37 Doppler Ultrasound in Early Pregnancy Including Miscarriage, Ectopic Pregnancy, and Implantation

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37.1 Introduction

37.1.1 Types of Doppler and Their Application in Early Pregnancy

Doppler ultrasound in early pregnancy is used to evaluate and estimate blood flow in both the major and the minor vessels of the internal genital tract. The Doppler mode uses a phenomenon called "Doppler shift," which is a change in frequency from the sent to the returning sound wave. These "shifts" are generated by sound waves reaching moving particles. The change of the frequency (or "shifts") correlate with the direction and velocity of particle motion (Fig. 37.1). The velocity of particle motion can be measured by the so-called Pulsatility Index (PI) and Resistance Index (RI) by using Pulsed-Wave Spectral Doppler (PWSD).

There are six different types of Doppler modes: Continuous-Wave Doppler (CWD), Color-Doppler (CD), Pulsed-Doppler (PD), Spectral Doppler (SD), PWSD (pulsed-wave spectral Doppler) and 3D power Doppler [1].

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CWD utilizes continuous transmission and reception of ultrasound waves. This is accomplished by two dedicated transducer elements: one that only sends Doppler signals and another one that only receives (Fig. 37.2). As no pulses are emitted, CWD does not allow us to determine where exactly the wave is reflected. We only know that the velocity curve emerges somewhere along the path of the ultrasound transmitted wave, which is called the CWD line.

CD is able to show blood flow or tissue motion in a selected two-dimensional area. Direction and velocity are color-coded and superimposed in the B-mode (2D ultrasound) (Fig. 37.3).

PD does not examine flow velocity or the direction of the flow. Instead, it reflects the amplitude of the returning wave and it is able to detect very low flows (Fig. 37.4). This subtype of Doppler mode is very useful when assessing gynecological vascular emergencies such as ovarian torsion and ectopic pregnancies.

SD is a continuous and pulsed-wave form allowing for the conversion of Doppler shift signals into audible frequencies over a loudspeaker (no image is produced). This technique is often utilized at the bedside to demonstrate fetal tones during advanced pregnancy.

PWSD shows the "spectrum" of the returned Doppler wave in a two-dimensional shape. Arterial waves are more triangle-shaped whereas venous waves display a more continuous band-like shape.

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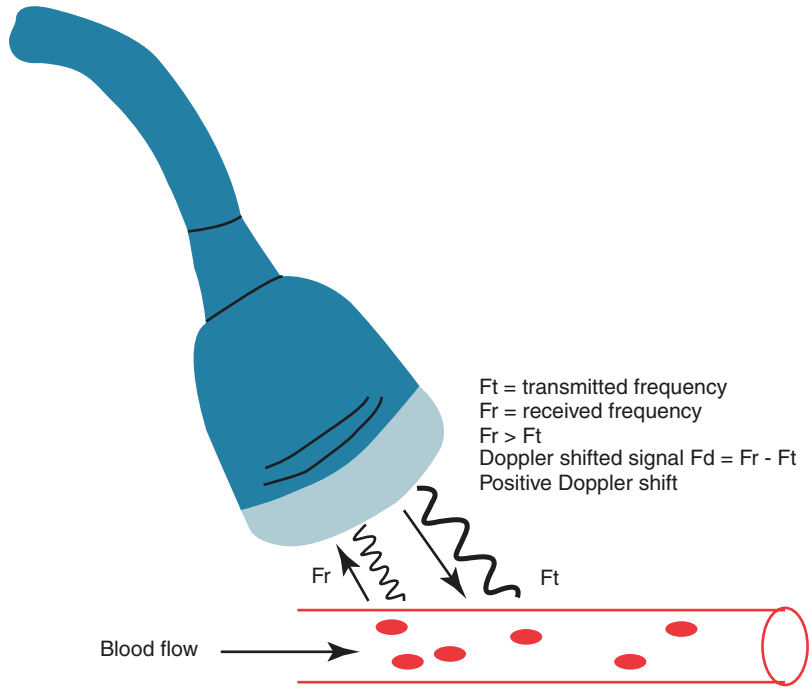

Fig. 37.1
Representation of the "Doppler Shift"

