, prenatal noninvasive risk assessment for chromosomal abnormalities during early gestation involves multiple modalities, such as the sonographic assessment of nuchal translucency and measurement of multiple analytes. The efficacy of incorporating the ductus venosus Doppler in these algorithms is further discussed later.

Ductus Venosus Doppler Screening for Congenital Heart Disease

Ductus venosus Doppler waveforms reflect fetal central hemodynamics, especially that of the right heart. Functional and anatomical abnormalities are expected to alter this waveform. This prompted many to explore its screening potential for the early detection of fetal cardiac disease.

Matias and coworkers performed Doppler velocimetry of the ductus venosus in 200 singleton fetuses with increased nuchal translucency, at 10–14 weeks' gestation, immediately before fetal karyotyping [22]. The results suggested that in euploid fetuses with increased nuchal translucency, the presence of abnormal ductus venosus blood flow recognized those with major cardiac defects.

In a study involving over 41,000 euploid fetuses, reversal of ductus venosus a-wave was observed in about 28 % of the fetuses with cardiac anomalies and in about 2 % of the fetuses with no cardiac anomalies [31]. The authors estimated that comprehensive fetal echocardiography would detect approximately 39 % of major cardiac defects, at an overall false-positive rate of about 3 %, in cases with nuchal translucency above the 99th centile and those with reversed a-wave, independent of the nuchal translucency measurement.

This has been further confirmed, more recently, by Borrell and associates who studied the efficacy of various first-trimester ultrasound screening strategies for the recognition of major cardiac malformations, in euploid fetuses [32]. The sonographic methods included fetal nuchal translucency and Doppler indices of the ductus venosus. If the ultrasound findings were abnormal, early echocardiography was recommended. Verification of the fetal cardiac status was performed by fetal echocardiography in mid- and late gestation, neonatal assessment or autopsy. Of the 37 euploid fetuses with a major cardiac malformation, the nuchal translucency was above the 99th centile in 27 % cases and the ductus venosus a-wave was absent or reversed in 39 % of the fetuses. The authors noted a 47 % detection rate of major heart defects, with a false positive rate of about 3 %.

These and other investigations suggest a role for ductus venosus Doppler to identify early those fetuses at a higher risk of CHD. Early fetal echocardiography can be challenging and may not obviate the need for comprehensive ultrasound examination at mid-pregnancy. However, Zidere and associates recently demonstrated that, in expert hands, it could achieve a high degree of accuracy [33]. Future research should further address the effectiveness of early fetal echocardiography in clinical practice.

Doppler Investigation of Tricuspid Flow in the First Trimester

Over the recent years, there has been a progressively wider use of Doppler echocardiography for assessing fetal cardiac function in early pregnancy. Of the various aspects of fetal cardiac function, the tricuspid flow patterns have received the most attention, especially regarding its association with congenital cardiac malformations and aneuploidy.

Doppler Insonation Technique

The Doppler echocardiographic modalities used for assessing tricuspid flow include two-dimensional image of the fetal heart, which directs spectral Doppler interrogation. It is beyond the scope of this review to discuss the technique in detail. The principles are essentially the same as in later gestation [5]; however, Huggon and associates have addressed the specific technical issues related to first-trimester application [34]. Briefly, an apical or a basal four chamber view is preferred, as it allows aligning the Doppler beam with the atrioventricular flow direction, with a minimal angle of insonation, which should be kept below 30°. As described earlier with the ductus venosus Doppler, the high pass filter should be set to the lowest level allowed by the device, and the power output should be kept as low as possible. Color Doppler flow will show reversed flow related to the regurgitation and color M-mode has the advantage of providing more accurate temporal resolution. However, color modes are seldom used for the first-trimester screening, because of their inconsistency in depicting intracardiac flow in early gestation. In common practice, spectral Doppler interrogation is guided by two-dimensional B mode imaging, which assists in placing the Doppler sample volume across the tricuspid valves.

Tricuspid Flow Pattern

Spectral Doppler insonation of the atrioventricular flow reveals a biphasic flow pattern, reflecting the contributions of ventricular relaxation and atrial contractions to the Doppler flow velocity waveforms (Fig. 12.8). The first peak, called the E wave, represents the peak flow velocity due to the atrial systole. The second peak, A wave, is the peak flow velocity caused by the ventricular diastole. In the right heart, the A wave is substantially greater than the E wave, whereas in the left heart the waves are less discrepant. This observation suggests a physiologically lower compliance of the right ventricle compared to the left. Neonates and infants demonstrate a similar pattern.

