Doppler Sonography in Early Pregnancy

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Introduction

Doppler sonography was introduced into obstetrical practice in the 1980s and has revolutionized fetal and maternal investigations [1, 2]. Spectral and color Doppler ultrasound provide noninvasively hemodynamic information [3] and have broad clinical applications, including high-risk fetal surveillance and fetal echocardiography [4, 5].

Although Doppler ultrasound investigations frequently target the second and third trimesters of pregnancy, first-trimester Doppler insonation of fetal and maternal circulations has also proven beneficial for risk assessment. Current first-trimester applications include Doppler assessment of the fetal ductus venosus, tricuspid valve, and 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 predicting subsequent development of preeclampsia.
4. Doppler of the placental implantation site for early detection of placenta accreta spectrum.

Doppler Sonography of the Ductus Venosus

Anatomy and Hemodynamics

The ductus venosus is a venous shunt that preferentially streams oxygenated blood from the placenta, via the umbilical vein, to the fetal heart and brain. Although traditionally depicted as an anatomically contiguous vascular structure with the umbilical vein, more recent autopsy dissections in 14–19-week fetuses demonstrated that the umbilical vein ends in the portal sinus. The portal sinus is a venous confluence that gives rise to the ductus venosus and the right and left portal veins [6] (Fig. 13.1).

The ductus venosus is a conical branchless structure with a narrow proximal inlet, called the isthmus, and a broad distal outlet that joins the portal sinus. This configuration increases blood flow velocity, propelling it to the foramen ovale and onto the left atrium. There is a com-

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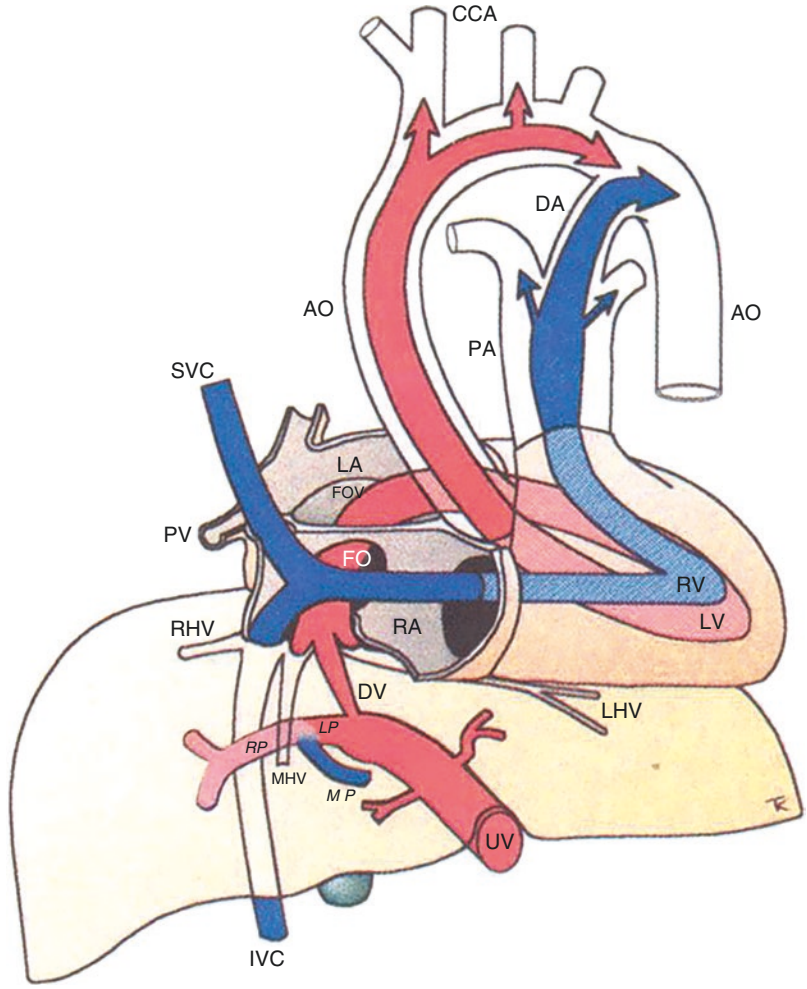

Fig. 13.1 The fetal circulatory pathways show the three shunts: ductus arteriosus (DA), ductus venosus (DV), and the foramen ovale (FO). The via sinistra (red) directs blood from the umbilical vein (UV) through the DV and FO to the left atrium (LA), left ventricle (LV), and ascending aorta (AO), thus 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 directed 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: Kiserud T, Rasmussen S, Skulstad S. Blood flow and the degree of shunting through the ductus venosus in the human fetus. Am J Obstet Gynecol. 2000;182(1 Pt 1):147–53. doi: https://doi.org/10.1016/s0002-9378(00)70504-7. PMID: 10649170)

plex interrelationship between the umbilical vein, ductus venosus, and hepatic-portal circulations that maintain vital organ perfusion. Under pathological conditions, such as fetal growth restriction, oxygen and nutrient delivery to the heart and brain is supported by increasing the ductus venosus blood flow at the cost of perfusion of the liver [7].

The ductus venosus was first identified in the sixteenth century, but Doppler sonography has only recently revealed its importance in fetal circulatory physiology and pathology [8].

Utilizing two-dimensional, color Doppler, and pulsed spectral Doppler sonography, Kiserud and colleagues studied the ductus venosus flow longitudinally in normal pregnancies from 18 weeks to term and noted an increase in the mean peak velocity throughout gestation. They also reported reversed flow during atrial systole in two cases with fetal cardiac disease.

Over the last two decades, numerous investigators demonstrated the value of ductus venosus Doppler in understanding circulatory pathophysiology and its predictive utility in complicated pregnancies, especially with fetal growth restriction [9]. 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, addressed in this review.[1] A detailed discussion of the ductus venosus is beyond the scope of this chapter, but Kiserud has comprehensively reviewed the topic elsewhere [10, 11].

Doppler Imaging Technique for the Ductus Venosus

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

The high-pass filter is set as low as permitted by the device, usually about 50 Hz, and a Doppler frequency range is selected adequate to accommodate peak velocities without aliasing. The acoustic power output (the mechanical and thermal indices) should be as low as feasible to achieve reasonable image quality [13]. The anterior sagittal fetal plane is optimal for imaging the ductus (Fig. 13.2). However, a posterior sagittal plane may also be helpful. These approaches promote viewing the ductus venosus in the 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.