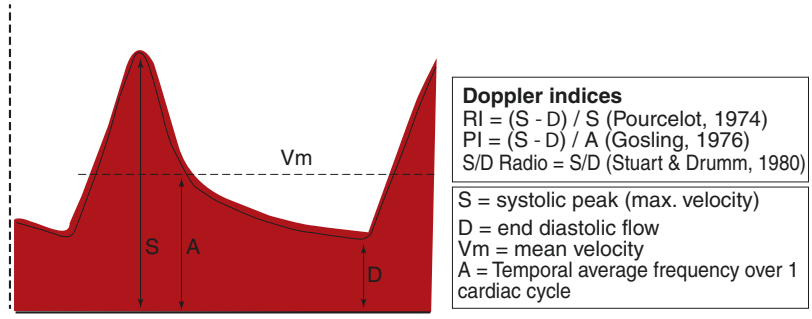

Fig. 37.2
Representation of the Doppler indices

Calculation of the **three 3D power Doppler** ultrasound vascular indices, the Vascularization Index (VI), Flow Index (FI), and Vascularization Flow Index (VFI) is based on and related to the total and relative amounts of power Doppler information within a volume of interest. VI denotes the ratio of color-coded voxels to all voxels within the volume and is expressed as a percentage, FI represents the mean power Doppler signal intensity from all color-coded voxels and VFI is the simple mathematical relationship derived from multiplying VI by FI and dividing the result by 100. Both FI and VFI are unitless and are expressed as numerical values ranging from 0 to 100. The indices are thought to reflect the number of vessels within the Volume of Interest (VI), the intensity of flow at the time of the 3D sweep (FI), and both blood flow and vascularization (VFI) [1].

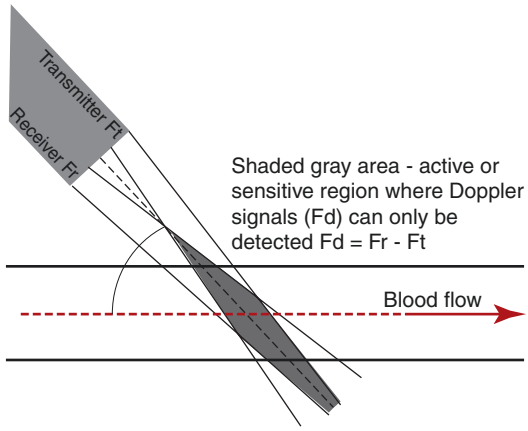

Fig. 37.3 Ultrasound transducer transmitting a Doppler signal with a Continuous wave. These two elements are set at an angle to each other so that the transmit and reception beams overlap one another. The crossover region is known as the active or sensitive area and is where Doppler signals can only be detected. *Fd* Doppler shift signals; *Fr* Doppler received signals; *Ft* Doppler transmitted signal

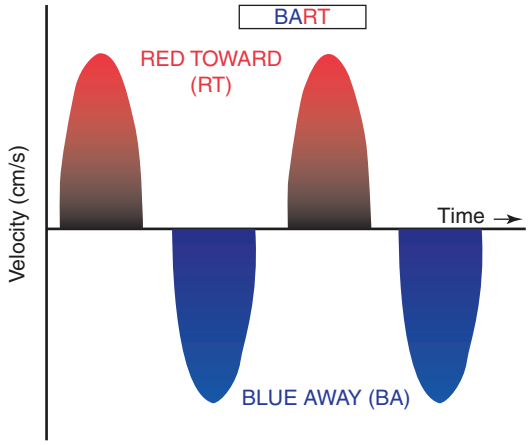

Fig. 37.4 Representation of the PD mode

37.1.2 Normal Pelvic Blood Flow During the Ovulation, Luteal Phase, Implantation, and Early Pregnancy: General Concepts

Transvaginal Doppler Sonography (TVDS) is a valuable tool in the assessment of the luteal phase, implantation, and early pregnancy [1].

Normal menstruating women are preferably scanned on days 3–10 of the menstrual cycle to exclude changes in the pelvic blood flow associated with ovulation, especially in the ovarian vessels. There are physiologic flow patterns important to recognize when assessing the female pelvis by using the Doppler mode in the iliac, uterine, and ovarian arteries in pregnant and non-gravid women.

The common and external iliac arteries (which are part of the aorto-femoral segment) show a triphasic flow, with an early diastolic flow reversal, a diastolic forward flow, and a systolic flow.

The internal artery, in contrast, shows a high-velocity biphasic flow.