Tricuspid Regurgitation

Normal atrioventricular flow is unidirectional, from the atrium to the ventricle. Reversal of this pattern indicates tricuspid incompetence, with the flow regurgitating from the right ventricle to the right atrium (Fig. 12.9). In the fetus, however, this finding is not always pathological. Utilizing color Doppler, Maulik et al. noted mild tricuspid regurgitation in normal fetuses in mid-pregnancy [35]. Others have extensively demonstrated this.

For example, utilizing color Doppler and color M-mode, Gembruch et al. demonstrated a 6 % prevalence of tricuspid regurgitation in a cross-sectional study of 289 normal singleton fetuses [36]. Makikallio and associates utilized Doppler

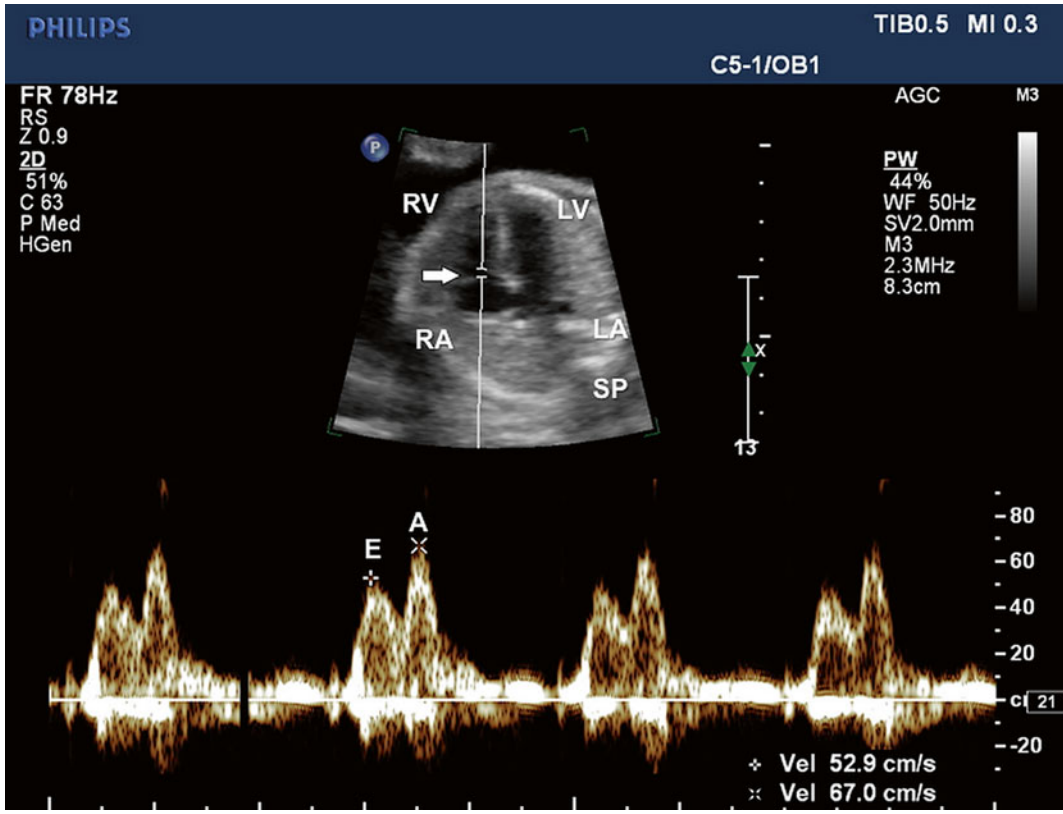

Fig. 12.8 Doppler imaging of the tricuspid flow in the first trimester of pregnancy is depicted here. The *upper panel* shows two-dimensional echocardiography of an apical four-chamber view of the fetal heart at 13 weeks' gestation. The *horizontal arrow* indicates the Doppler sampling location. Note the optimal alignment of the ultrasound beam path with the flow direction (*vertical white line*). The Doppler spectral display of the biphasic blood flow velocities across the tricuspid orifice is shown in the *lower panel*. E, peak flow velocity during ventricular diastole; A, peak flow velocity during the atrial systole; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; SP, spine