The fetal image should be large enough to include just abdomen and thorax in early pregnancy, which minimizes measurement errors related to small size. The sample volume is adjusted to include only the target vein to avoid collecting signals from other veins in proximity, such as the umbilical vein, the hepatic vein, or the inferior vena cava. The imaging is performed when the fetus is at rest, without body movements, breathing, or hiccups.

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. 13.2). The first peak, the S wave, is the highest velocity during the ventricular systole. The second peak, termed the D wave, is the highest velocity during 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 are analyzed quantitatively or qualitatively.

The quantitative assessment is based on actual velocity values, which require an optimal insonation angle and angle correction. However, various pulsatility indices obviate the need for angle correction. In all measurements, the maximum frequency shift envelope of the waveform is utilized (see Fig. 13.2).

The qualitative assessment constitutes the most relevant and frequently used approach in clinical practice and comprised of the visual assessment of the a-wave, which is related to atrial contraction. A zero or negative waveform indicates an increased end-diastolic filling pressure in the right heart (Fig. 13.3).

[1] See also Chap. 12.

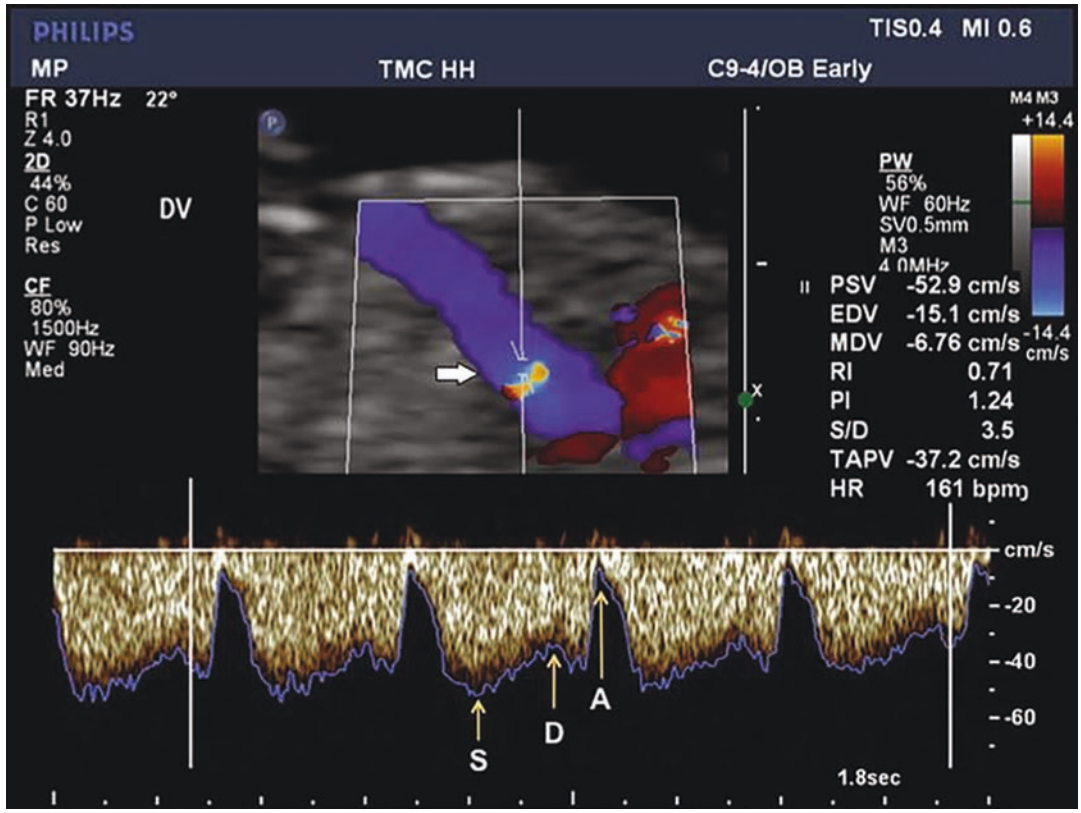

Fig. 13.2 Doppler ultrasound imaging of ductus venosus flow in the sagittal plane at 12 weeks' gestation in color Doppler and spectral Doppler modes. The upper panel shows a color Doppler flow pattern with lighter color area related to high velocity, which guides the placement of the Doppler sample volume (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. S, peak systolic velocity; D, peak diastolic velocity; A, lowest peak velocity due to atrial contraction

Factors Affecting the Ductus Venosus Waveform

In early pregnancy, blood flow velocity in the ductus venosus increases with gestational age, and the increase is present 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 peak velocity (Vta) but a significant decline in the pulsatility index for veins (PIV) [14]. 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 [15]. 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 this study's ductus venosus Doppler velocity components are depicted in Figs. 13.4, 13.5, 13.6, and 13.7.

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 [16], which is the rationale for not assessing the ductus venosus Doppler

