Chapter 17

Doppler Velocimetry of the Uteroplacental Circulation During Early Pregnancy

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Throughout pregnancy marked changes in uterine blood flow are observed that are related to a decrease in the resistance to flow in uterine vessels and to an increase in their diameter. Fetal growth is directly related to the incremental increase in uterine blood flow, and any long-term alteration in normal flow patterns could disrupt the oxygen and nutrient supply to the growing conceptus and result in an adverse pregnancy outcome.

Early normal pregnancy is characterized by profound morphologic changes in uterine vessels destined to supply the developing placenta. The trophoblast invades the inner third of the myometrium as early as 8 weeks' gestation and migrates through the entire length of the spiral arteries, a process completed by approximately 20 weeks. During these "physiologic changes" the spiral arteries lose their musculoelastic tissue and are transformed into markedly dilated uteroplacental arteries. These changes are probably responsible for the marked reduction in the resistance to flow in the uterine arteries during the first half of gestation and determine the large increase in uterine blood flow that is evident throughout pregnancy. The developing uteroplacental circulation is also regulated by systemic and local vasoactive substances. Of particular interest are the endothelium-derived relaxing and contracting substances.

In the event that the physiologic processes are absent or incomplete, the course of pregnancy may be abnormal, and such complications as pregnancy-induced hypertension and fetal growth restriction could arise. That has become evident is that abnormal conditions during late pregnancy that could adversely affect both the mother and her fetus may reflect abnormal morphologic processes that have occurred at early stages of gestation. Under such circumstances it is theoretically possible to predict such conditions by detecting abnormal blood flow patterns during early pregnancy. Obviously we first have to know the normal characteristics of uteroplacental perfusion.

With the development of sophisticated Doppler ultrasonographic techniques, including color flow imaging, it has become possible to study the uteroplacental vascular bed more accurately and in greater detail than ever before. In this chapter we focus on the morphologic and physiologic changes of the uteroplacental circulation during the first half of pregnancy and on systemic and local factors that regulate uterine blood flow. Methodologic and anatomic aspects related to Doppler flow measurements of the uteroplacental circulation are highlighted, and patterns of uterine blood flow in normal and abnormal gestations are described. Finally, the use of Doppler sonography to predict pregnancy-induced hypertension, preeclamptic toxemia, and intrauterine growth restriction are discussed.

Maternal Vascular Response to Placentation

The human placenta is hemochoroidal. Its maternal arterial blood supply is derived from the paired uterine arteries and, to some extent, from the ovarian arteries. The uterine arteries branch in the myometrium, giving rise to the arcuate arteries that encircle the uterus. The arcuate arteries have multiple branches called the radial arteries, which are directed centripetally. As the radial arteries enter the endometrium and approach the uterine cavity, they become the spiral arteries. During early pregnancy, as the maternoplacental circulation is established, profound morphologic and histologic changes take place in the spiral arteries. These morphologic changes are essential during normal pregnancy, as they provide for the ever-increasing demand imposed on the maternoplacental circulation by the advancing gestation. These "physiologic changes" are the result of retrograde intraluminal endovascular trophoblastic growth [1]. The endovascular trophoblasts invade the walls of the spiral arteries, converting them into funnel-shaped, dilated uteroplacental arteries. This transformation occurs in two steps: In the first step, the internal elastic lamina of the spiral arteries disintegrates, so a thin layer of basement membrane is all that remains between the endothelium and the smooth muscle. Next the trophoblast penetrates the arteries, and the media is replaced by a matrix containing cytotrophoblast and fibrin fibers. These morphologic changes

are limited to the decidual portion of the spiral arteries during the first trimester. During the early second trimester a new wave of endovascular trophoblast migration penetrates as far as the myometrial portion of the spiral arteries [2]. The second wave of trophoblastic migration is complete in most women by 20 weeks' gestation [3]. Normal uterine blood supply to the placenta is shown in Fig. 17.1. The physiological changes are functionally complete by 17 weeks as was demonstrated by measuring spiral artery blood flow using color Doppler ultrasound in the second trimester [4].

By 19 weeks' gestation the coiling of the spiral arteries disappears [5]. This event is probably due to stretching of the uterine wall, as the shape of the uterus changes from spheroidal to cylindrical as it grows [6].

The disappearance of musculoelastic tissue from the decidual and myometrial spiral arteries allows them to attain a substantial increase in diameter. A 30-fold increase in diameter, compared to that of the nonpregnant state, has been described [7]. The physiologic correlate of these structural alterations is a reduction in vascular resistance in the spiral arteries and increased uteroplacental flow rates throughout gestation [8]. This change has also been verified by radioisotopic techniques [9–11] and Doppler flow studies [12–14].

In normal pregnancy the trophoblast invades all spiral arteries in both the decidual endometrium and the myometrium. A defective maternal vascular response at the time of placentation is found in pregnancies complicated by preeclampsia and in a proportion of those with small-for-gestational-age (SGA) fetuses [15, 16]. In those pregnancies the vascular changes in the spiral arteries are restricted to the decidual segments or are totally absent. The arterial vascular response may be partial, so only a portion of the spiral arteries undergo normal "physiologic changes", whereas others are not affected by endovascular trophoblast and remain in the same state as in the nonpregnant uterus. It is believed that a defective maternal response to placentation is due to failure of the second wave of intravascular trophoblastic migration [17]. The myometrial segments of the spiral arteries are unaltered in their musculoelastic architecture and so are responsive to vasomotor influences (e.g., vasoactive peptides). Figure 17.2 demonstrates abnormal uterine blood supply to the placenta secondary to abnormal placentation.

Intraluminal trophoblast is a normal finding, then, during the first and second trimesters of normal pregnancy, where it plays a role in establishing placentation [18]. A defective interaction of trophoblast and uterine tissue, well established in preeclampsia and some forms of fetal growth restriction, may be due to immunologic maladaptation [18, 19]. Disturbance of trophoblastic invasion during early pregnancy is frequently associated with renewed trophoblastic migration during the third trimester [16, 20]. The luminal lining in the uteroplacental arteries remains trophoblastic and not endothelial [20]. The disrupted endothelium may be responsible for endothelial cell dysfunction, thought to be of pathogenetic importance in preeclampsia [21]. In addition, many of the affected vessels demonstrate necrotizing vascular lesions – deposition of fibrinoid material and adjacent foam cell invasion – a process also termed atherosis [22].

Hemodynamic studies using radioisotope clearance values [10, 11], dynamic placental scintigraphy [23],

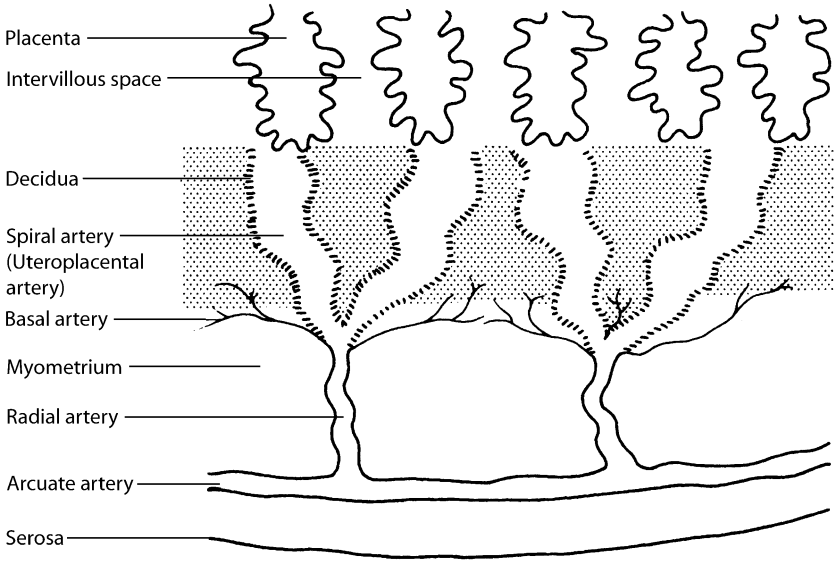

Fig. 17.1. Normal blood supply to the placenta. Note the termination of radial arteries each into two spiral arteries that have been physiologically converted to uteroplacental arteries (*dotted areas*). (Reprinted from [16] with permission)

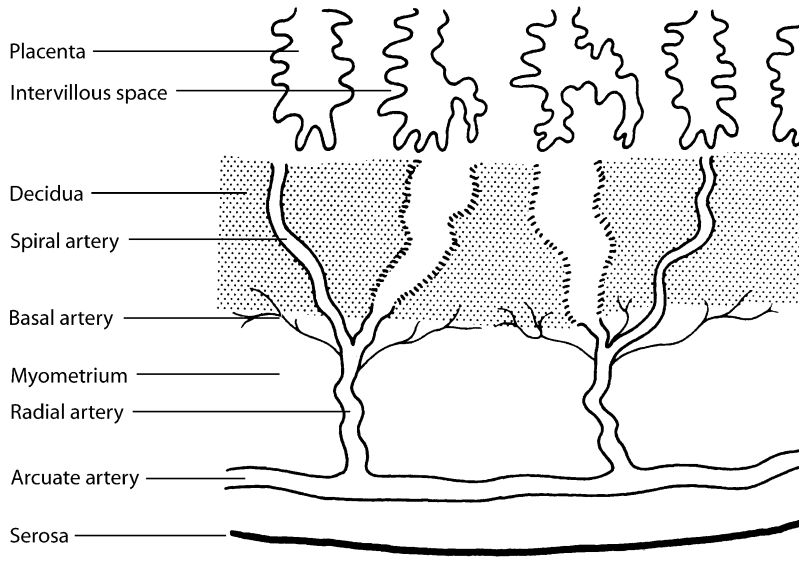

Fig. 17.2. Abnormal blood supply to the placenta. Physiologic changes (*dotted areas*) in some decidual segments of spiral arteries are absent. Myometrial segments are shown without physiologic changes as in preeclampsia or some cases of fetal growth retardation. (Reprinted from [16] with permission)

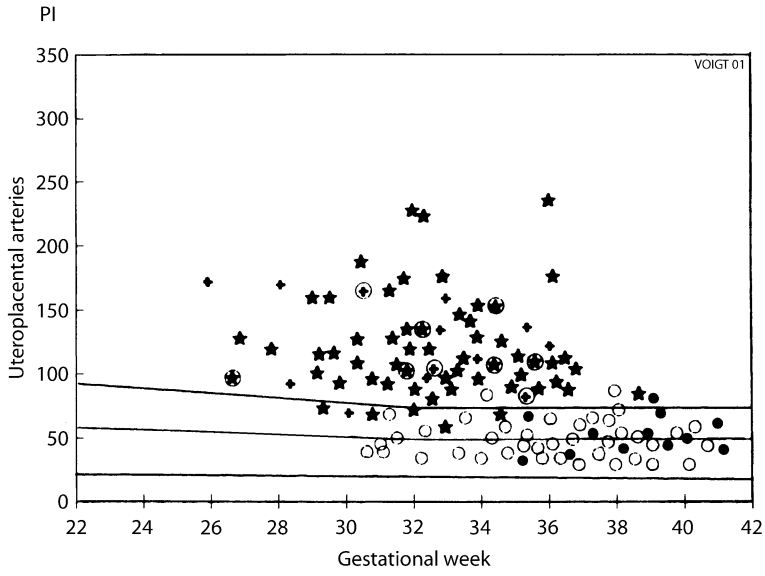

Fig. 17.3. Pulsatility indices (PI) of uteroplacental arteries prior to delivery plotted against the normal reference curve (3rd, 50th, and 90th percentiles). Cases with normal placental bed biospsies are marked by *open* and *closed circles*, and those with pathologic findings are marked by *stars* and *crosses*. The PI values in the group with uteroplacental insufficiency but no hypertension are marked by *encircled stars* and *crosses*. (Reprinted from [28] with permission)

and Doppler flow measurements [12, 24, 25] demonstrated reduced uterine blood flow in cases of preeclampsia and fetal growth restriction. Although these studies were performed during late gestation, it should be recalled that abnormal placentation begins during the early second trimester (with the second wave of trophoblastic invasion) or even during the first trimester. For example, acute atherosis in the decidua, usually found during the third trimester in cases of preeclampsia, has also been observed during the first trimester, from as early as 8 weeks (R. Laurini, personal communication). It is not surprising therefore that abnormal flow patterns (using Doppler flow measurements) can be detected as early as the second trimester [26, 27]. An association between abnormal Doppler flow patterns in the uterine artery and histomorphologic changes in the placental bed has been demonstrated [28–30] (Fig. 17.3). However, all studies reported a considerable overlap in the degree of physiologic changes between normal and complicated pregnancies. The association between pregnancy complications and increased uteroplacental resistance as indicated by abnormal Doppler flow cannot then be solely explained by abnormal uteroplacental vessel histopathology [29]. Impaired physiological adaptation of the spiral arteries may not be the single causal factor in preeclampsia and the concept of heterogeneous causes of preeclampsia as was recently suggested [31].