The ovarian artery is a high-impedance system with low Doppler shifts with low velocity. The waveform shape varies with the state of activity of the ovary [2]. Throughout the menstrual cycle, the dominant-follicle containing ovary will usually show decreased impedance thus increasing the blood flow to that ovary in order to promote ovulation and maintain the corpus luteum at the same time (the corpus luteum will therefore act as a low-impedance ovarian shunt). Conversely, the non-ovulating ovary will show low-end diastolic flow.

Intra-ovarian circulation however is very different from ovarian artery circulation. Near the ovarian hilum, the penetrating vessels are coiled and tortuous, demonstrating high-impedance blood flow [2]. The intra-ovarian vascular network is dynamic throughout the menstrual cycle, increasing the number of numerous arteriovenous shunts during the luteal phase. These changes in the intra-ovarian blood flow may involve angiogenesis and the production of hormonal factors before the ovulation during the proliferative phase, while vascular accommodation and low impedance are important in the luteal phase in order to maintain the corpus luteum throughout the second half of the menstrual cycle and the first 12 weeks in pregnancy.

The uterine arteries are direct branches from the internal iliac or hypogastric arteries and typically show a high-resistance/low-diastolic-flow velocity waveform with a characteristic notch during early diastole in the first trimester and non-gravid uterus. CD analysis allows the identification of the small vessels within the myome-

trium (e.g., arcuate arteries and their branches). Schulman and colleagues described the typical shape of the uterine waveform on PW, which has a rapid rise and fall in the flow velocity during systole and a "notch" in the descending waveform in early diastole [3]. The type of velocity waveform obtained depends on the phase of the menstrual cycle, pregnancy state, age of the patient, and pathologic conditions.

Successful intra-uterine implantation is the result of a complex process involving the interaction between different molecules with the genital tract (especially with the endometrium), and ultrasonography can give important information on many of these. The endometrium thickens and undergoes morphologic changes under the influence of increasing estradiol levels from the developing ovarian follicles. This process is also associated with increased vascularity from the basal arteries with the growth of vessels developing along with the glandular crypts of the functional layer during the luteal phase [3].

Ultrasound monitoring of the endometrium in a natural or stimulated transfer cycle usually involves measuring the Endometrial Thickness (ET) and studying changes in morphology up to the time of ovulation. ET is measured in the mid-sagittal plane of the uterus as the maximum distance between the two interfaces of the endometrial–myometrial junction, as per IETA recommendations [4, 5].

Subendometrial vascularity is usually assessed by visually assessing images of endometrial vascularity before the ovulation trigger injection in ART (artificial reproductive techniques). Vascular penetration of the endometrium is usually graded as grade 1 (no subendometrial blood flow detected); grade 2 (subendometrial blood flow detected); and grade 3 (both endometrial and subendometrial blood flow detected). Most studies show that grade 3 flow is associated with significantly higher clinical pregnancy rates [6].

Measurement of uterine vascular supply on PWSD gives valuable information about uterine perfusion. The increased impedance of uterine artery blood flow presenting as reverse blood flow and elevated UAPI and UARI have been associated with low implantation rates in IVF cycles and increased risk of miscarriage. Additionally, UAPI during the first trimester (11–13 gestational weeks) has been demonstrated to be a useful tool to predict up to 75% of preterm pre-eclampsia and 47% of term preeclampsia in combination with other factors [7]. However, mean UAPI measured at <11 weeks' gestation does not appear to be a useful marker for the prediction of placental-related adverse pregnancy outcomes [8].

37.2 Early Pregnancy States: Definitions

During the first trimester (before the 12th gestational week), we can define different early pregnancy states, including [9]:

- *Intra-uterine Pregnancy of Uncertain Viability*
- Intrauterine mean gestational sac <25 mm in diameter or containing a fetal pole with crown-rump length <7 mm with no fetal cardiac activity visualized.
- *Viable Intrauterine Pregnancy (IUP)*
- Intrauterine gestational sac containing embryo (s) with visible cardiac activity.
- *Non-viable IUP*
- Intra-uterine gestational sac containing the presence of embryo with crown-rump length ≥7 mm without demonstrable cardiac activity on the first scan; OR presence of an embryo with crown-rump length ≤7 mm with no demonstrable cardiac activity at the first scan and then at the second scan 7 days later with still no fetal cardiac activity; OR absence of an embryo in a gestational sac with a mean diameter of >25 mm or a mean gestational sac diameter <25 mm with no growth at ultrasound follow-up.
- *Ectopic Pregnancy (EP)*
- Presence of an adnexal mass separate to the ipsilateral ovary in form of inhomogeneous mass ("blob" sign), gestational sac ("bagel" sign), or gestational sac containing an embryonic pole with or without cardiac activity [10].
- *Pregnancy of Unknown Location (PUL)*