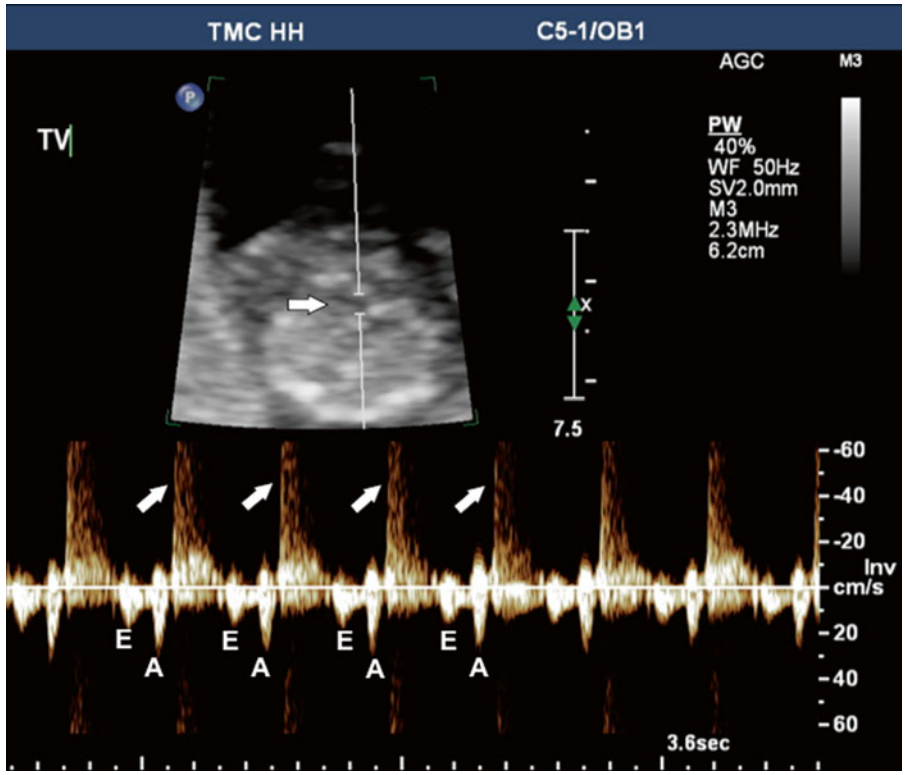

Fig. 12.9 The sonogram illustrates tricuspid regurgitation in a first trimester fetus. The *upper panel* shows placement of the Doppler sample volume. E, peak flow velocity during ventricular diastole; A, peak flow velocity during the atrial systole. The upward oblique *arrows* indicate the high velocity regurgitant flow jets from the right ventricle to the right atrium. Note aliasing of the flow jets due to their high velocity

echocardiography to characterize fetal cardiac function in 16 uncomplicated pregnancies, between 6 and 10 weeks [37]. They noted that the atrioventricular flow was initially monophasic and became biphasic after 9+ weeks. The regurgitant atrioventricular flow was common after 10 weeks. The isovolumetric relaxation time significantly increased from 6 to 7 weeks, indicating progressive maturation of fetal cardiac diastolic function.

Tricuspid Doppler Screening for Aneuploidy and Congenital Heart Disease

Rizzo and colleagues performed Doppler echocardiography to investigate cardiac function in 20- to 23-week euploid fetuses with an elevated nuchal translucency, but without any major malformations, and observed that the ratios between the E-wave and A-wave and the ratios between the E-wave and time velocity integral were significantly decreased at both the mitral and tricuspid valves, suggesting diastolic dysfunction [38]. Lopes and colleagues performed echocardiography in 275 fetuses with elevated nuchal translucency between 12 and 16 weeks' gestation [39]. Subsequent follow up included fetal and neonatal echocardiography, chromosomal analyses, and autopsy. Structural malformations were detected in 37 (14 %) and functional abnormalities in 24 (9 %) fetuses. Of the latter group, 2 (8.3 %) had isolated tricuspid regurgitation and trisomy 21.

Falcon and coworkers comprehensively addressed the role of tricuspid regurgitation in prenatal diagnosis, in 1557 fetuses at 11+0–13+6 weeks' gestation [40]. The authors

successfully performed Doppler assessment of tricuspid flow in 98.8 % cases and observed tricuspid regurgitation in 4.4 % of the euploid fetuses. In contrast, fetuses with trisomy 21 and 18 had a substantially higher occurrence of the regurgitation (67.5 %, 33.3 %, respectively). Moreover, trained sonographers were able to assess reliably tricuspid regurgitation during the first trimester.