Regulation of Uteroplacental Blood Flow

During normal pregnancy maternal systemic and uterine vascular functions demonstrate impressive changes. Alterations in the systemic cardiovascular system include a 50% increase in blood volume [32], a similar increase in cardiac output, and a decrease in blood pressure beginning in early pregnancy and reaching a nadir at the midtrimester [33]. The blood pressure is reduced because peripheral vascular resistance during pregnancy is reduced significantly from the normal nonpregnant level [34]. The falls in blood pressure and peripheral resistance occur despite marked activation of the renin-angiotensin-aldosterone system during gestation. Plasma levels of renin, renin activity, angiotension II, and aldosterone increase early in pregnancy and remain elevated until term [35]. Angiotension II is thought to have an important role in maintaining blood pressure during normal pregnancy. Thus administration of captopril to normal pregnant women during the first and second trimesters triggers a significant hypotensive response [36].

At the same time, the uterine vasculature undergoes marked alterations, the most prominent being physiologic modification of the spiral arteries, as described before. These changes permit a four- to tenfold increase in uterine blood flow [11, 14], which is necessary to meet the respiratory and nutritional requirements of the growing uterus and gestational products.

Decreased blood pressure in the face of elevated plasma levels of angiotensin II suggests that pregnant women are resistant to its pressor effects [37]. Systemic and uterine vascular beds also exhibit refractoriness to other vasoconstrictors, including vasopressin and norepinephrine [38, 39]. In ovine pregnancy the uterine vascular bed is even less reactive than the systemic vasculature to the vasoconstrictive effects of angiotension II [40] (Fig. 17.4). It has been proposed that the reduced peripheral vascular resistance of pregnancy is due to increased production of vasoactive substances. The substances believed to fill this role are prostacyclin (prostaglandin I_2, or PGI_2) [41] and endothelium-derived relaxing factor (EDRF) [42], considered to be the most important mediators of vasodilation. Both are produced by endothelial cells, lining all vessels in the body. Through these vasodilating substances, the endothelium plays a major role in regulating vascular smooth muscle responses to endogenous vasoconstrictors [43]. An eicosanoid, PGI_2 is a powerful vasodilator and inhibitor of platelet aggregation [41]. After its discovery [42] EDRF was found to be nitric oxide (NO) [44, 45], formed with L-arginine as a precursor. In contrast to the effects of prostaglandin synthesis inhibitors, addition of the false precursor N^g-monomethyl-L-arginine causes a hypertensive response in both rats and humans [46].

Increased production of these vasoactive substances dilates the maternal vasculature, rendering it less sensitive to the pressor effects of endogenous vasoconstrictive hormones. A compensatory increase in the activity of the renin-angiotensin-aldosterone system along with increasing estrogen production by the fetoplacental unit combine to increase maternal blood volume and cardiac output. The resulting hemodynamic situation is one of high volume, high flow, and low resistance. This point is particularly emphasized in the uteroplacental circulation, where the vessels are maximally dilated [47], volume flow rates are increasing steadily [14], and the resistance to flow rapidly declines during the first half of gestation [13, 14].

Autoregulation is a physiologic mechanism for maintenance of constant organ blood flow with varia-

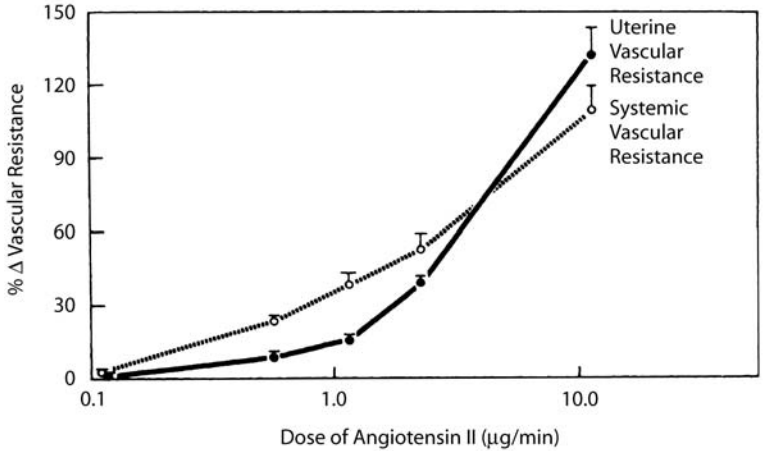

Fig. 17.4. Relative changes in uterine and systemic vascular resistance expressed as the percent of control values at various doses of systemically infused angiotension II. Uterine vascular resistance was significantly lower ($p < 0.01$) than systemic vascular resistance at angiotensin II doses of 2.3 μg/min. (Reprinted from [40] with permission)

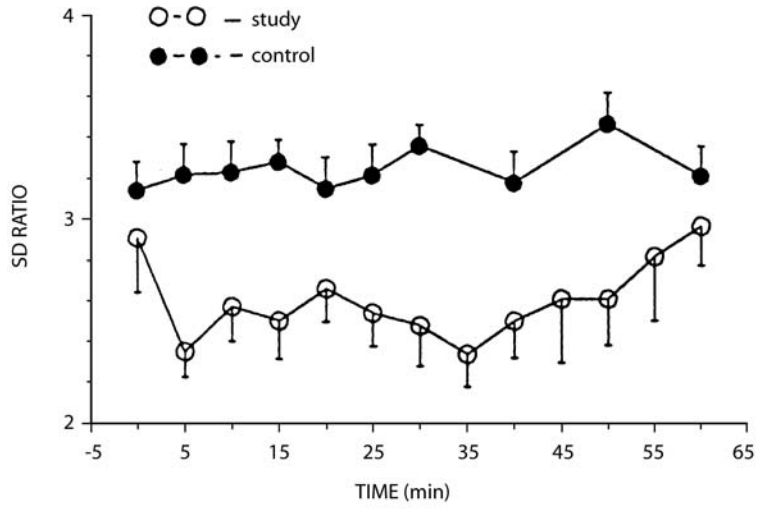

Fig. 17.5. Systolic/diastolic (*S/D*) ratio in the uterine artery in women receiving sublingual nifedipine (*open circles*) or placebo (*closed circles*). The decrease in S/D ratio coincided with a decrease in systemic blood pressure. (Reprinted from [51] with permission)

tions in arterial pressure. It may have an important role in the regulation of uterine blood flow during pregnancy. Although not detected in sheep [48], autoregulation has been demonstrated during pregnancy in rabbits [49] and humans [50]. In the latter study, a fall in maternal blood pressure following sublingual nifedipine was not associated with any significant change in uterine blood flow. Lowering of maternal blood pressure by sublingual nifedipine during the midtrimester was associated with a fall in uterine arterial resistance, preventing large changes in flow rates [51] (Fig. 17.5). Autoregulation may operate, with various autacoids probably mediating the action of one another.

Intensive research has been conducted regarding the role of endothelial autacoids in the regulation of uterine blood flow and in the decreased sensitivity of uterine and systemic vasculature to various vasoactive substances. The important autacoids are described in the following sections with particular emphasis on their relation to uteroplacental hemodynamics during pregnancy.

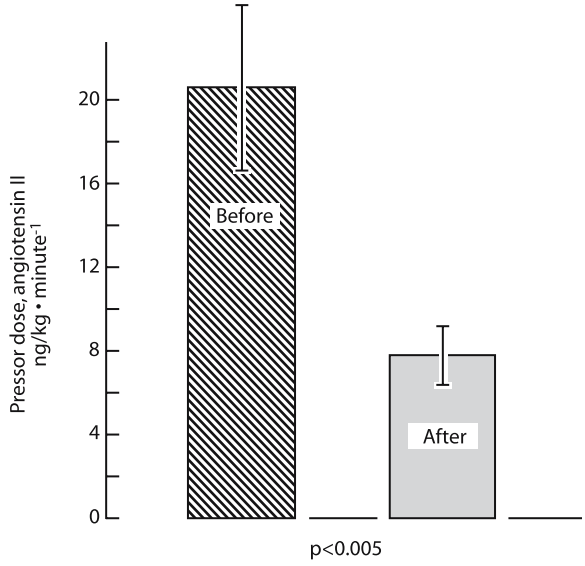

Fig. 17.6. Mean effective pressor dose of angiotensin II before and during indomethacin treatment in 11 normotensive pregnant women. (From [129], with permission)

Prostacyclins

Endothelium-derived prostacyclin (PGI_2) is the primary prostaglandin produced by the uterine and systemic vasculature. Direct infusion of PGI_2 into the uteroplacental circulation does not change uteroplacental vascular resistance or placental blood flow [52, 53], a finding in agreement with the hypothesis that uterine arteries are maximally dilated during pregnancy [47]. However, a role for prostaglandins in uterine arterial autoregulation, acting directly on the vessel wall, may be obtained from reports where indomethacin, an inhibitor of prostaglandin synthesis, enhances the vasoconstrictor effects of angiotensin II and norepinephrine [54, 55] (Fig. 17.6). Experimental data support the view that prostaglandins are unlikely to be responsible for normal maintenance of uterine blood flow. However, prostaglandins, possibly PGI_2, may be important in controlling vascular reactivity to vasoconstriction. As previously stated, the uterine vasculature is less responsive than the systemic vasculature to infused angiotensin II [40]. Because of this differential sensitivity to the vasoconstrictor effects of angiotensin II, uterine blood flow may increase during systemic infusion of physiologic doses of angiotensin II. This increase in uterine blood flow is reflective of the interaction between the rise in perfusion pressure at a time when the increase in uterine vascular resistance is significantly less than that of the sys-

temic vascular resistance [40]. The difference between the uterine and systemic vascular beds may reflect an adaptive mechanism necessary for the maintenance of uteroplacental perfusion and fetal well-being, as angiotensin II normally increases during pregnancy and likely increases even more, although intermittently, during the course of normal daily activities. The systemic concentrations of the stable metabolite of prostacyclin, 6-ketoprostaglandin $PGF_{1\alpha}$, is increased during pregnancy [56]. Furthermore, the synthesis of prostacyclin by ovine uterine artery is increased during pregnancy [57] (Fig. 17.7). This increased synthesis by the uterine artery cannot by itself explain the blunted response to vasoconstrictors, as indomethacin-treated vessels from pregnant animals are still less sensitive to vasoconstrictors than untreated vessels from nonpregnant animals [55]. Other vascular factors, such as EDRF, may compensate for the loss of endothelial PGI_2 in the uterine vascular bed.

Prostacyclin has been demonstrated in trophoblastic tissues at 6 weeks' gestation and is known to increase during the first trimester [58]. Both villous core cells and cytotrophoblasts produce thromboxane A_2 and prostacyclin during the first trimester [59]. It has been hypothesized that successful invasion of trophoblast into the spiral arteries may be dependent on a delicate balance between thromboxane A_2 and PGI_2 [59].

While prostanoids have been proposed to play a major role in the regulation of uteroplacental blood flow, studies on the effect of hypoxia on the production of prostaglandin E(2)(PGE(2)), thromboxane B(2)(TXB(2)), and prostacyclin (measured as 6-keto-PGF(1alpha)) by human term trophoblast cells and villous placental explants have shown that hypoxia could be responsible for abnormal profiles of prostanoid production commonly observed in women with preeclampsia [60]. The results indicate a putative link between hypoxia and compromised placental perfusion.

Endothelium-Derived Relaxing Factor

Endothelium-derived relaxing factor, thought to be mainly nitric oxide, originates from endothelial cell metabolism of L-arginine [44]. The vasodilating effects of EDRF and nitric oxide are ultimately mediated by stimulation of soluble guanylate cyclase (cGMP) [44]. Competitive inhibitors of nitric oxide synthetase such as *N*-monomethyl-L-arginine (L-NMMA) or L-nitroarginine methylester (L-NEMA) reduce the production of nitric oxide (Fig. 17.8). The relation between EDRF and cardiovascular changes during pregnancy is being extensively investigated; in the meantime, experimental data have accumulated demonstrating that EDRF is elevated during normal pregnancy and that the uterine vasculature has a greater ability to release endogenous EDRF. The EDRF-mediated decrease in the uterine artery contractile response to norepinephrine during pregnancy has been described [55, 61] and could result from either increased basal or stimulated release of EDRF.