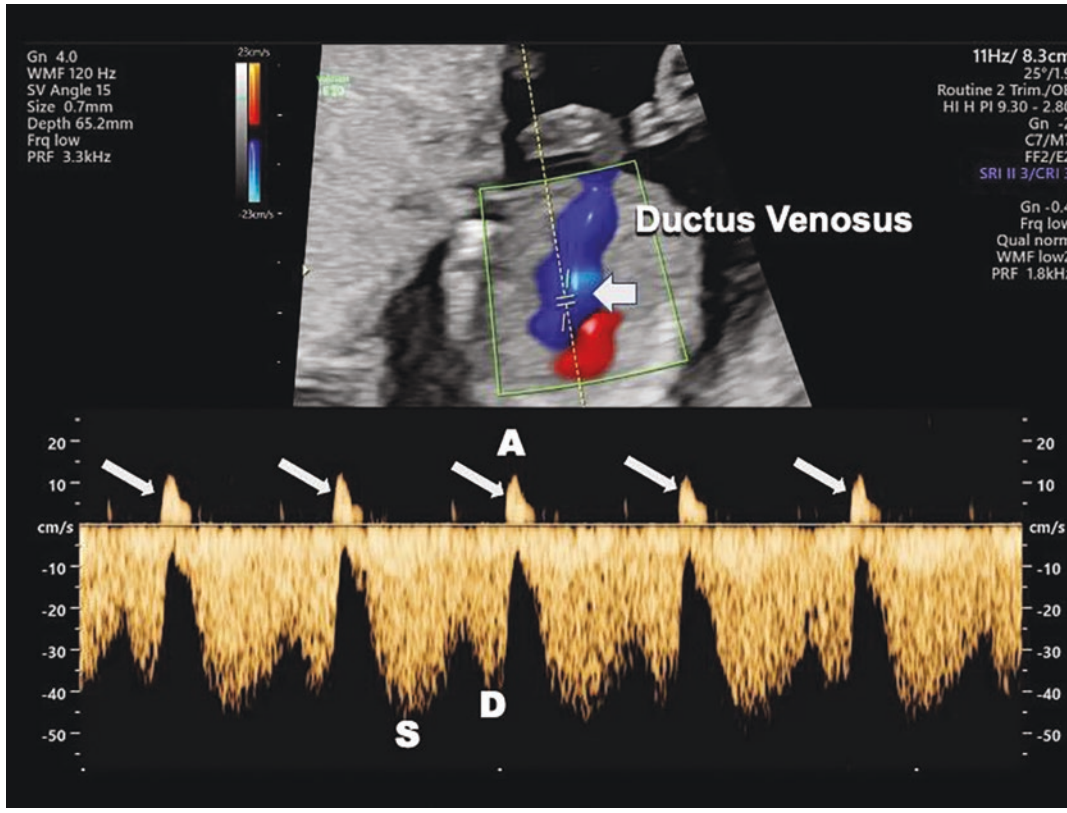

Fig. 13.3 Reversal of flow in the ductus venosus is depicted in color Doppler directed spectral Doppler display. The upper panel, in the oblique axial plane, shows the color Doppler flow in the ductus, and the lower panel the spectral display. The oblique arrows indicate the reversal of flow. The horizontal arrow shows the placement of the Doppler sample volume

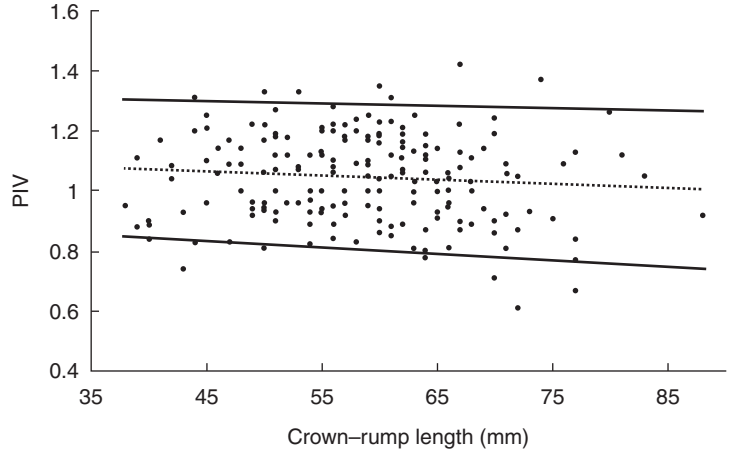

Fig. 13.4 Ductus venosus pulsatility index for veins (PIV) measurements according to crown-rump length in 198 fetuses presented with 5th, 50th, and 95th centiles. The equation for the 50th centile is $y = -0.0014x + 1.1279$ and for the standard deviation is SD = $0.0004x + 0.1233$. (Reprinted from Prefumo 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)

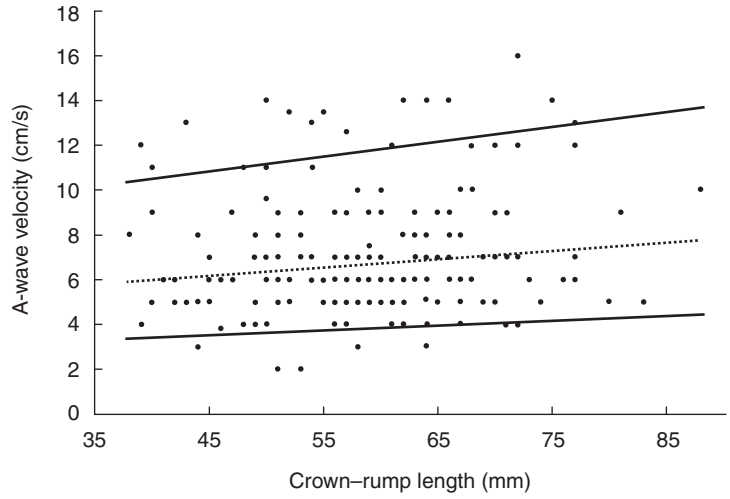

Fig. 13.5 Ductus venosus A-wave velocity measurements according to crown-rump length in 198 fetuses presented with 5th, 50th, and 95th centiles. The equation for the 50th centile is $y = 0.1304x + 22.083$ and for the standard deviation is SD = $0.0448x + 4.862$. (Reprinted from Prefumo F, Risso D, Venturini 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)

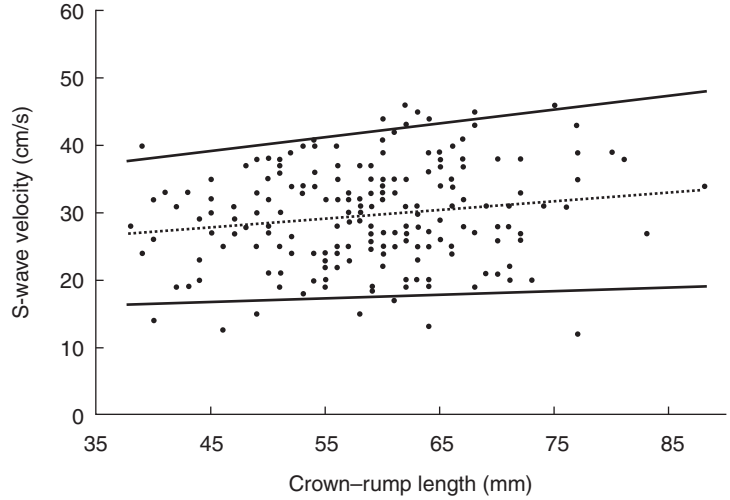

Fig. 13.6 Ductus venosus S-wave velocity measurements according to crown-rump length in 198 fetuses presented with 5th, 50th, and 95th centiles. Log10 transformation was performed for data analysis; data are displayed after antilog transformation. The equation for the 50th centile is $y = 100.0024x + 0.679$, and the standard deviation is SD = 100.1492. (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)

hemodynamics during fetal breathing. Breathing movements in early gestation are not regular and become more frequent as the fetus approaches mid-gestation [17]. 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 an enhanced a-wave. In a sheep model, Gudmundsson and