Biophysical, Biochemical, and Molecular Screening in Early Pregnancy

With the availability of multiple first-trimester screening tests, including the fetal Doppler and the rapid adoption of cell-free DNA testing, it is immensely important to determine the most effective approach for first-trimester aneuploidy screening. The advent of blood molecular tests may potentially replace personnel-intensive procedures such as nuchal translucency and fetal Doppler measurements. Only a few studies have comprehensively assessed which approach provides the optimal, yet cost-effective, care.

Nicolaides analyzed prospectively collected data to determine the effectiveness of a contingent screening approach for trisomy 21, that combined maternal age, first-trimester biomarkers, and cell-free DNA testing in 93,545 singleton pregnancies [41]. The authors observed that a detection rate of 98 % of fetuses with trisomy 21, with an overall chorionic villous sampling rate <0.5 %, may be accomplished by offering cell-free DNA testing to about 36 %, 21 %, and 11 % of cases identified by first-line screening, using the combined test alone, the combined test with the addition of serum placental growth factor (PlGF) and alpha fetoprotein (AFP), and the combined test with the addition of PIGF, AFP, and ductus venosus Doppler pulsatility index for veins, respectively.

Although cost effective strategies were not specifically analyzed, the authors observed that the existing protocols that include biomarkers, biophysical modalities including venous Doppler, and the use of cell-free DNA in selected cases, would reduce the need for chorionic villous sampling, with a very high detection rate and a very low false positive rate. Although universal cell-free DNA testing would have an even higher detection rate, the cost may substantially increase. Clearly, there are other complex factors that influence the efficacy and economy of the various screening approaches, which requires more focused scrutiny.

Doppler Ultrasound Imaging of the Uterine Artery in the First Trimester

Introduction of Doppler sonography of the uterine artery, a few decades ago, ushered in exciting opportunities to investigate uteroplacental circulation [42]. Its potential was apparent, as this circulation constitutes the maternal supply line to the fetus that is essential for its survival, sustenance and growth. In order to fulfill fetal demand, the uteroplacental circulation undergoes enormous changes that include early transformation of the spiral endometrial arteries, supplying the placental intervillous space, into large conduits of low impedance flow. This is achieved by the invasion of specialized trophoblastic cells that invade and replace the intima and media of these arteries [43]. This process starts in early pregnancy and extends to the myometrial course of these arteries by the middle of second trimester. These changes are reflected in the uterine artery Doppler waveforms. Inadequacy of this remodeling process has been associated with the subsequent development of preeclampsia and fetal growth restriction [44, 45]. This offers a potential for using uterine artery Doppler for the prediction and prognostication of these pregnancy complications. Early investigators used continuous wave Doppler probes but this blind approach was soon replaced by pulsed Doppler interrogation guided by color Doppler imaging [46–48].

Doppler Imaging Technique for the Uterine Artery

Several investigators have described the current methods for Doppler interrogation of the uterine artery and international guidelines exist [13, 49].

In the first trimester, the uterine arteries can be interrogated either transabdominally or transvaginally. In the transabdominal approach, the paracervical site at the level of the internal os is preferred over iliac crossover site as it is easier to obtain. In a prospective longitudinal study of fetuses at 11–13 and 21–22 weeks of gestation, Lefebvre and colleagues successfully obtained adequate Doppler signals from both the uterine arteries in all the cases at the paracervical site at the os level, but only in about 60 % of the cases at the iliac crossover site [50]. Using color Doppler, the uterus and the cervix are imaged in a mid-sagittal plane at the level of the internal os, lateral manipulation of the transducer reveals the ascending branch of the uterine artery, which is sampled to obtain the uterine artery spectral Doppler signals.

In the transvaginal approach, the transducer is placed in the anterior fornix and manipulated laterally. The color Doppler image reveals the uterine artery and pulsed Doppler interrogation is performed. Consistent with the general principles of the Doppler insonation, the angle of insonation should be less than 30°, the frequency range should accommodate the peak velocities without aliasing, the high pass filter should be set at the lowest possible level and the power setting should be minimized consistent with an adequate image quality.