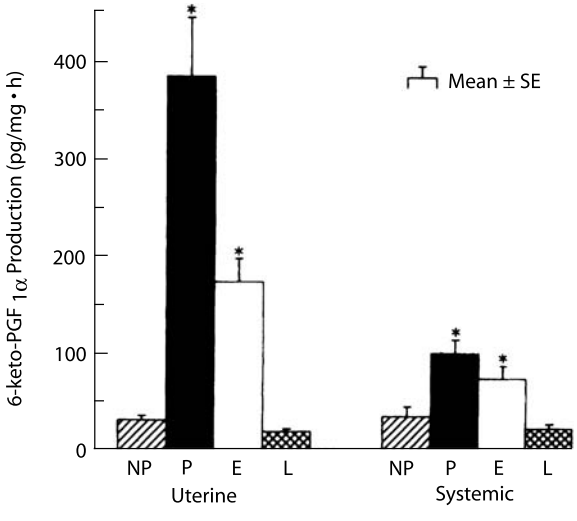

Fig. 17.7. In vitro basal production of 6-keto-prostaglandin $F_{1\alpha}$ (*$PGF_{1\alpha}$*) by nonpregnant (*NP*), pregnant (*P*), early postpartum (*E*), and late postpartum (*L*) uterine and omental (*systemic*) arteries, $*p < 0.05$, values different from NP and L. (Reprinted from [57] with permission)

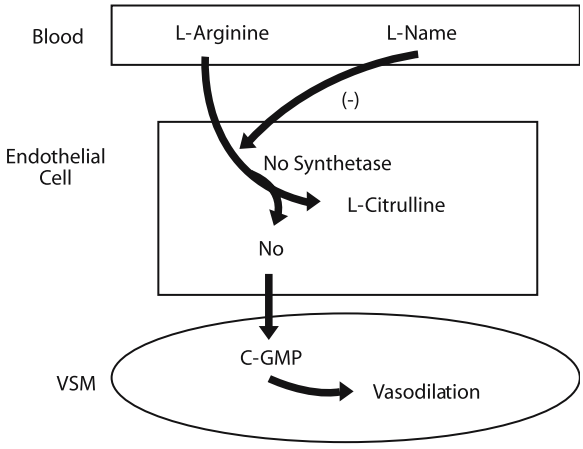

Fig. 17.8. Nitric oxide synthetase pathway in which L–arginine is converted to L-citrulline, giving off nitric oxide in endothelial cells, which leads to stimulation of cyclic guanosine monophosphate (*c-GMP*) in vascular smooth muscle and vasodilation. L-Nitroarginine methyl ester (*L-NAME*) competes with L-arginine as substrate for nitric oxide (*NO*) synthetase and is able to block the synthesis of nitric oxide. VSM, vascular smooth muscle. (Reprinted from [64] with permission)

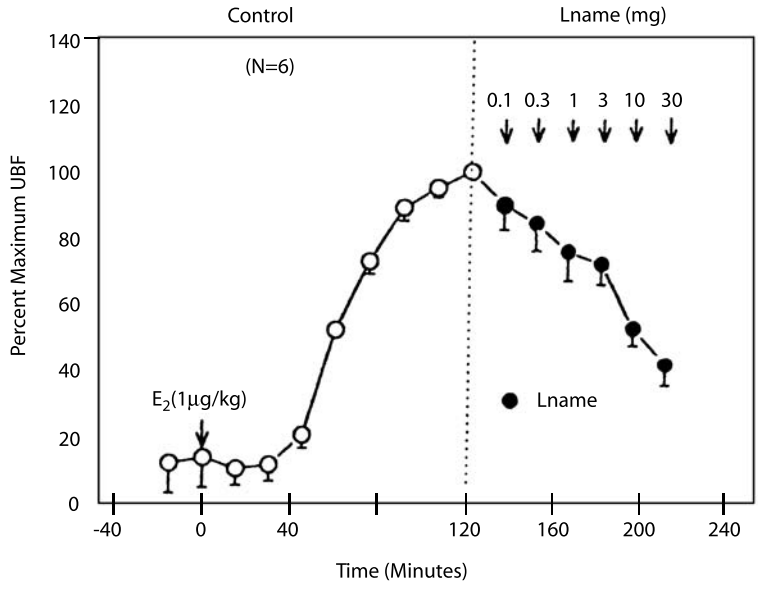

Fig. 17.9. Increases in uterine blood flow as percent of maximum response to estradiol-17β (E_2) 1µg/kg plotted against time. Beginning at 120 min after E_2, L-nitroarginine methylester (*L-NAME*), a nitric oxide synthetase inhibitor, was administered as an intraarterial bolus injection of increasing doses. UBF, uterine blood flow. (Reprinted from [64] with permission)

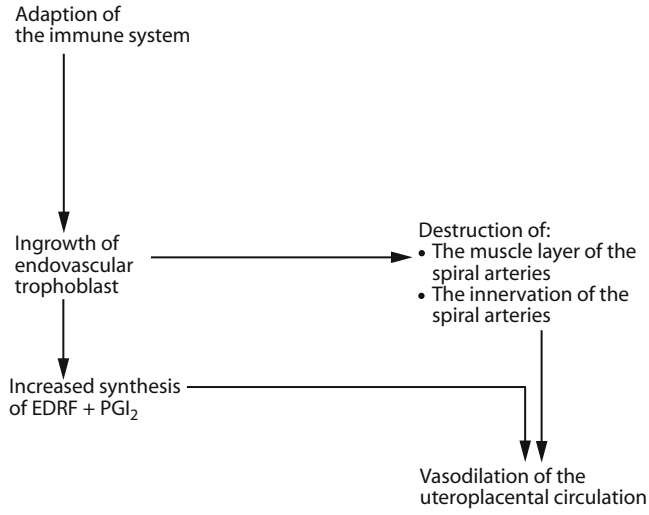

Fig. 17.10. Factors leading to vasodilation of the uteroplacental circulation in normotensive pregnancy. (From [130] with permission)

Indirect evidence supports both mechanisms. Compounds that are known to release EDRF (e.g., acetylcholine, bradykinin, histamine) increase uterine blood flow when infused directly into the uterine vascular bed of chronically instrumented sheep [62, 63]. Acetylcholine increases uterine vascular conductance in nonpregnant and pregnant sheep [63]. Also, local injection of L-arginine analogs causes local decreases in uterine blood flow while avoiding alterations in blood pressure that could directly influence uterine blood flow [69].

An important observation in this regard was the finding that estradiol-17β-induced increases in uterine blood flow are mediated by nitric oxide [64]. Moreover, L-NEMA antagonizes the vasodilating effects of estradiol-17β on the uterine vasculature in a dose-dependent manner [64] (Fig. 17.9). This antagonism of estrogen-induced vasodilation demonstrates that nitric oxide is important for mediating the vasodilating effect of estradiol-17β, and it could play a role in regulating uterine and possibly uteroplacental blood flow during pregnancy.

When administered systemically, L-arginine analogs increase blood pressure and reverse pregnancy-induced refractoriness to vasopressor agents [65]. These observations support the notion that blunted pressor responsiveness during normal gestation is due largely to increased elaboration of endothelium-derived nitric oxide, which also plays a key role in regulating blood pressure during pregnancy. It has been demonstrated that endothelium-derived relaxing factors (e.g., prostacyclin and EDRF) reduce the con-

tractile response of the uterine artery to thromboxane. Data suggest that the attenuated vascular reactivity of pregnancy is modulated by the interaction of EDRF and PGI_2, and that one system can adapt when the other is inhibited. Figure 17.10 summarizes the various factors leading to vasodilation of the uteroplacental arteries.

Endothelin

Control of uterine vascular function by the endothelium is more complex than anticipated because the cells not only release various vasodilator substances but also mediate contractions of the underlying smooth muscle with diffusible endothelium-derived contracting factors [66]. Endothelium-dependent contractions are elicited by thromboxane [56] or by the release of endothelin [67] and superoxide anion [68]. Endothelin-1, a 21-amino-acid peptide, is the most potent natural pressor substance known [67]. It is a vasoconstrictor in the human uterine artery, and the effect is mediated by receptors on smooth muscle cells [69, 70]. This peptide may play an important role in the regulation of vascular resistance on the maternal side of the uteroplacental unit [71].

More studies are needed to evaluate the relation between these (and perhaps other) endothelial mediators of vascular function during pregnancy. Such information can increase our understanding of the physiologic factors that regulate uterine blood flow during normal pregnancy and the pathophysiologic mechanisms involved in disease states where uteroplacental blood flow may be deranged.

Doppler Velocimetry of the Uteroplacental Circulation

Methodology

The Doppler devices commonly used for clinical or investigational measurements during early pregnancy are the continuous-wave and pulsed-wave systems. The former consists of a simple transducer that continuously sends ultrasonic sound waves; it is attached to a second transducer, which continuously receives the reflected echoes returning from the sound's beam path. The main advantages of this system are its ease of operation, portability, low output sound intensity ($< 25\ mW/cm^2$), and relatively low price. In addition it permits high-frequency shifts (i.e., high blood flow velocities) to be measured, even in deep vessels. It does not, however, permit visualization of the sound beam as it crosses the tissues or of the blood vessels themselves. Moreover, it is not range-specific, and the rather large volume of overlap between the two probes' crystals may contribute to the Doppler shift, which is displayed after spectrum analysis. In fact, any vessel that happens to lie across the sound's beam path is sampled and "contaminates" the sonogram obtained. These limitations make the continuous-wave Doppler system unsuitable for sampling small, specific vessels or for obtaining flow measurements from vascular segments at a particular location (e.g., the main branch of the ascending uterine artery or the umbilical artery adjacent to its placental location) [72].

Early Doppler studies of uterine arteries were performed with a continuous-wave Doppler apparatus using either the abdominal [12, 13] or the transvaginal [14] approach. Subplacental vessels [12] and uterine vessels [13] can be studied with this method. Flow velocity waveforms in the uterine vessels were captured by pointing the probe into the paracervical area via the lower abdomen [13]. The vaginal route has the advantage of being close to the main branch of the uterine artery as it enters the lower part of the uterus [13]. Vaginal studies are performed by inserting the transducer (covered by a rubber condom and lubricated with coupling jelly) into the vaginal fornix and directing it along the paracervical area. During the first trimester the failure rate was reported to be 10%. The mean intraobserver and interobserver error between examinations was 4%, with a standard deviation of 2.3% [13].

With pulsed-wave Doppler systems, the transducer sends short pulses of high-frequency sound waves repetitively. The same transducer is used to receive the reflected echoes during the intervals between sending the pulses. With such pulse-echo systems the range (or depth) of the target can be estimated from the corresponding time delay in the reception of echoes following transmission of the ultrasonic pulse, assuming a constant value for the speed of ultrasound (1,540 cm/s). This range-gated detection permits selection of Doppler frequency shift signals from moving targets according to their distance from the ultrasonic probe.

This principle is implemented in duplex scanning, where a pulsed-wave Doppler transducer is integrated into a two-dimensional ultrasound imaging unit to permit accurate identification of the volume in space from which Doppler-shifted frequencies are to be received. This volume is commonly termed the sample volume, and both its width and distance from the transducer can be controlled by the user. This orientation in space and the depth selectivity make the pulsed duplex systems much superior to the continuous-wave Doppler systems [72, 73].

A significant limitation when using pulsed Doppler systems is the maximum range limitation, or the range-velocity limitation [72, 73]. Analog signals

(such as Doppler shift signals) can be unambiguously represented by samples only if they are sampled at a rate that exceeds twice the highest frequency in the signal itself (also known as the Nyquist limit). It means that when high flow velocities are encountered, the pulse repetition frequency must be increased sufficiently to accommodate this limitation. If the vessel is situated far from the transducer (e.g., when performing Doppler studies on deep pelvic vessels using an abdominal probe), the potential increase in pulse repetition frequency is limited by the pulse-echo round-trip delay time. Under such conditions false signals are displayed, a phenomenon termed aliasing [72, 73]. One way to partially overcome this problem is to use a lower-frequency transducer when operating in the Doppler mode on duplex systems. The Doppler shift frequency would then be lower for any given velocity of the target, and the range-velocity ambiguity problem would be less likely to arise [72, 73].

The optimal method for performing pelvic Doppler flow measurements during early pregnancy is the transvaginal image-directed pulsed Doppler system [74]. With such a duplex Doppler system, two-dimensional real-time scanning enables appropriate placement of the ultrasonic Doppler beam. Using real-time imaging, pelvic anatomic structures can be scanned, and particular vessels can be identified (Fig. 17.11). As the female pelvis contains various soft tissue structures that have similar acoustic properties (and are therefore poor reflectors) the transvaginal ultrasonic probe offers the most suitable approach. The close proximity of the transducer probe to the pelvic organs makes it possible to increase its frequency (typically 5–7 MHz). At this range attenuation is still acceptable, and images resolution is greatly improved. As the vagina is a rather elastic organ, the probe can be manipulated so as to bring it as close to a specific structure as possible, thereby placing it within the focal region of the transducer. With the probe situated close to the vessel, the range-velocity ambiguity problem is largely overcome [73, 74]. This technique also makes it possible to use a higher-frequency Doppler transducer and obtain a higher-frequency shift at any angle of insonation, thereby increasing the accuracy of the measurement. Moreover, the examination is performed with an empty bladder, preventing distortion of normal anatomy and vessel displacement. Using this approach, one can study patterns of blood flow in uterine vessels (including spiral arteries and decidual vessels), ovarian vessels, and embryonal and fetal vessels (e.g., umbilical artery, intracranial vessels, aorta) [75].