- Defined as a positive pregnancy test with no signs of intra- or extra-uterine pregnancy on transvaginal ultrasonography and an absence of products of conception. PUL is a descriptive term and not a final diagnosis. Women classified with PUL require follow-up visits to determine the final diagnosis: failed PUL (FPUL) (accounting for 44—69% of the PUL group), intrauterine pregnancy (IUP) (30–47% of the PUL), ectopic pregnancy (EP)(814% of the PUL) or persistent PUL (PPUL) (1–3% of the PUL) [9]. As far as we know, Doppler ultrasound examination has not been demonstrated to add useful information to serial Human Chorionic Gonadotrophin (hCG) and progesterone determination in predicting PUL outcome.
- *Persistent PUL (PPUL)*
- Ongoing PUL state classification on TVS over time with serial serum hCG level monitoring without evidence of spontaneous resolution; in our unit, PPUL is classified at D7 if the hCG was plateauing by D7 (initial hCG ratio between 0.80 and 0.99 followed by an increase in hCG on D7) or increasing on D7 with no visible pregnancy on repeat TVS [9].
- Doppler ultrasound may add useful information to conventional 2D pelvic ultrasound examination to confirm viable intrauterine and ectopic pregnancies.

37.3 Role of Doppler Ultrasound in the Diagnosis of Intrauterine Viable Pregnancies

Although the myocardium begins to contract rhythmically by 3 weeks after conception it is first visible on sonography around 6 weeks of gestation. The Fetal Heart Rate (FHR) is then usually around 100–120 beats per minute (bpm) [11].

FHR then increases progressively over the subsequent 2–3 weeks to (mean) 110 bpm by 5–6 weeks and 170 bpm by 9–10 weeks.

A slow FHR is termed fetal bradycardia and is usually defined as FHR <100 bpm before 6.3 weeks gestation, or FHR <120 bpm between 6.3 and 7.0 weeks [12]. A rapid FHR is termed a fetal tachycardia and is usually defined as FHR >160–180 bpm. FHR around 170 bpm may be classified as borderline fetal tachycardia. A rapid and irregular fetal heart rate is usually termed a fetal tachyarrhythmia [13, 14].

Embryonic heart rate below 100 bpm at 6–7 gestational weeks is an ominous finding. The survival rate is zero at heart rates (hr) below 70 bpm at 6–8 weeks of gestation. Embryos having an abnormally slow heart rate between 6 and 7 weeks of gestation that subsequently increases to a normal hr at 8 weeks of gestation remain at increased risk for loss [12, 15].

37.4 Role of Doppler Ultrasound in the Diagnosis of Intra-cavitary Retained Products of Conception (RPOC)

Pelvic ultrasound is the first-line imaging modality in the evaluation of RPOC. The diagnosis should be made promptly because RPOC may act as a source of prolonged bleeding or as a nidus for infection. Evacuation of RPOC often requires dilation and curettage; however, this procedure should be used carefully because there is a risk of uterine perforation and intra-cavitary adhesions (Ashermann's syndrome) after dilation and curettage, especially in the presence of concomitant endometritis.

The assessment of RPOC on PD is subjective and based on the PD Color Scoring (PDCS) system which was adopted from the IOTA group's color scoring system for adnexal masses [16]. While the IOTA group used this scoring system to describe the amount of blood flow within the solid components of ovarian masses, the same principle can be applied to the RPOC within the endometrial cavity. A PDCS of 1 was given when no blood flow was found within the RPOC, a PDCS of 2 when only minimal blood flow was detected, a PDCS of 3 when rather strong blood flow was detected, and a PDCS of 4 when very strong blood flow was detected. Previous studies in a miscarriage population have demonstrated that the presence of any vascularity in the endo-

metrium is associated with a high likelihood of underlying RPOC, with a PPV of 96%. When moderate-high vascularity intra-cavitary patterns were considered separately, all had positive findings for RPOC [16]. The absence of blood flow in residual trophoblastic tissue on PD is associated with a significant improvement in successful expectant management of incomplete miscarriage according to a recent publication [17]. In conclusion, because blood clots and debris can mimic RPOC on grayscale imaging, detection of intrinsic vascularity is helpful in distinguishing simple clots and decidua from RPOC and maybe a helpful tool for the management of patients with incomplete miscarriage.