Uterine Artery Doppler Waveform

The uterine artery Doppler waveform in early pregnancy demonstrates a rapid acceleration and deceleration of the flow velocity during systole, followed by an early diastolic deceleration, known as the diastolic notch, and then a slight rise in the late diastole (Fig. 12.10). Factors that

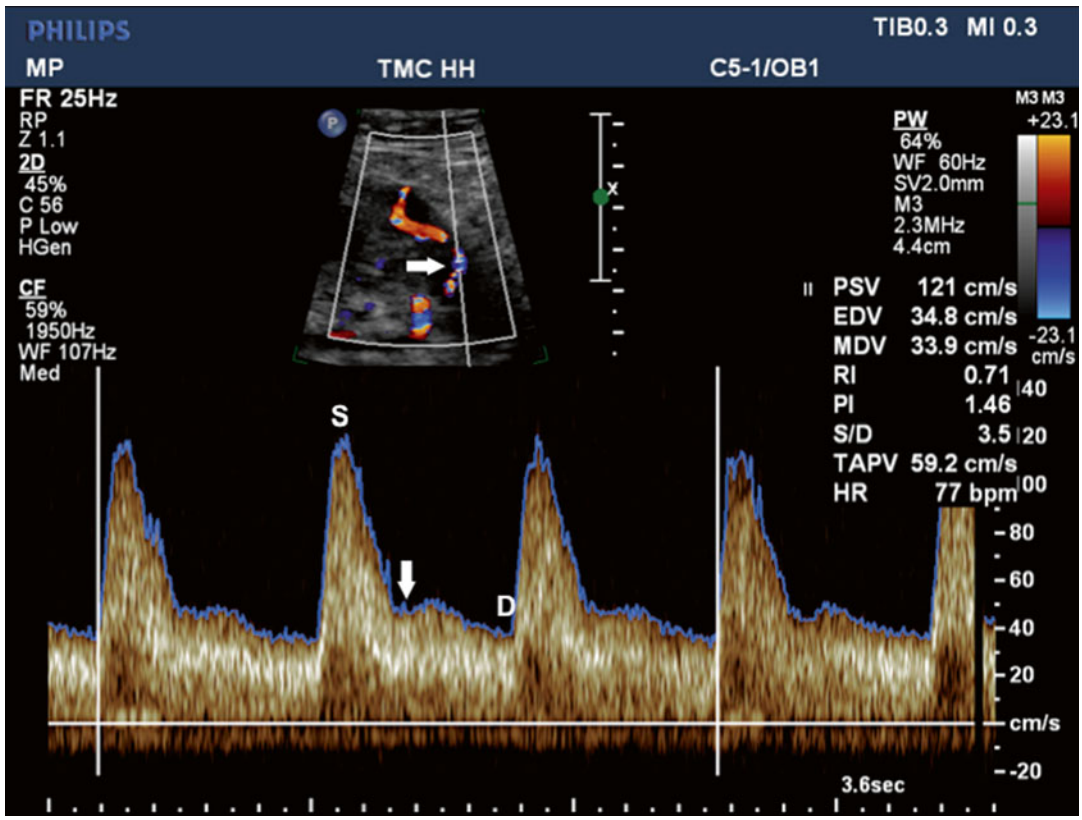

Fig. 12.10 The figure shows uterine artery Doppler waveforms in the first trimester of pregnancy. The *upper panel* shows color Doppler flow in the ascending branch of the uterine artery. The *horizontal arrow* indicates the site of Doppler sampling, The *lower panel* depicts the spectral Doppler waveforms. The *blue margin* of the waveform shows the peak velocity envelope through the maternal cardiac cycle. S, the peak systolic velocity; D, the end diastolic velocity. The *vertical down arrow* indicates the diastolic notch

influence the waveform include gestational age, maternal heart rate, placental location and the location of the measurement in the uterine artery system.

The pulsatility of the waveform declines rapidly between 14 and 16 weeks of pregnancy, then slowly until about 26 weeks, stabilizing thereafter until the end of pregnancy [42]. A more recent study, however, reported a continuous decline until 34 weeks [51]. These changes reflect profound decline in the uteroplacental circulatory impedance during early pregnancy, consequent to the dramatic transformation of the spiral endometrial arteries, with the invasion of the specialized trophoblastic cells.

The effect of maternal heart rate on the diastolic run-off time modifies the waveform and its pulsatility. A higher rate will shorten the diastolic run-off time, leading to a decrease in the pulsatility and vice versa. Uterine artery waveforms from the ipsilateral placental site show a lower pulsatility than those from the contralateral location [52]. Finally, the pulsatility declines as the Doppler sampling site is moved from upstream to downstream, in the uteroplacental arterial system [46]. Thus, Doppler waveforms from the spiral arteries show significantly lower pulsatility than those from the main artery, reflecting progressive decline in the circulatory impedance down the arterial tree.