The introduction of color flow mapping has made vessel localization much simpler. The user can identify the required vessel with certainty, and the duration of the examination is considerably shortened [76]. The main application of duplex scanning is the detailed study of well-defined anatomic regions. Such systems do not readily convey information about blood flow throughout the entire scan plane. Doppler color flow mapping is particularly helpful, as it produces real-time two-dimensional images that are color coded according to flow conditions and superimposed on real-time two-dimensional gray-scale pulse-echo images of anatomic structures. It facilitates evaluation of vessels within organs or those that are not readily delineated by conventional scanning. Color Doppler sonography is based on the Doppler autocorrelation flow detector, which rapidly extracts Doppler signals line by line as the ultrasonic beam is scanned through the image plane. The resulting display image is a combination of Doppler and anatomic information. The output from the autocorrelation detector consists of directional real-time velocity (or Doppler frequency) signals. These signals are arranged to color code the real-time gray-scale image. Forward flow is usually presented in red and reverse flow in blue. The degree of turbulence is color coded in green.

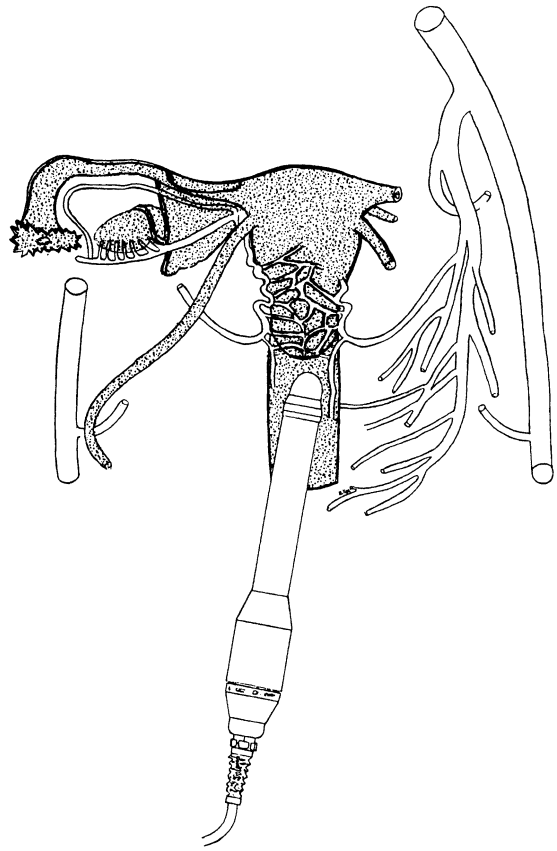

Fig. 17.11. Transvaginal probe in relation to the female pelvic vessels. (From [131] with permission)

Best results are obtained using electronically scanned linear or phased array [72, 73].

During the transvaginal Doppler examination the patient lies in the supine position on a gynecologic examination table or a two-level mattress, with the upper part of the body on the higher level [77]. This positioning enables the examiner to manipulate the probe at various angles, applying the push-pull technique, and locate the vessel of interest [77]. A coupling gel is applied to the vaginal probe, which is subsequently covered with a lubricated rubber glove and is inserted into the vaginal fornix. A real-time image of the uterine artery is obtained employing color flow imaging if practical, and the line of insonation of the Doppler beam is adjusted so it crosses the vessel at the smallest possible angle. Several measurements of vessel diameter are obtained at this stage, and the mean diameter is calculated. The sample volume is then placed to cover the entire cross-sectional area of the vessel (Fig. 17.12). Once achieved, the system is switched to the dual-mode operation, where both the two-dimensional scanning and the range-gated pulsed Doppler operate in a quasisimultaneous mode. The flow velocity waveforms are displayed after spectral analysis in real time. Once a good-quality signal is obtained based on audio recognition, visual waveform recognition, and maximum measured velocity, the image is frozen, including good-quality waveform signals. Figure 17.13 demonstrates flow velocity waveforms in the main uterine artery obtained by transvaginal pulsed Doppler ultrasonography before and during pregnancy. Once the vessel is located and displayed, the angle of insonation is determined by aligning a linear cursor parallel to the long axis of the vessel itself. All the flow parameters are calculated at this stage, and the results are displayed on a separate video display unit. The images and values obtained can be recorded on a video tape for subsequent review. An immediate hard copy can also be obtained using video printer. A high-pass filter of 100 Hz is activated to remove low-frequency/high-intensity echoes originating from vessel wall movements [77].

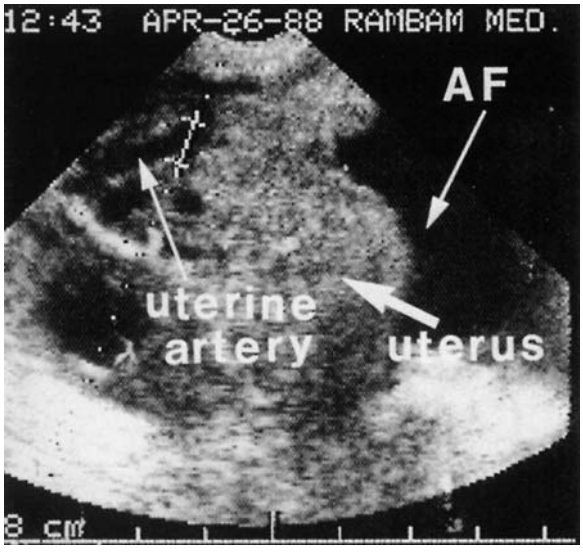

Fig. 17.12. Transvaginal sonographic scan demonstrating a short segment of the uterine artery, sample volume (situated between the *two short parallel lines*), uterine wall, and amniotic sac (*AF*). (Reprinted from [75] with permission)

Some investigators use a combination of continuous-wave Doppler ultrasound and color flow imaging of the uterine artery to calculate the resistance to flow as well as the mean velocity and volume flow [78]. By placing the transducer in the lower lateral quadrant of the uterus and angling it medially, an apparent crossover of the external iliac artery and vein and the main uterine artery can be identified. This "crossover" is used as a reference point to identify the main uterine artery and is easily reproducible. A clear image of a length of the artery can be obtained and the diameter of the artery measured. Direct visualization of the artery and knowledge of the angle of insonation of the vessel enable the calculation of resistance, mean velocity of flow, and total volume of flow to the uterus in both uterine arteries [78].

Anatomic Considerations

Because investigators use different methodologies it is not surprising that the reported flow impedance values in the uterine arteries for normal pregnancy vary considerably [12, 13, 79–81]. In early studies a large uteroplacental vessel was sampled in the lateral uterine wall by duplex equipment close to the bifurcation of the common iliac artery [24, 80]. The investigators called these vessels the "arcuate arteries". Other groups obtained signals from subplacental vessels using a continuous-wave Doppler apparatus [12, 79]. Another group of investigators used a continuous-wave Doppler system to locate the uterine artery in the lower uterine segment on both sides and averaged the readings [13]. Other groups studied the main branches of the ascending uterine arteries at the level of the internal os [14, 82] using a transvaginal pulsed Doppler system. Figure 17.14 demonstrates the various insonation sites used to study the uteroplacental circulation.

Investigators may then use different Doppler ultrasound equipment and insonate different parts of the uteroplacental circulation. Moreover, different indices of impedance to flow have been used, with each group defining their own normal range, often constructed from measurements obtained in small numbers of retrospectively defined, normal women fol-

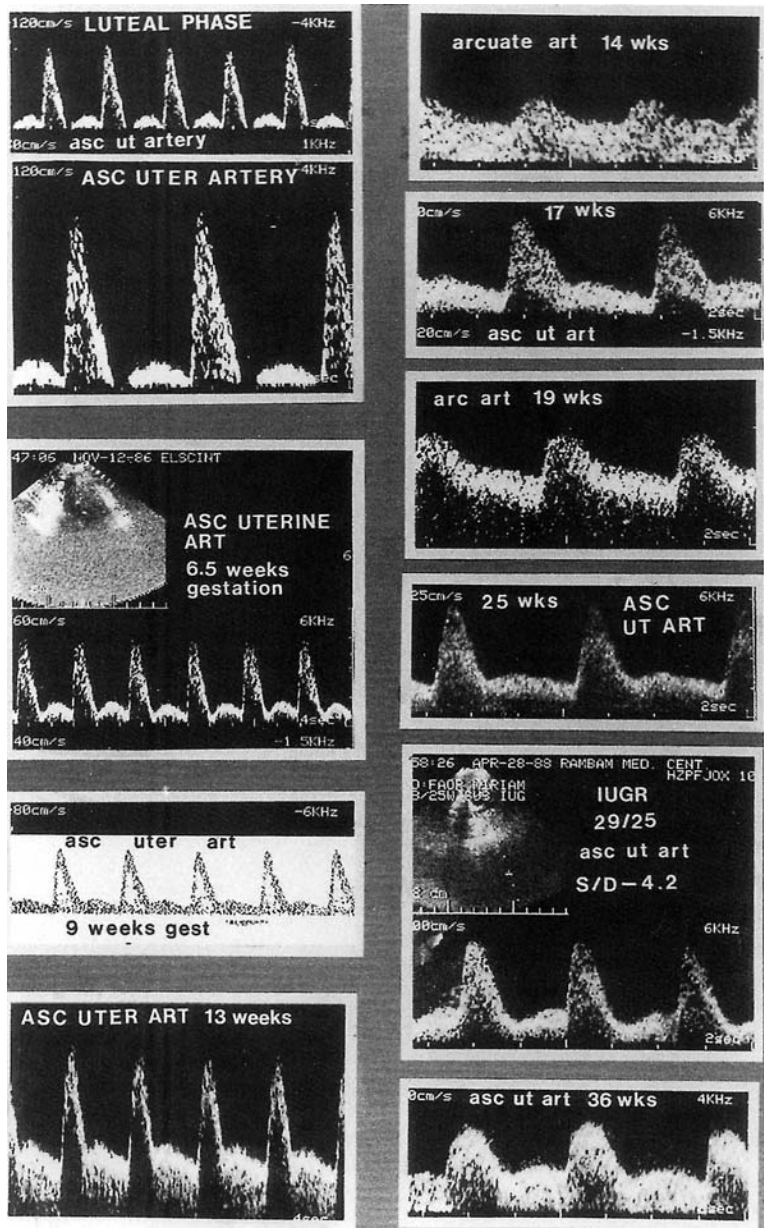

Fig. 17.13. Flow velocity waveforms in the ascending uterine artery and arcuate vessels obtained by transvaginal pulsed Doppler transducer before and during various stages of pregnancy. (Reprinted from [75] with permission)

lowed longitudinally. Some groups also include a description of flow velocity waveforms, particularly the presence of a dicrotic or early diastolic notch as an indicator of high resistance to flow [24, 25, 83]. With so many techniques, the results obtained are hardly comparable. For example, the mean resistance index (RI) at 20 weeks' gestation has been reported as ranging between 0.31 [80] and 0.57 [13].