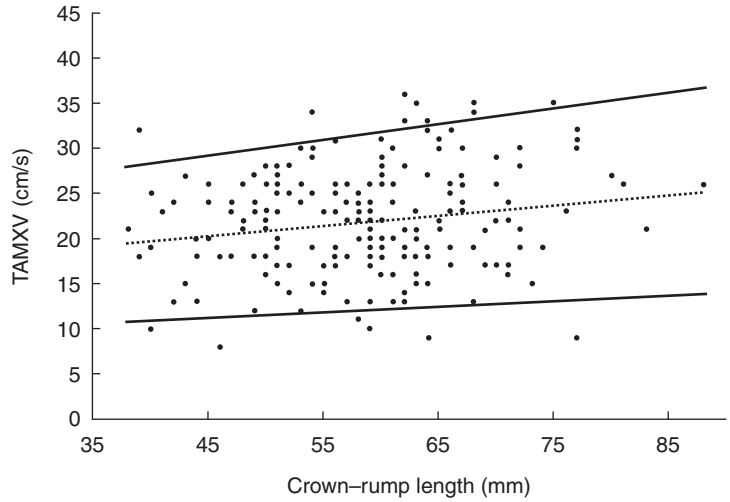

Fig. 13.7 Ductus venosus time-averaged maximum velocity (TAMXV) measurements according to crown-rump length in 198 fetuses presented with 5th, 50th, and 95th centiles. The equation for the 50th centile is $y = 0.1174x + 14.95$ and for the standard deviation is $SD = 0.0342x + 3.9375$. (Reprinted from 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)

coworkers noted changes in ductus venosus velocity waveform directly related to fetal bradycardia consequent to fetal hypoxemia [18]. Any increase in fetal myocardial compliance will lead to changes in the ductal waveform. Thus, hypoxia, acidosis, or intrathoracic lesions such as pleural effusion compressing the heart will lower cardiac compliance, leading to augmented a-waves [10, 19]. Blood viscosity also modifies venous Doppler waveforms, seen in fetal anemia. Lam and co-investigators reported significant increase in S, a-wave, and Vta in nonhydropic fetuses between 12 and 13 weeks with homozygous alpha thalassemia-1 [20], attributed to lower blood viscosity in anemia and hypoxia.

Ductus Venosus Doppler in First-Trimester Aneuploidy Screen

The most frequent and significant utilization of ductus venosus Doppler in the first trimester of pregnancy is for aneuploidy screening. Various investigators have demonstrated its efficacy, with or without the nuchal translucency and biomarkers. Selected reports are discussed below and summarized in Table 13.1 [21–30].

Borrell and colleagues reported Doppler velocimetry of the ductus venosus before performing invasive diagnostic procedures for trisomy 21 in 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 in 486 consecutive singleton pregnancies between 10 and 14 weeks, just before fetal karyotyping [22]. Of the 63 fetuses with a chromosomal anomaly, 57 (90.5%) had reverse or absent a-wave. Abnormal ductus venosus Doppler indices were observed in 13 (3.1%) of the 423 euploid fetuses. Multivariate regression analysis demonstrated that only the abnormal a-wave showed significant independent discrimination between the euploid and the aneuploid cases.

Maiz and colleagues performed a combined first-trimester screening test in a cohort of about 20,000 singleton pregnancies, examining variables including maternal age, fetal nuchal

Table 13.1 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 were not reported, given that not all aneuploid cases in this study had DVD findings reported

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 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, 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.

Most fetuses with abnormal ductus venosus Doppler are euploid, and not all fetuses with aneuploidy will have abnormal findings. Table 13.1 summarizes several first-trimester ductus venosus Doppler studies demonstrating abnormal Doppler findings in 70% of aneuploid fetuses but only in 4% of the euploid fetuses.

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 into these algorithms is discussed later.

Ductus Venosus Doppler Screening for Congenital Heart Disease

Ductus venosus Doppler waveforms reflect fetal central hemodynamics, especially in the right heart. We expect that effect of functional and anatomical abnormalities will alter this waveform. This hypothesis 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 significant cardiac defects.

In a study involving over 41,000 euploid fetuses, the reversal of ductus venosus a-wave was observed in about 28% of the fetuses with cardiac anomalies and 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.

These findings were confirmed 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. When ultrasound findings were abnormal, early echocardiography was recommended. Fetal cardiac status was verified by fetal echocardiography in the second and third trimester, neonatal assessment, or autopsy. Of the 37 euploid fetuses with a major cardiac malformation, the nuchal translucency was above the 99th centile in 27% of 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 for the early identification of fetuses at a higher risk of CHD. Early fetal echocardiography can be challenging and may not eliminate the need for a comprehensive ultrasound examination in mid-pregnancy. However, Zidere and associates recently demonstrated that, in expert hands, early ultrasound might achieve a high degree of accuracy [33].

More recently, the value of nuchal translucency (NT), ductus venosus Doppler, and tricuspid Doppler measurements in detecting significant CHD in the first trimester was further explored by Minella et al., who conducted a retrospective analysis of prospectively collected routine ultrasound information from over 93,000 singleton gestations between 11 and 13 weeks [34]. Those with known aneuploidy or malformations were excluded. Reversal of ductus venosus a-wave was associated with a detection rate of 27.5% with a false-positive rate of 1.8%. The use of NT measurement, tricuspid regurgitation, or reversal of the ductus venosus a-wave was associated with over 50% cases of major CHD. This is further discussed below.