The pulsatility of the uterine artery waveforms are analyzed utilizing the maximum frequency shift envelope of the Doppler frequency shift (see Fig. 12.10). The standard indices are calculated, including the pulsatility index, resistance index and systolic-diastolic ratio. A high Doppler index is associated with adverse pregnancy outcome, especially development of preeclampsia and/or fetal growth restriction. This is further discussed later. Any transient decelerations, called notches, have been described during the systolic or the diastolic phase [53–55]. Such a notch implies a high impedance in the uterine circulation. Gomez and coworkers noted that bilateral notch declined from about 49 % of the waveforms at 11 weeks to about 14 % at 22 weeks; however its persistence beyond mid-gestation was associated with adverse outcome.

Clinical Applications of the Uterine Artery Doppler

High pulsatility indices and persistent notch in the uterine artery Doppler have been associated with subsequent preeclampsia, fetal growth restriction, and adverse perinatal outcomes [48, 49]. Recent reports have been variably consistent.

In a study involving 3324 consecutive singleton pregnancies, Martin and associates studied the efficacy of uterine artery Doppler, between 11 and 14 weeks of gestation, for the prediction of subsequent development of preeclampsia and fetal growth restriction [56]. Preeclampsia developed in about 2 % and fetal growth restriction in about 10 % of the cases. The sensitivity of a mean pulsatility index > 2.35 was only 12 % for isolated fetal growth restriction and 27.0 % for preeclampsia with or without coexisting fetal growth restriction. However, the sensitivity for these complications requiring delivery before 32 weeks of gestation was 60 % for preeclampsia, and 28 % for fetal growth restriction. Gomez and associates reported that persistence of abnormal Doppler findings, such as bilateral notch and elevated pulsatility index into the second trimester, increased adverse outcomes [51]. The highest risk was related to the persistent abnormal pulsatility index (OR, 10.7; 95 % CI, 3.7–30.9). In a prospective study, however, involving a Scandinavian population, with a prior risk for developing hypertension in pregnancy, Skrastad and colleagues observed only modest efficacy of a first-trimester protocol that combined maternal attributes, mean arterial pressure, uterine artery pulsatility index, PAPP-A, and PIGF [57].

In a systematic review of 74 studies of preeclampsia, with a total population of almost 80,000 patients, Cnossen and associates noted that an elevated uterine pulsatility index with notching carried a positive likelihood ratio of 21 in high-risk and 7.5 in low-risk mothers for developing preeclampsia [58]. For fetal growth restriction, a review of 61 studies, with a population of over 41,000 low risk women, showed a positive likelihood ratio of 14.6 for developing severe growth restriction. Uterine artery Doppler

was more predictive when performed in the second rather than in the first trimester.

Others, however, could not corroborate the predictive efficacy of the first-trimester uterine artery Doppler. Audibert and associated did not observe any further improvement in the predictive efficacy, when the uterine artery Doppler results were combined with biomarkers for the development of preeclampsia [59]. In a prospective cohort study of patients presenting for first-trimester aneuploidy screening between 11 and 14 weeks' gestation, Goetzinger and others observed that, for a fixed false-positive rate of 10 %, A-disintegrin and metalloprotease 12, PAPP-A, and uterine artery Doppler pulsatility index, in combination with maternal attributes, identified 50 %, 48 %, and 52 % of patients who subsequently developed preeclampsia, respectively, and their combination did not enhanced predictive efficiency [60].

There are numerous studies that have addressed the efficacy of early pregnancy uterine artery Doppler for predicting pregnancy complications. In a meta-analysis, involving 18 studies and 55,974 women, Velauthar and associates investigated the efficacy of abnormal uterine artery Doppler for predicting preeclampsia and fetal growth restriction [61]. For the early onset preeclampsia, the sensitivity and specificity were 47.8 % (95 % confidence interval: 39.0–56.8) and 92.1 % (95 % CI: 88.6–94.6), and for early-onset fetal growth restriction they were 39.2 % (95 % CI: 26.3–53.8) and 93.1 % (95 % CI: 90.6–95.0), respectively. For any preeclampsia and fetal growth restriction, the sensitivities were 26.4 % (95 % CI: 22.5–30.8) and 15.4 % (95 % CI:12.4–18.9), respectively, and the specificities were 93.4 % (95 % CI: 90.4–95.5 %) and 93.3 % (95 % CI: 90.9–95.1), respectively. The numbers of women with abnormal Doppler needed to treat with aspirin to prevent one case of early-onset preeclampsia were 173 and 421 for background risks varying between 1 % and 0.4 %, respectively. The authors recommended the use of aspirin in low-risk pregnancies with abnormal uterine artery Dopplers for preventing certain pregnancy complications.