These methodologic problems were highlighted in a large cross-sectional study in which reference ranges for uteroplacental waveforms during the second trimester were established [84]. A 4-MHz continuous-wave Doppler system was used to insonate the uteroplacental vessels of an unselected group of 977 women. The uterine artery was investigated near its origin ('U'terine site, Fig. 17.14) and in the anterolateral uterine wall halfway between the fundus and the most lateral point, parallel to the abdominal surface insonating only the uterine wall ('A'rcuate site, Fig. 17.14). The placental site was also noted. The RI was always higher at the uterine site than at the arcuate site regardless of placental location [84] (Fig. 17.15). At each site the RI was always lower on the placental side (Fig. 17.15). The fall in resistance with placental site and with distance from the origin of the uterine artery can be explained by the increasing

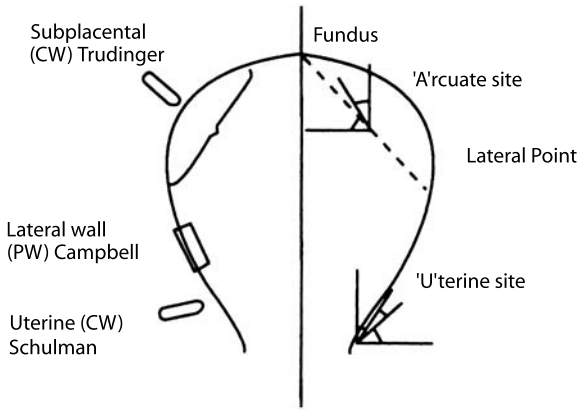

Fig. 17.14. Insonation sites used to study the uteroplacental circulation. (Reprinted from [84] with permission)

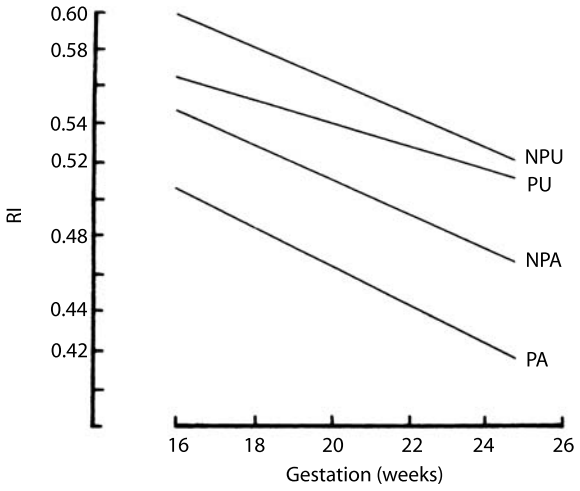

Fig. 17.15. Mean resistance index (*RI*) at four insonation sites: nonplacental uterine (*NPU*), placental uterine (*PU*), nonplacental arcuate (*NPA*), and placental arcuate (*PA*) sites. It shows the difference between uterine and arcuate sites and the effect of placental location. (Reprinted from [84] with permission)

cross-sectional area as the uterine artery branches from its origin, and pressure and impedance fall continuously from the uterine artery to the intervillous space. These facts can be summarized to indicate that it is not possible to study the uteroplacental circulation without having clear definition of the site studied and the position of the placenta. It is likely that Doppler measurements should be obtained from the main uterine vessels. Such measurements should provide more predictive information on impaired uteroplacental perfusion as the major vessels reflect the sum of resistances of the placental bed and therefore are more likely to provide an overall picture of placental perfusion [79, 83]. Moreover, measurements of the main uterine artery are more reproducible [83], and the likelihood of demonstrating a systolic or diastolic notch in flow velocity waveforms increases [83].

Changes in Uteroplacental Blood Flow During Early Normal Pregnancy

The development of uterine artery compliance throughout pregnancy was studied by continuous-wave Doppler sonography [13]. Although no significant changes were observed during the first trimester, there was a rapid decline in the systolic/diastolic flow velocity ratio (S/D ratio) starting early in the second trimester. These changes plateaued at 22–24 weeks. When a transvaginal image-directed pulsed Doppler system was used, the resistance to flow (expressed by the S/D ratio or the pulsatility index, or PI) rapidly declined in the ascending branch of the uterine artery from as early as 5 weeks and continued to 22 weeks' gestation [14, 85].

Figure 17.16 demonstrates the decline in S/D ratio from 5 to 28 weeks. During this period the vessel diameter increased linearly (Fig. 17.17), and the volume of blood flow to the uterus increased by more than 50% [14] (Fig. 17.18). At 20–22 weeks the second wave of trophoblastic migration is mostly complete [3], and any further increase in volume flow rates may be attributed to an increase in vessel diameter and cross-sectional area of the entire uterine vascular bed [14]. The rate of increase of uterine blood flow was found to be maximal between 20–24 weeks (39 ml/min/week) as was the increase in uterine artery diameter, in a study where uterine blood flow was measured between 20 and 38 weeks' gestation [86]. The rate of increase in mean quantified volume

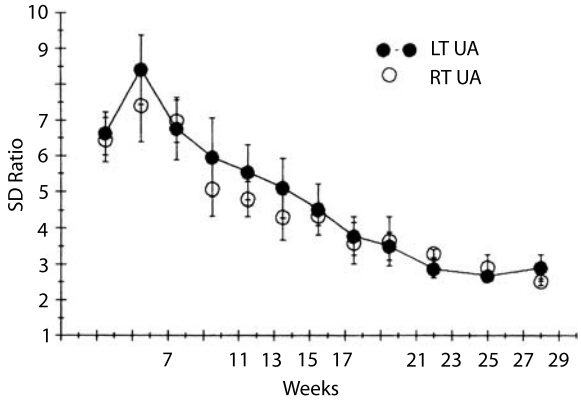

Fig. 17.16. Changes in S/D ratio in the uterine arteries (*UA*) during the first and second trimesters of pregnancy

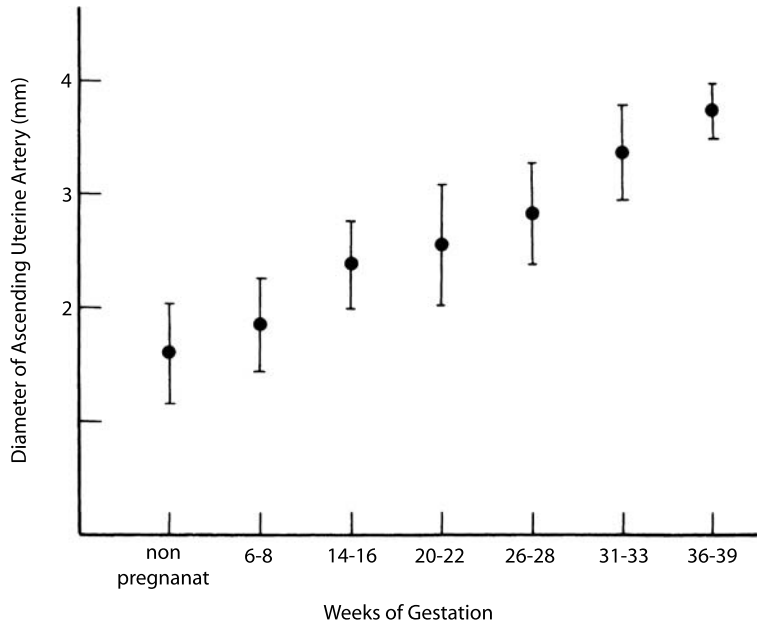

Fig. 17.17. Changes in diameter of the main uterine artery at various gestational ages. (Reprinted from [14] with permission)

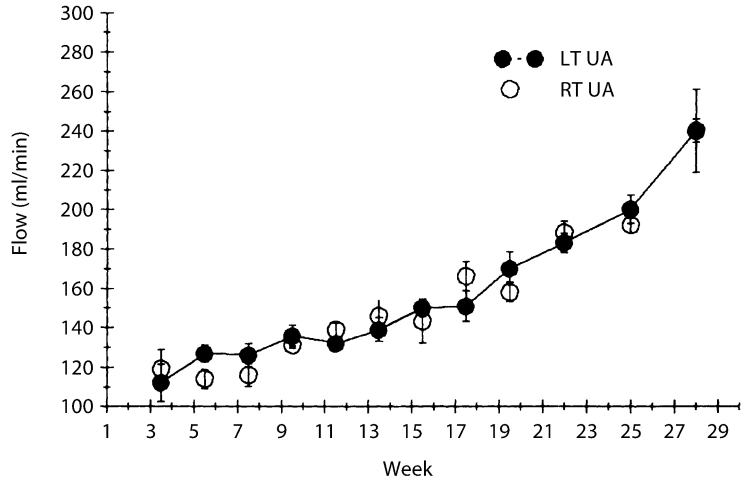

Fig. 17.18. Changes in blood flow in the uterine arteries (*UA*) during the first and second trimesters of pregnancy

flow per week declined to 14 ml/min/week between 36–38 weeks' gestation [86].

During the first and early second trimesters the decline in resistance to flow occurs not only in the main uterine artery [14, 86] but also in the arcuate [87], radial [88], spiral [88], and trophoblastic [87, 89] vessels. Trophoblastic Doppler signals are obtained by placing the sample volume in the hyperechoic area adjacent to the gestational sac. As could be expected, the resistance to flow was progressively lower as one moved from the main branch of the uterine artery through the arcuate, radial, spiral, and trophoblastic vessels. This phenomenon is demonstrated in Fig. 17.19. When these measurements are performed in a twin pregnancy, the resistance to flow is consistently lower and volume flow rates are consistently higher than those of singleton pregnancies (Tables 17.1 and 17.2, respectively). Values are presented as the mean ± SEM. These changes in the resistance to flow during the early second trimester are consistent with endovascular trophoblastic invasion of the decidual portion of the spiral arteries, as previously described [1–3].

Many investigators described a difference in blood flow velocity between the left and right uterine arteries during the first trimester [85, 90, 91] (Table 17.3). In the latter study [91] there appeared to be no essential difference in frequency or magnitude be-

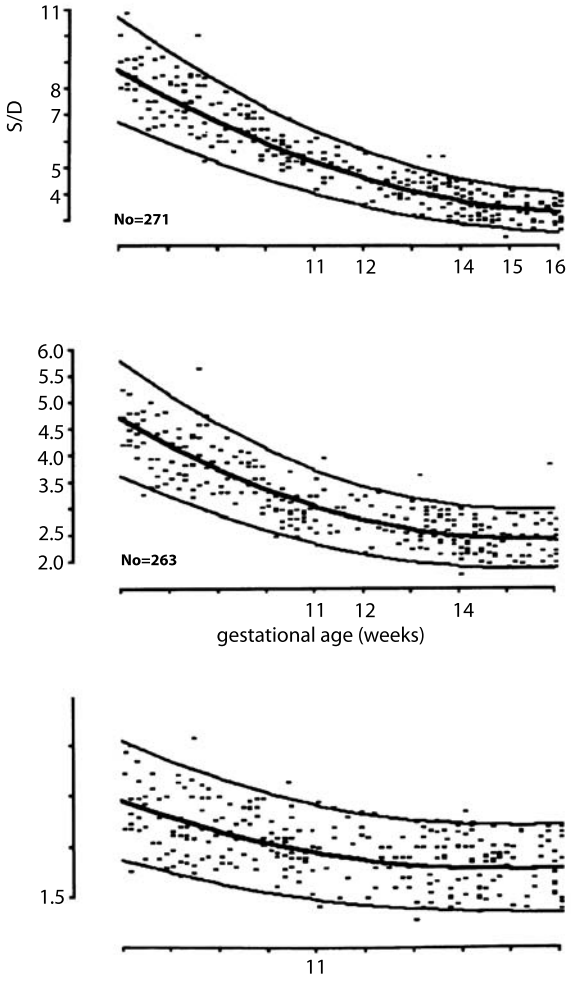

Fig. 17.19. Reference ranges (mean ± 2 SD) and individual values of systolic/diastolic (*S/D*) ratio from both main uterine arteries (*top*), arcuate arteries (*middle*), trophoblastic vessels (*bottom*). (Reprinted from [27] with permission)

tween left (L > R) and right (R > L) predominance for both PI and RI values. On average there appeared to be no difference between the left and right uterine arteries. The most likely explanation for the difference in the PI or RI between the left and right uterine arteries is that changes in down-stream impedance in the uterine artery supplying the placenta precede those in the uterine artery on the nonplacental side of the uterus. As clear delineation of the placenta is often impossible during early gestation, one can only assume about the relation between the resistance to flow and placental location at this stage of gestation [91]. Some investigators prefer to calculate the mean RI or PI of both sides of the uterus, which would indicate the total downstream impedance [85, 90, 91].

Table 17.1. S/D ratio in uterine arteries during the first and early second trimesters for singleton and twin pregnancies

Gestational age (weeks)	S/D ratio (mean ± SEM)		
	Singleton	Twins	*p*
4–7	7.63 ± 0.45	6.77 ± 0.34	NS
8–11	5.56 ± 0.36	4.37 ± 0.26	< 0.01
12–15	4.60 ± 0.33	2.84 ± 0.16	< 0.0001
16–19	3.23 ± 0.15	2.38 ± 0.10	< 0.0001

NS, not significant; SEM, standard error of the mean.

Table 17.2. Total blood flow to the uterus[a] during the first and early second trimester for singleton and twin pregnancies

Gestational age (weeks)	Total blood flow (ml/min) (mean ± SEM)		
	Singleton	Twins	*p*
4–7	237.6 ± 6.15	242.8 ± 7.19	NS
8–11	251.2 ± 7.12	300.0 ± 8.96	< 0.0001
12–15	279.0 ± 7.19	343.4 ± 7.73	< 0.0009
16–19	323.4 ± 8.07	391.4 ± 8.69	< 0.0002

NS, not significant; SEM, standard error of the mean.
[a] Sum of flows in both uterine arteries.

Table 17.3. Frequency and magnitude of difference of PI between left and right uterine arteries of normal pregnancies at 8–13 weeks' gestation (from [91] with permission)

Gestation (weeks)	Differences in PI				
	No.	L > R	No.	R > L	R = L (No.)
8	7	0.64 ± 0.37	6	0.86 ± 0.67	–
9	3	0.27 ± 0.24	4	0.35 ± 0.23	2
10	5	0.50 ± 0.39	4	0.60 ± 0.32	1
11	5	0.54 ± 0.31	5	0.53 ± 0.33	–
12	12	0.48 ± 0.59	12	0.51 ± 0.30	2
13	8	0.60 ± 0.24	9	0.43 ± 0.40	2

Results are means ± SD of the differences between the left uterine artery (L) and right uterine artery (R).
L > R, left predominance; R > L, right predominance; R, L indicates no predominance.