37.5 Role of Doppler Ultrasound in the Diagnosis of Ectopic Pregnancies

The most common site for ectopic pregnancies is the Fallopian tube. The diagnosis of ectopic pregnancy remains challenging for the clinician despite advances in ultrasound technology. CD and PD imaging have been added to TVS in an attempt to improve the diagnosis on ultrasound. A "ring of fire" characterizes the appearance of flow around an ectopic pregnancy; importantly the ectopic pregnancy mass is separate to and moves separately to the ipsilateral ovary when pressure is applied using the transvaginal probe. The process of placentation is similar whether it occurs within the uterine cavity or out of it. Therefore, not surprisingly a similar high velocity, low-impedance flow pattern of placental perfusion characterizes ectopic pregnancies [18]. When this pattern is seen outside the uterus while the uterine cavity has no Doppler signal, the diagnosis should be considered. However, it is also important to be aware that luteal flow can be confused with the flow from an ectopic pregnancy. The cut-off value for the RI of the corpus luteum blood flow has been described to be 0.4 and the RI of peritrophoblastic blood flow is below 0.4 [19]. CD is most helpful when an extra ovarian mass has not yet been found, because the use of Doppler may allow for the detection of an ectopic surrounded by loops of bowel. Luteal flow can be helpful in identifying an ectopic because about 90% of ectopic pregnancies occur on the same side as the corpus luteum [18, 19]. Other variations of ectopic pregnancies include interstitial/cornual pregnancy, cervical pregnancy, and ovarian pregnancy, sharing similar Doppler characteristics with tubal ectopic pregnancies.

37.6 Role of Doppler Ultrasound in the Diagnosis of Gestational Trophoblastic Disease

Transvaginal US is the accepted standard imaging technique in the evaluation of early pregnancy and suspected complications, including Gestational Trophoblastic Disease (GTD). There is some support for a role for Doppler US in the initial diagnosis and post evacuation follow-up of patients with GTD [19, 20]. A lower Uterine Artery Resistance Index (UARI) before molar evacuation is associated with the development of trophoblastic tumors, a potentially useful means to prospectively recognize patients who are at high risk for progression and, therefore, the need for closer follow-up [21, 22]. In a prospective analysis of 246 women with complete mole, Doppler PI showed potential as a predictor of subsequent development of Gestational Trophoblastic Neoplasm (GTN) [23]. Doppler US can also confirm the absence of vascular flow within a mass, a useful technique in patients with GTD where clots or blood products may simulate solid tissue [20].

37.7 Safety of Ultrasound During Early Pregnancy

The safety of ultrasound examinations during early pregnancy has been subject to debate. Ultrasound has the potential to induce tissue changes through different effects including thermal (heating), cavitation, and microstreaming. The safety of ultrasound use has been correlated

to the increase in temperature that it can produce. Studies have shown that temperature rises to 1 °C are considered to be safe for the developing embryo [24]. The Thermal Index (TI) is a concept that has been introduced to give a guide of the possible increase in temperature by ultrasound, and it depends on the organ being scanned. A TI of 1.0 means that the temperature might increase by 1 °C under worst-case conditions. Additionally, the Mechanical Index (MI) is the complementary index for the mechanical effects of ultrasound. As in the case of TI, MI value of less than 1.0 is considered to be safe for the embryo. The ultrasound examiner, however, should always adhere to the "as-low-as-reasonable achievable (ALARA)" rule, by using the lowest output settings in order to obtain the desired information, and should aim at not prolonging the examination time if it's not necessary. The British Medical Ultrasound Society has also issued recommendations about the duration of ultrasound examinations at different TI and MI [25].

According to World Federation of Ultrasound in Medicine and Biology, Doppler ultrasound should not be used in early pregnancy assessment, unless there is an indication for its use [26–28], in which case TI should be less or equal to 1.0, and the exposure time should be kept as short as possible. All of these concerns justify using only M-mode ultrasound, if possible, to document and measure the fetal heart rate in routine early pregnancy assessment.

37.8 Conclusions

Doppler ultrasound is a promising diagnostic tool that complements grayscale 2D and 3D ultrasound during early pregnancy and holds the promise of being as helpful for the investigation of infertility and early pregnancy loss as Doppler analysis of uterine and umbilical blood flow has demonstrated to be during the first and second trimesters of pregnancy.

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