Doppler Investigation of Tricuspid Flow in the First Trimester

Over the recent years, there has been a 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 a two-dimensional image of the fetal heart, used to direct 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 use [35]. An apical or a basal four-chamber view is preferred, aligning the Doppler beam with the atrioventricular flow, allowing an insonation angle below 30°. The high-pass filter is set at the lowest level allowed by the device and the power output as low as feasible. Color Doppler mode will show reversed flow depicting regurgitation. Color M-mode has the advantage of providing more accurate temporal resolution, but color modes are not routinely used for the first-trimester screening because of their inconsistency in depicting intracardiac flow in early gestation. In common practice, two-dimensional B mode imaging is utilized to place 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 veloc-

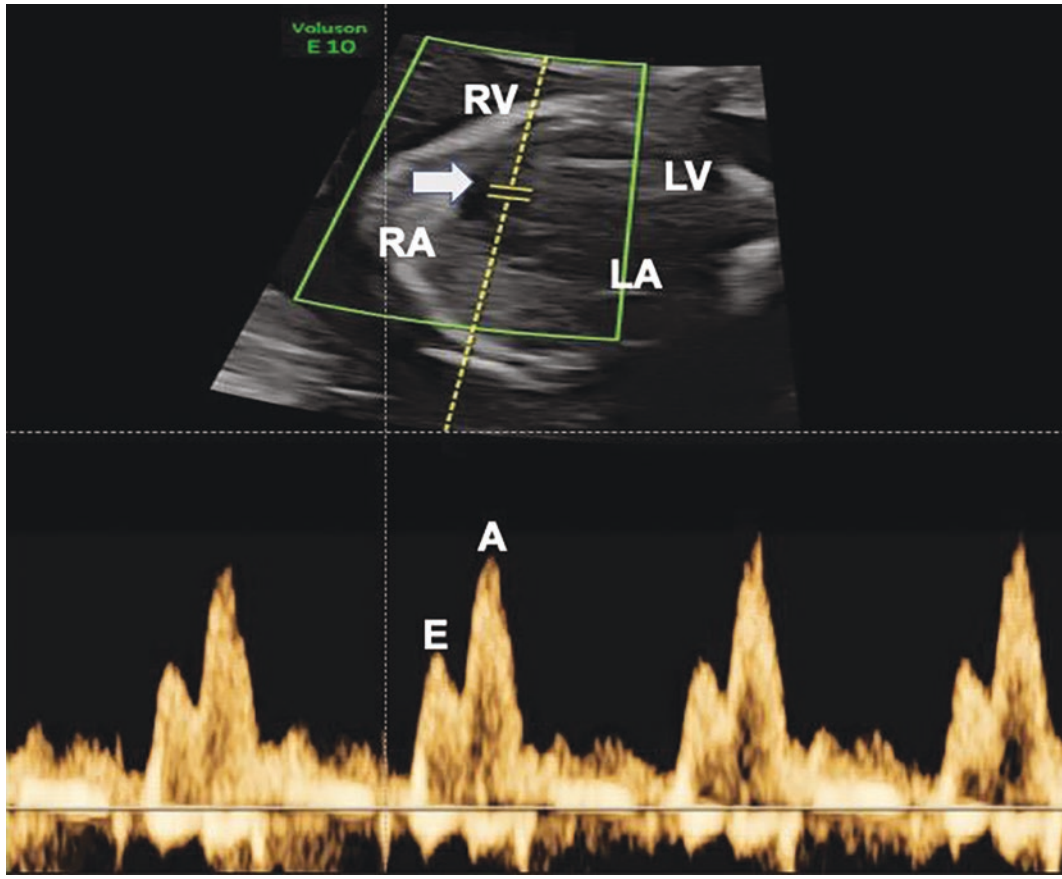

Fig. 13.8 Doppler imaging of the tricuspid flow in the first trimester of pregnancy is depicted here. The upper panel shows two-dimensional echocardiography of an apical four-chamber view of the fetal heart at 13 weeks' gestation. The horizontal arrow indicates the Doppler sampling location. Note the 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

ity waveforms (Fig. 13.8). 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 (mitral valve). These patterns reflect 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. 13.9). 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 [36]. Others have extensively demonstrated this.

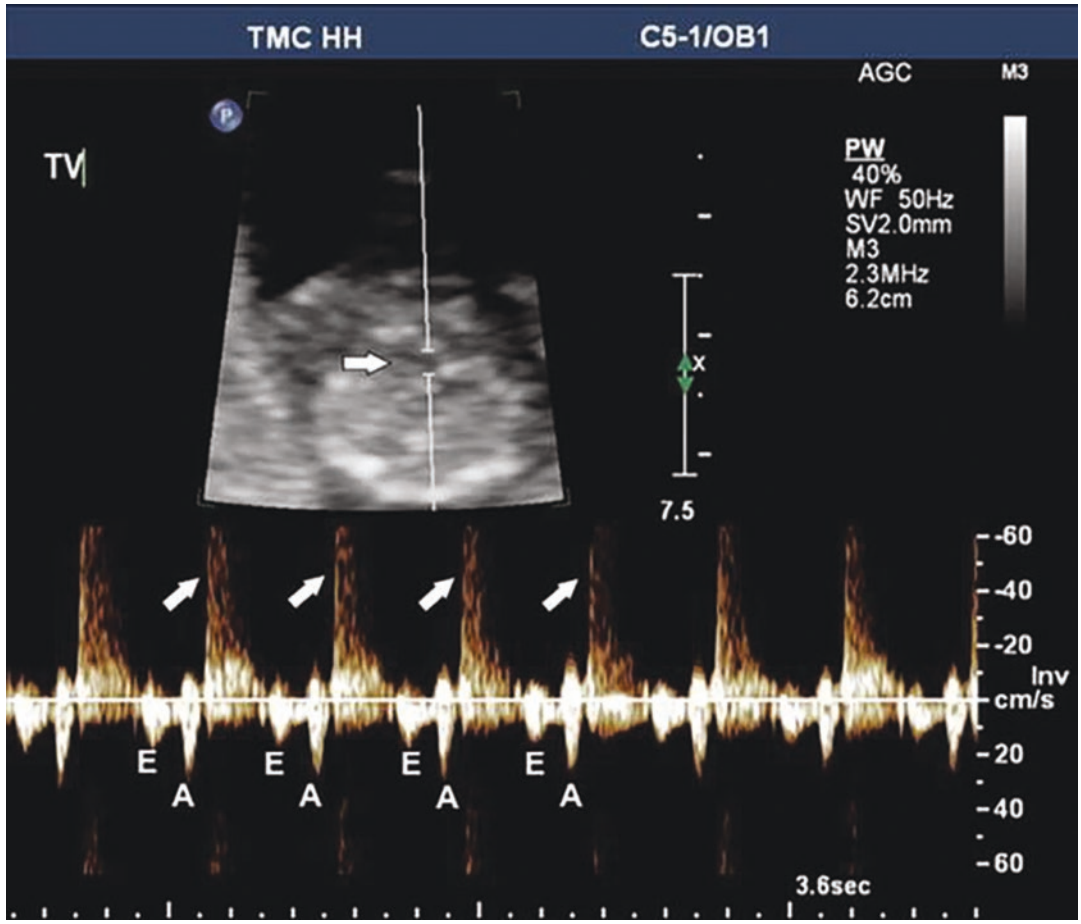

Fig. 13.9 The sonogram illustrates tricuspid regurgitation in a first-trimester fetus. The upper panel shows the placement of the Doppler sample volume. E, peak flow velocity during ventricular diastole; A, peak flow velocity during the atrial systole. The upward oblique arrows indicate the high-velocity regurgitant flow jets from the right ventricle to the right atrium. Note aliasing of the flow jets due to their high velocity