When using the transvaginal pulsed Doppler technique the intraobserver coefficient of variation ranged between 7.6% [84] and 9.0% [14]. The reported range for the continuous-wave Doppler method was between 4.0% [13] and 5.6% [91].

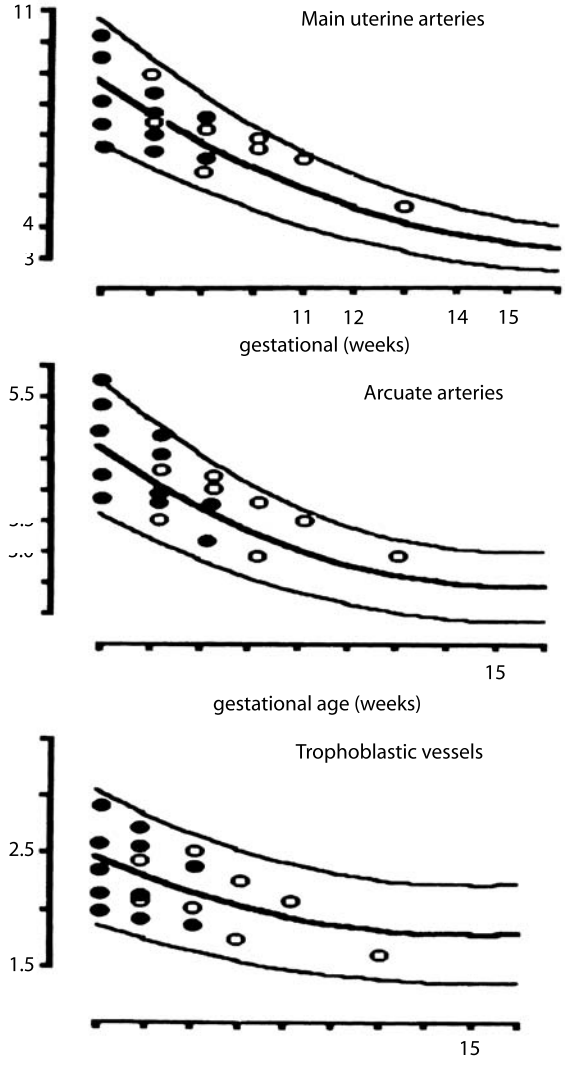

Fig. 17.20. Systolic/diastolic (*S/D*) ratios of 19 patients with anembryonic pregnancy (*closed circles*) and missed abortion (*open circles*), plotted on reference ranges for normal gestations. (Reprinted from [27] with permission)

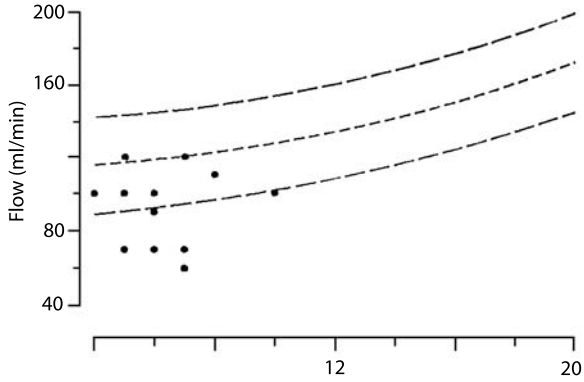

Fig. 17.21. Uterine blood flow in women who aborted (*closed circles*) plotted on normal reference ranges (5th, 59th, and 90th percentiles). Fifty percent were below the 5th percentile, and another 33% were below the 50th percentile

Doppler Velocimetry During Early Pregnancy and Pregnancy Outcome

Normal Early Pregnancy and Early Pregnancy Failure

Few investigations have been conducted to study the relation between Doppler velocimetry in the uteroplacental circulation and pregnancy failure; and of those undertaken, most investigators found no association. In one study, no significant modifications were observed in the velocity waveforms obtained from subplacental vessels of seven pregnancies with early failure [92]. In another study [87] flow velocity waveforms were recorded from different points of the uterine circulation in 19 patients with early pregnancy failure. The S/D ratio always fell within the normal range, in both anembryonic pregnancies and in cases of missed abortion (Fig. 17.20). Trophoblastic flow was observed in all cases studied. In another study [93], 77 pregnant women were followed longitudinally by Doppler flow measurements of the ascending uterine arteries, starting from as early as 4–5 weeks' gestation. Twelve patients subsequently aborted. The S/D ratio obtained prior to pregnancy loss fell within the normal range. Howerver, when volume flow rates were measured prior to pregnancy loss, the mean flow was significantly lower in women who aborted (95.8 ± 6.9 ml/min) than in those who did not abort (118.8 ± 3.16 ml/min, $p < 0.002$) (Fig. 17.21).

One group [94] reported lower RI values in the uterine artery in patients with blighted ovum ($n = 41$, $RI = 0.77 \pm 0.11$) or missed abortion ($n = 6$, $RI = 0.69 \pm 0.13$) than in those with normal pregnancies ($n = 6$, $RI = 0.81 \pm 0.06$). The mean RI in the trophoblastic region was 0.48 ± 0.08 in normal pregnancies compared to 0.42 ± 0.15 in cases of blighted ovum. In several patients with missed abortion and blighted ovum no trophoblastic flow could be detected. Vaginal bleeding with or without subchorionic hematoma was associated with increased radial artery impedance at 7 weeks of pregnancy [95]. Time-average velocity and peak systolic velocity did not change significantly and spiral artery blood flow remained unaffected. In another study, patients with threatened miscarriage also had significantly higher radial artery PI values compared to normal gestations [96]. PI, RI, and peak systolic velocity were measured in patients affected

by uterine bleeding and compared to women with normal intrauterine pregnancy [97]. No significant differences were found in any of the three vascular indices between the normal and the pathologic group of patients.

In another study [98] RI and PI in the uterine and spiral arteries, uterine artery peak systolic velocity, and intervillous blood flow were recorded by transvaginal color Doppler imaging in 30 missed abortions and 30 normal pregnancies matched for menstrual age. The mean uterine PI was significantly higher in missed abortions compared to normal controls, whereas the mean uterine RI and peak systolic velocity and spiral RI and PI did not differ. A continuous intervillous flow was found in 16 out of 23 (69.6%) of the complicated pregnancies before 12 weeks of gestation whereas it was not found in controls. In the missed abortion cases, the trophoblastic shell was fragmented or absent in 53% and trophoblastic infiltration and physiological changes in the spiral arteries were reduced or absent in 43% and 63%, respectively. Extended dislocation of the trophoblastic shell and a massive infiltration of the intervillous space and placental bed by maternal blood was also found in cases presenting with a continuous intervillous blood flow before 12 weeks of gestation. The authors concluded that abnormal flow velocity waveforms in early pregnancies complicated by embryonic death are related to deficient placentation and dislocation of the trophoblastic shell that follows embryonic demise. The premature entry of maternal blood into the intervillous space seems to disrupt the maternoembryonic interface and is probably the final mechanism causing abortion [98].

The absence of detectable intervillous flow during most of the first trimester has lent support to the concept that, during the first 3 months of gestation, blood flow to the intervillous space is largely inhibited. Subsequent studies at that period supported these findings [99, 100].

Subsequently this concept was strongly challenged. Intervillous blood flow was detected from early stages of the first trimester in a monkey model [101, 102] and was also observed in pregnant women [103, 104].

In a prospective study, intervillous and spiral artery flows were evaluated in 49 normal pregnancies (5–10 weeks of amenorrhea) using transvaginal color and pulsed-wave Doppler techniques. In all pregnancies, continuous nonpulsatile intervillous flow and spiral artery flow were detected [105].

Recently, the onset of the maternal–placental circulation was studied by Doppler ultrasonography in 65 pairs of age-matched normal and abnormal pregnancies [106]. In normal pregnancies intervillous blood flow increased with gestational age, being detected in 9 of 25 cases at 8–9 weeks but in 18 of 20 at 12–13 weeks. By contrast, in abnormal pregnancies flow was detected in nearly all cases (22 of 25) at 8–9 weeks. In addition, regional differences were observed between the groups. Early flow was restricted to the peripheral regions of most normal placentas, whereas in missed miscarriages it was most common in central regions or throughout the placenta. Immunoreactivity for heat shock protein 70 and nitrotyrosine residues was greater in samples from peripheral than from central regions of normal placentas and from missed miscarriages compared to controls. These results indicate, according to the authors, that oxidative damage to the trophoblast, induced by premature and widespread onset of the maternal placental circulation secondary to shallow trophoblast invasion, is a key factor in early pregnancy loss. High oxygen concentrations in the periphery of normal early placentas may similarly induce local regression of the villi, leading to formation of the chorion leave [106].

A clinical descriptive study was conducted using color Doppler ultrasound in 45 women with normal pregnancies (group A) and 44 with nonembryonic sac or missed abortions (group B) [107]. The mean gestational age in these two groups was 9.3 and 7.6 weeks, respectively ($p < 0.01$). The number of myometrial blood vessels (arteries and veins identified by power Doppler mapping), the quantity of intervillous flow, the RI for the arterial system, and the PI of the myometrial arteries were evaluated. The number of myometrial blood vessels in group A was lower than that in group B. The intervillous flow was observed in some cases from early pregnancy and more often after 10 weeks. This characteristic was observed significantly more frequently in group B than in group A. The RI and PI in the uterine arteries were significantly higher in group A than in group B. The RI and the PI of the uterine arteries decreased with the advance of gestational age in both groups.

As it turns out, color Doppler ultrasound provides information about uteroplacental circulation during the first trimester and indicates early development of intervillous circulation. Although a greater uteroplacental blood circulation was observed in failed pregnancies, the overlapping between groups severely limits the application of this characteristic in clinical practice [107].

Screening for Preeclampsia and Intrauterine Growth Restriction

Pregnancy hypertension – including pregnancy-induced hypertension (PIH) and preeclamptic toxemia (PET) – is a disease exclusively associated with pregnancy. It occurs in 6%–8% of all pregnancies beyond 24 weeks [108] and is the most common single cause of maternal mortality [109]. According to the World

Health Organization it is also the most prevalent cause of perinatal mortality and morbidity [110].

Intrauterine growth restriction occurs in 5%–10% of pregnancies and is associated with a four- to tenfold increase in perinatal mortality and a substantial increase in perinatal morbidity, including neurodevelopmental disorders [111, 112]. Pregnancy hypertension is the most common cause for abnormal fetal growth [113], although the latter condition is also associated with other maternal or fetal disorders.

In many cases no discernible etiologic cause can be elicited. The term fetal growth restriction refers here only to cases where uteroplacental perfusion is decreased; other causes (e.g., fetal infections, fetal malformations) are excluded.

Early detection of pregnant women at risk for subsequent PIH/PET or fetal growth restriction of paramount importance. Close maternal surveillance, early detection on PIH/PET or fetal growth restriction, and above all the ability to provide preventive treatment [114, 115], can greatly improve pregnancy outcome and decrease maternal complications. Ideally, a screening test with a low false-negative rate and a reasonable false-positive rate would fulfill this goal. To implement such a test in large populations, it must be easy, inexpensive, convenient for the mother, quick and simple, easily interpretable, and reproducible. To take maximal advantage of preventive therapy, it should be performed during the late first or early second trimester.

Blood flow studies have demonstrated that PIH/PET [23] and fetal growth restriction [116, 117] are often associated with decreased uteroplacental perfusion. These changes in uteroplacental blood flow reflect abnormal histomorphologic changes in the spiral arteries [15, 16, 32, 118, 119]. Doppler sonography of the uteroplacental circulation could reflect such abnormal morphology; and because it fulfils all the described criteria for a screening test, it could theoretically prove to be the optimal method for early prediction of those abnormal conditions.

Most screening studies have been undertaken between 16 and 30 weeks, with most investigators starting between 20 and 24 weeks [26, 27, 81, 120–123]. The sensitivity and predictive values vary considerably in these studies (Fig. 17.22). There are a variety of possible explanations for the discrepancies, some of which have been dealt with before. The most notable ones are different methods of insonation of the uteroplacental circulation, different vessels that were chosen for Doppler measurements, different cutoff levels of resistance indices, noncomparable defintions of pregnancy complications or outcome, and the mode whereby patients were selected. One study [123] gives a detailed description of the differences between the screening studies that could account for the wide variation in the results obtained. In a prospective cross-sectional trial, 175 women at high risk for developing hypertension or FGR were studied and compared with 172 low-risk pregnancies between 21 and 24 weeks' gestation [124]. In the high-risk group, PIH and/or fetal growth restriction were found in 58.3% if the Doppler studies were abnormal (i.e., persistent notching or elevated RIs of more than 0.68 in the main uterine arteries). Only 8.3% of women have such complications when Doppler studies were normal. Doppler was far less predictive in the low-risk group.