Any such recommendation, however, must be based on the evidence of effectiveness of early pregnancy aspirin prophylaxis. There have been several randomized clinical trials addressing this issue. Yet, none of the studies, had sufficient power. In a meta-analysis of 42 randomized controlled trials of the effectiveness of low-dose aspirin prophylaxis involving 27,222 women, Roberge and associates noted a significant reduction in adverse perinatal outcome, when the prophylactic therapy was initiated at or before 16 weeks of gestation [62]. The selection criteria for therapy included clinical risk factors such as nulliparity and chromic hypertension, as well as abnormal uterine artery Doppler. Initiation of aspirin at or before 16 weeks gestation, as opposed to after 16 weeks, was associated with a 53 % decrease in preeclampsia and an 82 % decrease in severe preeclampsia. Moreover, statistically significant declines in perinatal mortality, fetal growth restriction and preterm births were also observed. This study provides the evidence-based justification for the initiation of low-dose aspirin before 16 weeks in women at risk for preeclampsia or other related adverse outcomes.

Of note, there were no differences in the outcomes, regardless of whether the patients were selected on the basis of risk assessment or abnormal uterine artery Doppler. Obviously, this intriguing finding does not fully establish the role of Doppler assessment, if indeed this simpler, less technology-intensive and low cost approach of risk evaluation is as effective as Doppler. This suggests the need for further investigations with adequate sample size and appropriate study design. The most recent Cochrane review on the uteroplacental Doppler came to a similar conclusion and suggested more research [63].

In summary, uterine artery Doppler in the first trimester of pregnancy has modest to moderate efficacy in identifying women destined to develop preeclampsia. It may also predict other adverse outcomes, including stillbirth, fetal growth restriction and preterm labor. There is evidence of its effectiveness in improving the pregnancy outcome, if low dose aspirin prophylaxis is used before 16 completed weeks of gestation. The intervention is less effective if aspirin is used after 16 weeks' gestation. It is uncertain, however,

whether the addition of the uterine artery Doppler to clinical risk assessment improves the latter's predictive efficacy for implementing early aspirin prophylaxis.

Teaching Points

- First-trimester Doppler of fetal and uterine circulation improves the risk assessment for fetal aneuploidy, congenital heart defects, and subsequent development of preeclampsia.
- Effective use of Doppler sonography in early pregnancy requires appropriate technical training and adhering to the best available evidence.
- First-trimester Doppler of the ductus venosus identifies fetuses at a higher risk of aneuploidy and congenital heart defects.
- The most relevant and frequently utilized attribute of the ductus venosus Doppler is absence or reversal of a-wave.
- Abnormal ductus venosus Doppler is encountered in approximately 70 % of the aneuploid fetuses but only in approximately 4 % of the euploid fetuses.
- The ductus venosus a-wave is absent or reversed in approximately 40 % of the fetuses with major cardiac defects
- First-trimester Doppler assessment of the tricuspid flow enhances the predictive accuracy of early pregnancy aneuploidy screening.
- The presence of tricuspid regurgitation in early pregnancy identifies fetuses at a higher risk of congenital heart defects. It is seen in 67 % of trisomy 21 fetuses but only in 4 % of euploid fetuses.
- The addition of first-trimester fetal ultrasound screening to the biomarkers and selective use of cell-free DNA testing may substantially improve the aneuploidy detection rate and may reduce the need for chorionic villous sampling.
- First-trimester uterine artery Doppler identifies pregnancies at a higher risk of developing preeclampsia and other adverse outcomes.
- Maternal prophylaxis with low-dose aspirin before 16 weeks of gestation reduces subsequent development of preeclampsia.
- It is uncertain whether the addition of the uterine artery Doppler to clinical risk assessment improves the predictive accuracy for implementing early aspirin prophylaxis.

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