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 [37]. Makikallio and associates utilized Doppler echocardiography to characterize fetal cardiac function in 16 uncomplicated pregnancies between 6 and 10 weeks [38]. They noted that the atrioventricular flow was initially monophasic and became biphasic after 9+ weeks and that regurgitant atrioventricular flow was typical 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 in 20–23-week euploid fetuses with an elevated nuchal translucency, but without any major malformations to investigate cardiac function. They 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 [39].

Lopes and colleagues performed echocardiography in 275 fetuses with increased nuchal

translucency between 12 and 16 weeks' gestation [40]. Subsequent follow-ups 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 to 13+6 weeks' gestation [41]. The authors successfully performed a Doppler assessment of tricuspid flow in 98.8% of 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 regurgitation (67.5%, 33.3%, respectively). Moreover, trained sonographers could reliably assess tricuspid regurgitation during the first trimester.

In the study by Minnella et al. as discussed previously, Doppler demonstration of tricuspid regurgitation showed a detection rate of 28.9% for any significant CHD with a false-positive rate of 1.2%. The use of NT measurement, Doppler of tricuspid flow, or ductus venosus flow allowed the detection of over 55% cases of major CHD [34]. The potential impact of cell-free DNA testing may potentially affect the wide use of multimodal ultrasound screening, which is further discussed below.

Biophysical, Biochemical, and Molecular Screening in Early Pregnancy[2]

With the availability of multiple first-trimester screening tests, including the fetal Doppler and the rapid adoption of cell-free DNA testing, it is critical to determine the most effective approach for first-trimester aneuploidy screening. The advent of molecular blood tests may eventually 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 prospectively analyzed 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 [42]. The authors observed that a detection rate of 98% of fetuses with trisomy 21, with an overall chorionic villous sampling rate <0.5%, might 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 explicitly analyzed, the authors observed that the existing protocols that include biomarkers, biophysical modalities including venous Doppler, and cell-free DNA in selected cases would reduce the need for chorionic villous sampling, with a high detection rate and a low false-positive rate. Although universal cell-free DNA testing would have an even higher detection rate, the cost may substantially increase. Other complex factors influence the efficacy and economy of the various screening approaches, which require more focused scrutiny.

Doppler Ultrasound Imaging of the Uterine Artery in the First Trimester

In the 1980s, Doppler sonography of the uterine artery ushered in exciting opportunities to investigate uteroplacental circulation [43]. The uteroplacental circulation undergoes enormous changes to fulfill fetal requirements, including the early transformation of the spiral endometrial arteries and remodeling of the placental intervillous space into large conduits of low impedance flow. Specialized trophoblastic cells invade and replace the intima and media of these arteries to cause this change [44]. This process starts in

[2] See also Chap. 9.

early pregnancy and extends to the myometrial course of these arteries by the middle of the second trimester.

These vascular changes are reflected in the uterine artery Doppler waveforms. Failure of this remodeling process is associated with the subsequent development of preeclampsia and fetal growth restriction [45, 46]. Uterine artery Doppler has the potential for prediction and prognostication for 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 [47–49].

Doppler Imaging Technique for the Uterine Artery

The uterine arteries can be interrogated either transabdominally or transvaginally in the first trimester. In the transabdominal approach, the paracervical site at the internal os level is preferred over the iliac crossover site as it is easier to obtain [50]. 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 [51]. Using color Doppler, the uterus and the cervix are imaged in a midsagittal 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.

The transducer is placed in the anterior fornix and manipulated laterally in the transvaginal approach. The color Doppler image reveals the uterine artery, and pulsed Doppler interrogation is performed. 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 at the lowest level providing adequate image quality.

Uterine Artery Doppler Waveform

In early pregnancy, the uterine artery Doppler waveform demonstrates a rapid acceleration and deceleration of the flow velocity during systole, followed by an early diastolic deceleration known as the diastolic notch, and a slight rise in the late diastole (Fig. 13.10). Factors that 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 until the end of pregnancy [43]. A more recent study reported a decline until 34 weeks [52]. These changes reflect the profound reduction in uteroplacental circulatory impedance during early pregnancy, consequent to the dramatic transformation of the spiral endometrial arteries by the invasion of 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 decreased pulsatility. In comparison, a lower rate will lengthen the diastolic run-off time, increasing pulsatility. Uterine artery waveforms from the ipsilateral placental site show a lower pulsatility than those from the contralateral side [53]. Finally, 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 uterine artery, reflecting the progressive decline in circulatory impedance down the arterial tree.

The pulsatility of the uterine artery waveforms is analyzed utilizing the Doppler frequency shift's maximum frequency shift envelope (see Fig. 13.10). The standard indices are calculated, including the pulsatility index, resistance index, and systolic-diastolic ratio. A high Doppler index is associated with adverse pregnancy outcomes, especially the development of preeclampsia and/or fetal growth restriction. Transient decelerations, called notches, have been described during