It should be emphasized that in none of the reported studies did the investigators include the presence of a dicrotic or early diastolic notch in the flow velocity waveform as an indicator of high resistance to flow. In a recent screening study of 1,300 women [78] a combination of continuous-wave Doppler so-

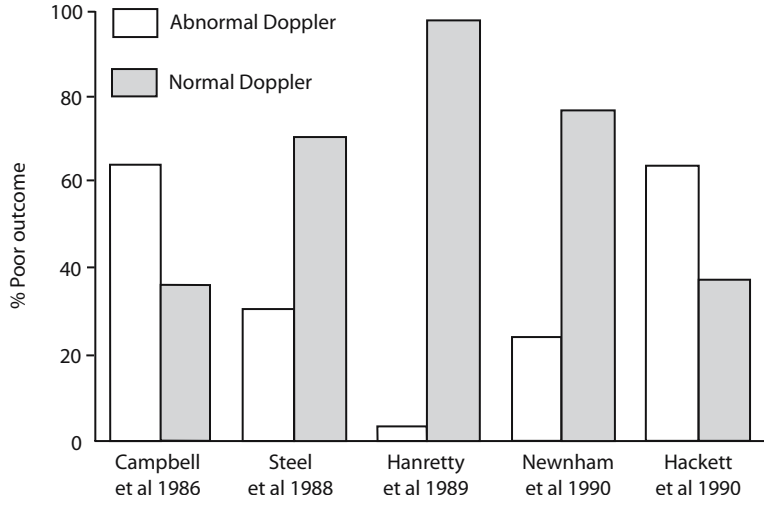

Fig. 17.22. Unselected screening studies demonstrating the relation between normal and abnormal Doppler findings. (Reprinted from [78] with permission)

Table 17.4. Resistance index above the 95th percentile or the presence of a diastolic notch for prediction of severe proteinuric pregnancy-induced hypertension (from [79] with permission)

Gestation (weeks)	Sensitivity (%)	Specificity (%)	PPV (%)	HPV (%)
20	79	85	7.6	99.6
24	79	96	25.9	99.7
26	79	98	36.6	99.7

PPV, positive predictive value; NPV, negative predictive value.
Studies of the uterine artery were performed in 1,300 pregnant women using continuous-wave Doppler ultrasonography to screen at 20 weeks and color flow imaging for follow-up at 24 and 26 weeks.

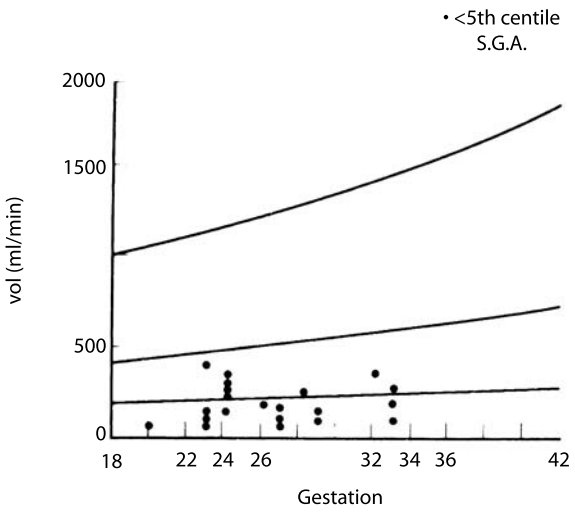

Fig. 17.23. Reference ranges of the total volume of flow in the uterine arteries and the total volume of flow in 21 women whose pregnancies were complicated by growth restriction. *S.G.A.* small for gestational age. (Reprinted from [78] with permission)

nography and color flow imaging of the uterine artery was used to calculate the resistance to flow as well as the mean velocity and volume flow. The women were recruited from the routine antenatal clinic and had a continuous-wave Doppler ultrasound examination of both uterine arteries at the 20-week admission scan. It the flow velocity waveforms obtained were found to have a high RI (>2 standard deviations from the mean of the normal range), an early diastolic notch, or both, the patient was asked to return for follow-up with color flow imaging initially at 24 weeks and then at 26 weeks if the results were still abnormal. Of the 1,300 women studied, 19 subsequently had severe proteinuric pregnancy-induced hypertension, and 15 of the 19 had abnormal findings on the uterine artery Doppler studies. The results are summarized in Table 17.4. A total of 206 women were identified as having an abnormal waveform at the admission scan; 95% of these women had an early diastolic notch (68% without and 27% with increased RI), and only 5% had an increased RI alone. These findings demonstrate that a notch is a much better predictor that a notch is a much better predictor of poor outcome than the RI alone.

The same investigators [78] also found that the total volume of flow in the uterine arteries in 21 women whose pregnancies were complicated by fetal growth restriction (most of whom were found to be hypoxemic at cordocentesis), was below the 50th percentile; 62% were below the 5th percentile (Fig. 17.23). What needs to be determined is whether patients with low volume of flow at or before 24 weeks have increased risk of having a pregnancy complicated by fetal growth restriction.

More recently a multicenter, cohort study was conducted to determine the utility of transvaginal color Doppler assessment of uterine arteries at 23 weeks' gestation in the prediction of preeclampsia and fetal growth restriction [125]. A mean PI of 1.63 (the 95th percentile) or more or bilateral notching was considered abnormal. In 932 of the 7,851 study patients (i.e., 11.9%) at least one of these abnormalities was present. The sensitivity, specificity, and positive and negative predictive values of an abnormal test were 83.3%, 88.5%, 3.8%, 99.9%, respectively, with a likelihood ratio of 7.3. The sensitivities in predicting either preeclampsia without fetal growth restriction or fetal growth restriction without preeclampsia were much lower, however (40.8% and 24.4%, respectively). The sensitivities in the prediction of either one of the two outcomes further decreased when only one of the uterine artery Doppler patterns was abnormal. The investigators concluded that Doppler screening at 23 weeks is valuable at identifying the more severe cases of preeclampsia and fetal growth restriction (and therefore the most clinically relevant cases).

Recently a metaanalysis was performed to examine how useful uterine artery Doppler flow velocimetry is in the prediction of preeclampsia, fetal growth restriction, and perinatal death [126]. Twenty-seven published and unpublished observational studies involving 12,994 pregnancies were analyzed. These pregnancies were classified into high-risk and low-risk for developing preeclampsia and its associated complications. Based on the results obtained the authors concluded that uterine artery Doppler flow velocimetry has limited diagnostic accuracy in predicting preeclampsia, fetal growth restriction, and perinatal death.

The second wave of trophoblastic migration is completed in most women by 20 weeks' gestation [3].

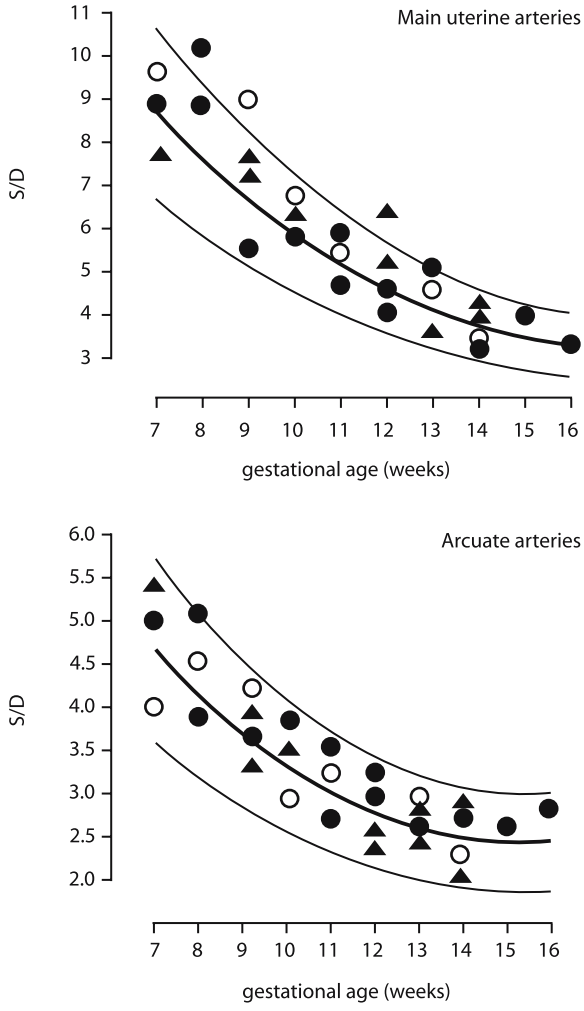

Fig. 17.24. Systolic/diastolic (*S/D*) ratio in the uterine and arcuate arteries of 29 women who developed gestational hypertension (*triangles*), intrauterine growth restriction (*closed circles*), or both complications (*open circles*), plotted on reference ranges. (Reprinted from [27] with permission)

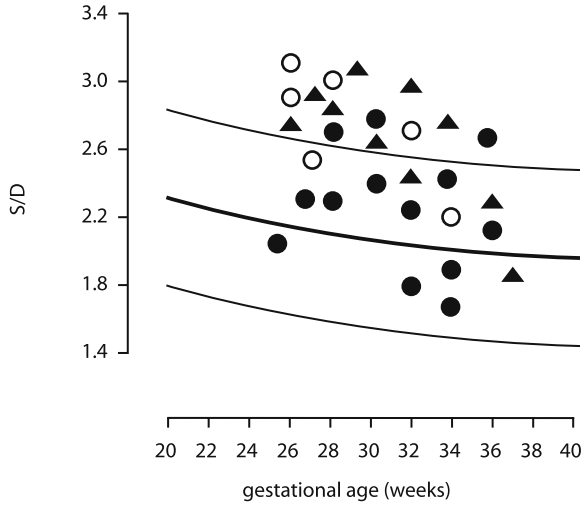

Fig. 17.25. Uterine artery systolic/diastolic (*S/D*) ratio during the second and third trimesters in 29 women who developed gestational hypertension (*triangles*), intrauterine growth restriction (*closed circles*), or both complications (*open circles*), plotted on reference ranges. (Reprinted from [28] with permission)

It seems logical that screening studies should be conducted at this period of gestation. By screening too early, the false-positive rate may be too high, leading to lower specificity because the process of physiologic changes is not completed. On the other hand, screening too late during the second trimester may mean that the pathologic process is already well developed and that preventive treatment may be less effective.

It should be recalled that the first wave of trophoblastic migration may also demonstrate abnormal features (R. Laurini, personal communication), which may be reflected in Doppler measurements of the uteroplacental circulation. One group investigated whether Doppler measurements during early pregnancy can predict adverse pregnancy outcome [27]. Reference ranges of uteroplacental waveform indices were constructed from a cross-sectional study of 282 women with retrospectively defined normal singleton pregnancies. This group of women was selected from a population with 330 low-risk pregnancies and was followed longitudinally throughout gestation. In the remaining 48 cases, pregnancy complications were evident either at the time of the study or later with advancing gestation. Of the 48 patients, 19 had an abortion and 29 subsequently had intrauterine growth restriction (IUGR), gestational hypertension, or both. The S/D ratio was measured in the main uterine arteries, the arcuate arteries, and in trophoblastic vessels using an image-directed transvaginal color Doppler system. Measurements were started from as early as 7 weeks' gestation. In the 29 women who subsequently had PIH/PET, IUGR, or both, all S/D ratio values were within the normal range in all vessels studied (Fig. 17.24). Fourteen patients had an increased S/D ratio (>2 standard deviations) in the main uterine artery during late second and third trimester of pregnancy (Fig. 17.25). The presence or absence of a notch in the uterine artery flow velocity waveforms was not reported in this study.