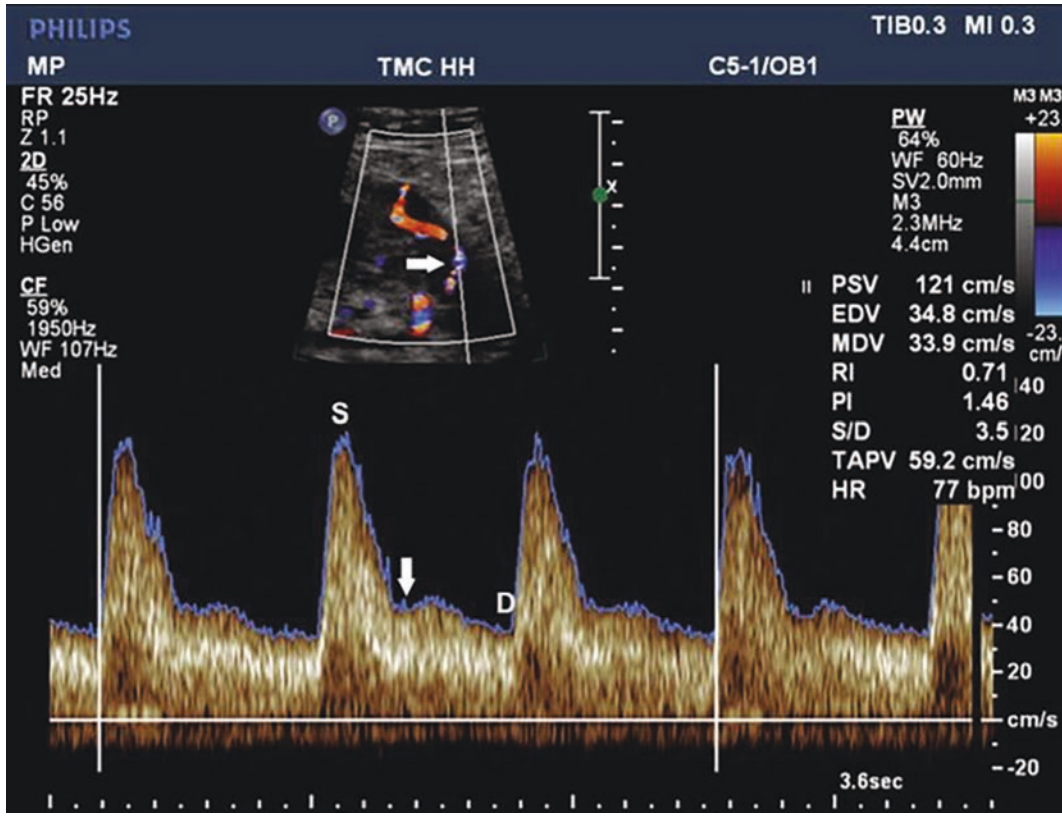

Fig. 13.10 The figure shows uterine artery Doppler waveforms in the first trimester of pregnancy. The upper panel shows color Doppler flow in the ascending branch of the uterine artery. The horizontal arrow indicates the site of Doppler sampling. The lower panel depicts the spectral Doppler waveforms. 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

the systolic or the diastolic phase [54–56]. Such a notch implies a high impedance in the uterine circulation. Gomez and coworkers noted bilateral notches declined from 49% of the waveforms at 11 weeks to 14% at 22 weeks; however, their persistence beyond mid-gestation was associated with adverse outcomes [52].

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, to predict subsequent development of preeclampsia and fetal growth restriction [57]. 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 the persistence of abnormal Doppler findings, such as bilateral notch and elevated

pulsatility index into the second trimester, increased adverse outcomes [52]. The highest risk was noted in those with persistent abnormal pulsatility indices (OR, 10.7; 95% CI, 3.7–30.9). Conversely, in a prospective study 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 [58].

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 [59]. 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 versus first trimester.

Others, however, could not corroborate the predictive efficacy of the first-trimester uterine artery Doppler. Audibert and associates 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 [60]. 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. Their combination did not enhance predictive efficiency [61]. More recently, the addition of maternal ophthalmic artery peak systolic velocity ratio may further enhance the first-trimester uterine artery Doppler detection rate of preeclampsia. A prospective observational study on 4066 pregnancies found the addition of the ophthalmic artery Doppler to first-trimester uterine artery assessment, mean arterial pressure, and maternal risk factors improved the detection rate of preterm preeclampsia from 65.9% to 70.6% [62].

Numerous studies 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 [63]. For 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 aspirin in low-risk pregnancies with abnormal uterine artery Dopplers to prevent certain pregnancy complications.

However, any such recommendation must be based on the evidence of the 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 outcomes when the prophylactic therapy was initiated at or before 16 weeks of gestation [64]. The selection criteria for treatment included clinical risk factors such as nulliparity and chronic hypertension, and abnormal uterine artery Doppler. Initiation of aspirin at or before 16 weeks' gestation, compared 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 an evidence-based justification for initiating 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 based on risk assessment or abnormal uterine artery Doppler. This intriguing study suggests the need for further investigations with an 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 [65].

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

Doppler of the Placental Implantation Site for Early Detection of Placental Accreta Spectrum[3]

The placenta accreta spectrum (PAS) is characterized by abnormal placenta invasion through the decidual myometrial junction into the myometrium and adjacent tissue. The heterogeneity of terminology to describe abnormally adherent placentas has made changes in prevalence over time challenging to assess. PAS encompasses placenta accreta, placenta increta, placenta percreta, morbidly adherent placenta, and invasive placentation. These conditions are associated with massive obstetrical hemorrhage with corresponding increases in fetal and maternal morbidity and mortality. Cook et al. estimated a population prevalence of PAS of 1.7/10,000. These risks jumped to 4.1% in women with one prior Cesarean delivery and to 13.3% after two or more cesarean deliveries [66].

The early diagnosis and management of PAS are critical, primarily because of increasing cesarean delivery rates. Other factors accelerating risks include placenta previa, placenta uterine anomalies, leiomyomata, prior uterine surgery, in vitro fertilization, and age greater than 35 [67]. In 2021, the Society for Maternal-Fetal Medicine (SMFM) issued a consensus report defining ultrasound markers, a systematic approach to examining pregnancies at risk for PAS, and recommended protocols for early and late first-trimester ultrasound examinations [68].

Doppler Imaging Technique

The techniques for first-trimester ultrasound diagnosis of PAS have been described in the SMFM review and are briefly summarized here. Transvaginal ultrasound is recommended in early pregnancy, and transabdominal ultrasound may be performed when appropriate. Detailed evaluation of the uterus in the midsagittal plane is performed to document the gestational sac (up to 8 6/7 weeks of gestation) and/or the placental location (up to 13 6/7 weeks of gestation). Documentation should include reference to the position of the sac and/or placenta relative to the bladder, cesarean scar (if present), and internal cervical os. Color Doppler imaging is performed using a low-velocity scale, low wall filter, and high gain to maximize detection of flow (adjusting as needed for body habitus and other clinical factors). The shape of gestational sac (up to 8 6/7 weeks of gestation) is performed. Imaging should be performed with a partially filled maternal bladder. The area of interest should be magnified so that it occupies at least half of the ultrasound image with the focal zone at an appropriate depth.

[3] See also Chap. 18.

First Trimester Ultrasound Markers

Several first-trimester PAS ultrasound markers have been identified and are divided into early first trimester (6–9 weeks) and late first trimester (10–14 weeks).

Early first trimester:

In patients having one or more prior cesarean sections, cesarean scar pregnancy (CSP) is characterized by the implantation of the gestational sac in the lower uterine segment proximal to or within the cesarean scar and abnormal color Doppler vascularity (Fig. 13.11a, b).

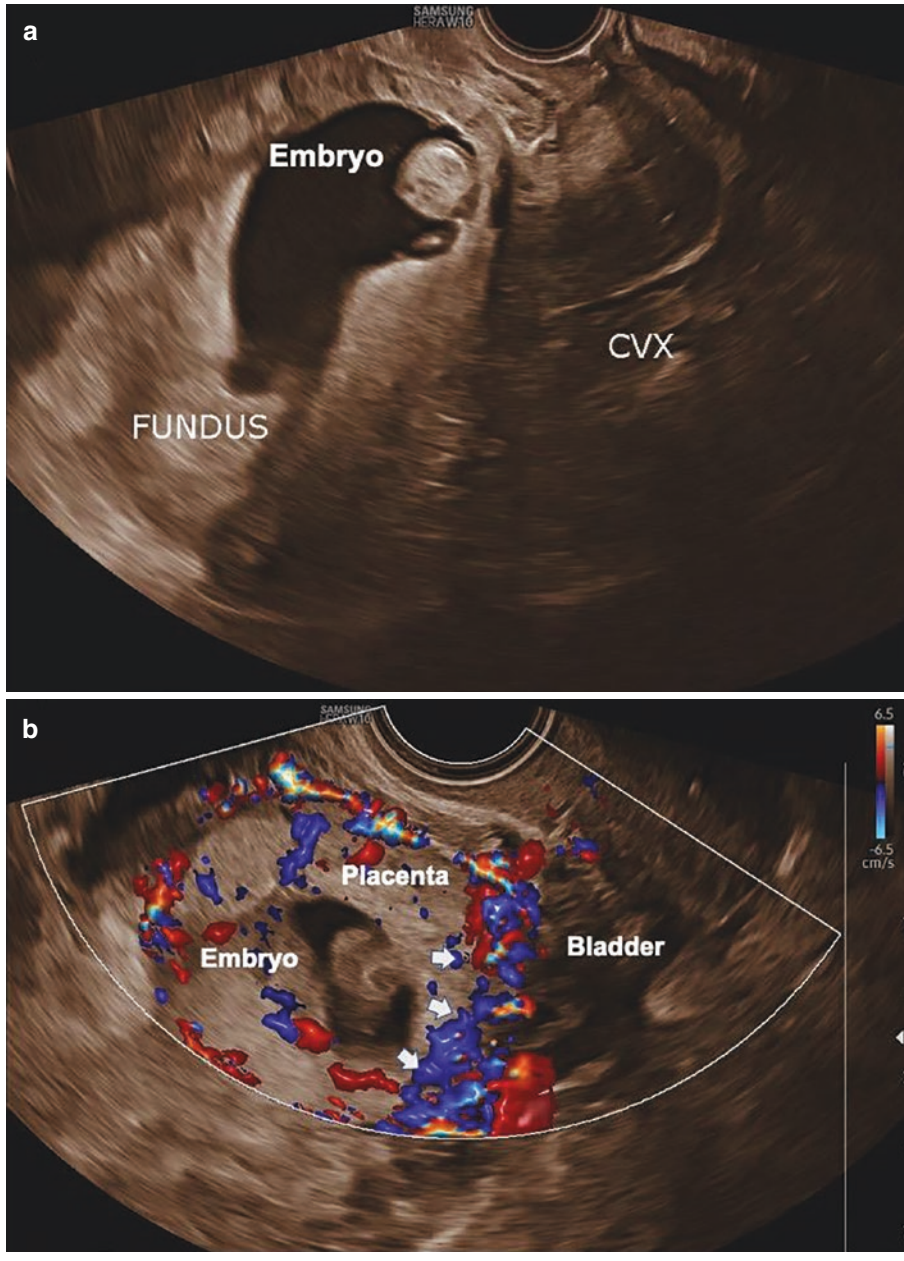

Fig. 13.11 (**a**) Transvaginal sonography showing low implantation of the gestation in the uterine cavity at 11 weeks' gestation. (**b**) Transvaginal sonography showing anterior placentation and increased vascularity and lacunae (white arrows) in the lower part

In CSP, the risks of placental tissue extending into the scar and the need for hysterectomy are high. The histopathology of CSP and PAS is indistinguishable. In a retrospective study of prenatally diagnosed PAS confirmed at delivery, all had low implantation of the gestational sac. A case-control study by Abinader et al. examined women with PAS who had first trimester ultrasounds with low implantation pregnancies, and found that controls had fewer lacunae with a median of 1 versus 5 in cases, had smaller lacunae, and had different patterns on color Doppler. Lacunar swirling was only seen in women with PAS, with swirling in 10/12 women using grayscale and 12/12 with color Doppler. The presence of an abnormal uteroplacental interface was only seen in cases [69].

Late first trimester:

There is a tendency toward fundal gestational sac growth throughout pregnancy. In a study of women having a histopathological diagnosis of PAS at delivery, 28% were identified with low implantation of the gestational sac between 11 and 14 weeks. In a meta-analysis evaluating first-trimester detection of PAS, D'Antonio et al. identified a gestational sac proximal to the uterine scar in 82% of women but with a sensitivity of only 44% [70]. Other markers traditionally described in the second and third trimesters were also identified in the late first trimester. Color Doppler is particularly effective in identifying placental lacunar feeding vessels, subplacental hypervascularity, hypervascularity of the uterovesical space, intraplacental hypervascularity, and bridging vessels. Multiple concurrent markers increase the diagnostic accuracy [71].

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 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 the absence or reversal of the a-wave.
- Abnormal ductus venosus Doppler is encountered in approximately 70% of the aneuploid 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 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 preeclampsia. It is uncertain whether adding uterine artery Doppler to clinical risk assessment improves the predictive accuracy for implementing early aspirin prophylaxis.
- Early and late first-trimester ultrasound incorporating color Doppler assists in the early recognition of PAS.

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