Another group [93] investigated the association between abnormal blood flow velocity waveforms and subsequent complications of pregnancy (PIH/PET or IUGR). Serial Doppler examinations of the uterine arteries were performed in 77 pregnant patients. The Doppler studies commenced at 5–6 weeks' gestation and were repeated every 2–3 weeks during the first trimester and every 4–6 weeks thereafter. A transvaginal image-directed pulsed Doppler ultrasound system

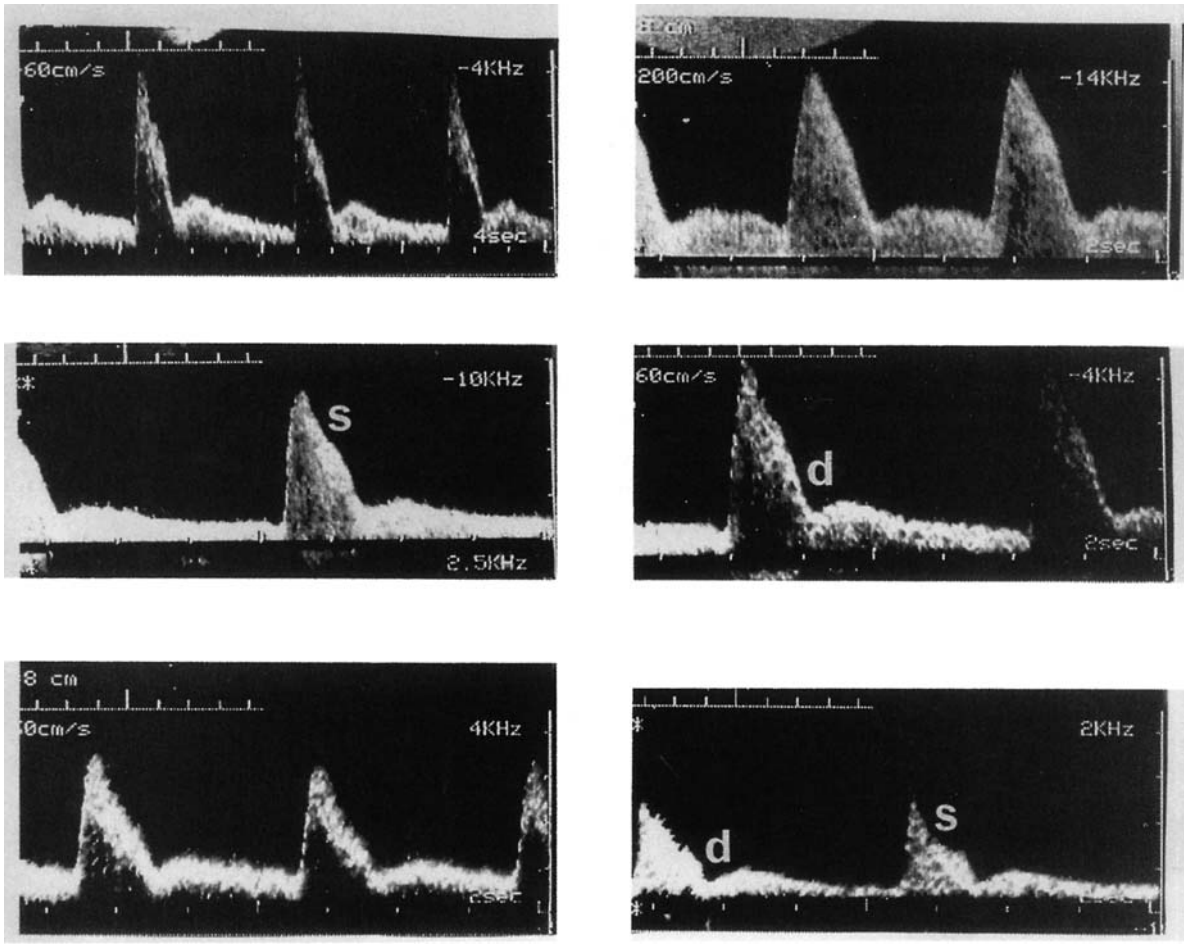

Fig. 17.26. Blood flow velocity waveforms in the uterine artery demonstrating systolic (*s*) and diastolic (*d*) notches. (Reprinted from [83] with permission)

was used for these measurements. A systolic notch was defined as a momentary decrease in the rate of decline of the maximal velocity of flow during the "decelerative" phase of the systolic wave. A diastolic notch was defined as a decrease in the maximal velocity of flow below the maximum diastolic velocities, occurring just after the systolic wave (Fig. 17.26). The presence or absence of a systolic or diastolic notch in each waveform was noted. The presence of a systolic or diastolic notch in uterine artery flow velocity waveforms on both sides of the uterus at 10–12 weeks ws considered a positive test. Twelve women aborted during the first or the early second trimester. Of the remaining 65 women, 30 had a positive test during the first trimester. Ten of these women (33%) subsequently had PIH/PET. In the remaining 35 women with a negative test, only 3 (8.6%) had this condition later in pregnancy ($p < 0.02$) (Fig. 17.27). Altogether, 10 of the 13 women (77%) who subsequently had pregnancy hypertension had a positive test during the first trimester. In comparison, only 38% of women who did not subsequently have PIH/PET had a positive test. Fourteen women had a multiple gestation. When the data were analyzed separately for singleton and multiple gestations, only 29% of women with singleton (who did not subsequently have PIH/PET) had a positive test, compared to 50% with a multiple gestation. Women who aborted had a similar incidence (Table 17.5). The mean S/D ratio in the uterine artery in women with a positive test was 6.31 ± 0.26 compared to 5.5 ± 0.17 in women with a negative test ($p < 0.02$). The performance characteristics of this test are shown in Table 17.6. The positive predictive value is similar to that obtained at 26 weeks [78]. These preliminary data suggest that screening during early gestation is feasible and may reflect abnormal placentation during the first wave of trophoblastic migration. The advantages of early screening were discussed before. The mean birth weight (± standard deviation) in women

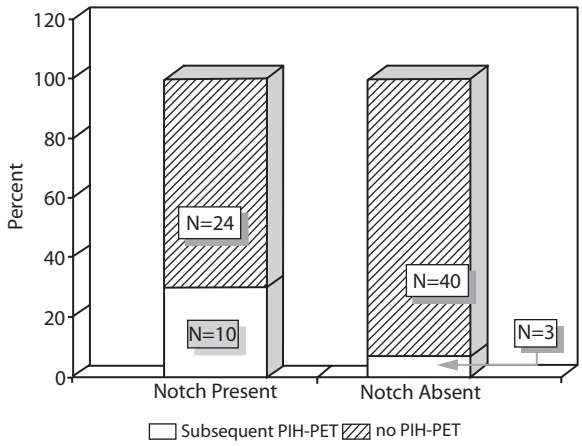

Fig. 17.27. Proportion of women who subsequently developed pregnancy-induced hypertension (*PIH*) or preeclamptic toxemia (*PET*) according to the presence or absence of a notch (both systolic and diastolic in at least one uterine artery) during the late first trimester. The number of women in each group is shown in a *box*. A total of 65 women were studied

with a positive notch was 2,647 ± 612 g, whereas in those with a negative test it was 2,999 ± 629 g. The presence of a notch, then, signifies impaired growth and is probably related to suboptimal uteroplacental perfusion throughout gestation in women with high resistance (i.e., the presence of notch) during the first trimester.

In a more recent study, uterine artery Doppler was performed at 11–15 weeks in 3,324 singleton pregnancies [127]. Both sides were measured and averaged, and the predictive value of a mean PI over the 95th percentile in the prediction of preeclampsia and/or fetal growth restriction was calculated. The sensitivity of a mean PI over 2.35 (the 95th percentile of the uterine artery mean PI) for preeclampsia (with or without fetal growth restriction) was 27% but for fetal growth restriction alone it was 11.7%. The respective sensitivities for these complications requiring delivery before 32 weeks of gestation were 60% and 27.8%. The sensitivity of the uterine artery mean PI over the 95th percentile in the prediction of preeclampsia and fetal growth restriction is lower when the test is carried out at 11–14 weeks than at 22–24 weeks. However, the potential advantage of earlier screening is that prophylactic intervention may be more effective in the prevention of the subsequent development of PET and fetal growth restriction. A similar study was performed in 380 women at 11–14 weeks [128]. The sensitivity of the uterine artery mean PI over the 90th percentile in the prediction of pregnancy complications (the 90th percentile of the uterine artery mean PI was 2.5) was 25%. However, there were no cases of PET in this series.

Table 17.5. Incidence of systolic and diastolic notch in uterine artery flow velocity waveforms in 77 women at late first trimester according to pregnancy outcome

Pregnancy outcome	No.	Incidence of notch (%)
Low risk	38	28.9
Abortions[a]	12	33.3
Twins	14	50.0
PIH-PET	13	77.0

[a] Women who subsequently had a spontaneous abortion.
PIH-PET, pregnancy-induced hypertension or preeclamptic toxemia.

Table 17.6. Value of systolic and diastolic notch in uterine artery flow velocity waveforms during late first trimester for prediction of pregnancy-induced hypertension or preeclamptic toxemia

Parameter	%
Sensitivity	76.9
Specificity	61.5
Positive predictive value	33.3
Negative predictive value	91.4

Although these studies demonstrate that Doppler sonography of the uterine arteries during early pregnancy may predict abnormal pregnancy outcome and can be used for screening purposes, more data are required to reveal the full potential of this test. Studies of the association between abnormal uterine arterial flow pattens and histomorphologic changes in the placental bed during the first trimester are currently under way and should provide us with greater understanding of the mechanisms involved.

References

1. Brosens I, Robertson WB, Dixon HG (1967) The physiological response of the vessels of the placental bed to normal pregnancy. J Pathol Bacteriol 93:567–579
2. Pijneborg R, Bland JM, Robertson WB et al (1983) Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy. Placenta 4:397–413
3. Pijneborg R, Dixon G, Robertson WB et al (1980) Trophoblastic invasion of human decidua from 8–18 weeks of pregnancy. Placenta 1:3–19
4. Matijevic R, Meekins JW, Walkinshaw SA, Neilson JP, MacFadyen IR (1995) Spiral artery blood flow in the central and peripheral areas of the placental bed in the second trimester. Obstet Gynecol 86:289–292
5. Ramsey EM (1981) The story of spiral arteries. J Reprod Med 26:393
6. Reynolds SRM (1965) Physiology of the uterus, 2nd edn. Hafner, New York, p 329
7. Bieniarz J, Yoshida T, Romero-Salinas G et al (1969) Aortocaval compression by the uterus in late human

pregnancy. IV. Circulatory homeostasis by preferential perfusion of the placenta. Am J Obstet Gynecol 1034: 10–31
8. Pinjeborg R, Robertson WB, Brosens I et al (1981) Trophoblast invasion and the establishment of haemochorial placentation in man and laboratory animals. Placenta 2:71–92
9. Browne JCM, Veall N (1953) The maternal placental blood flow in normotensive and hypertensive women. J Obstet Gynaecol Br Emp 60:141–147
10. Dixon HG, Browne JCM, Davey D (1963) Choriodecidual and myometrial blood flow. Lancet 1:369–373
11. Maini CL, Rosati P, Galli G et al (1985) Noninvasive radioisotopic evaluation of placental blood flow. Gynecol Obstet Invest 19:196–206
12. Trudinger BJ, Giles WB, Cook CM (1985) Uteroplacental blood flow velocity-time waveforms in normal and complicated pregnancy. Br J Obstet Gynaecol 92:39–45
13. Schulman H, Fleischer A, Farmakides G et al (1986) Development of uterine artery compliance in pregnancy as detected by Doppler ultrasound. Am J Obstet Gynecol 155:1031–1036
14. Thaler I, Manor D, Itskovitz J et al (1990) Changes in uterine blood flow during human pregnancy. Am J Obstet Gynecol 162:121–125
15. Brosens I, Robertson WB, Dixon HG (1972) The role of the spiral arteries in the pathogenesis of preeclampsia. Obstet Gynecol Annu 1:177
16. Khong TY, De Wolf F, Robertson WB et al (1986) Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. Br J Obstet Gynaecol 93:1049–1059
17. Robertson WB (1976) Uteroplacental vasculature. J Clin Pathol 29[Suppl 10]:9–17
18. Khong TY, Robertson WB (1992) Spiral artery disease. In: Coulam CB, Faulk WP, McIntyre JA (eds) Immunologic obstetrics. Norton, New York
19. Stirrat GM (1987) The immunology of hypertension in pregnancy. In: Sharp F, Symonds EM (eds) Hypertension in pregnancy. Perinatology Press, Ithaca, NY, p 249
20. Khong TY, Sawyer H, Heryet AR (1992) An immunohistologic study of endothelialization of uteroplacental vessels in human pregnancy: evidence that endothelium is focally disrupted by trophoblast in preeclampsia. Am J Obstet Gynecol 167:751–756
21. Sibai BM (1990) Preeclampsia-eclampsia. Curr Probl Obstet Gynecol Infertil 13:6
22. DeWolf F, Robertson WB, Brosens I (1975) The ultrastructure of acute atherosis in hypertensive pregnancy. Am J Obstet Gynecol 123:164–174
23. Lunell NO, Nylund L, Lewander R et al (1982) Uteroplacental blood flow in preeclampsia: measurements with indium-113 and a computer-linked gamma camera. Clin Exp Hypertens 11:105–117
24. Campbell S, Griffin DR, Pearce JMF et al (1983) New Doppler technique for assessing uteroplacental blood flow. Lancet 1:675–677
25. Fleischer A, Schulman H, Farmakides G et al (1986) Uterine artery Doppler velocimetry in pregnant women with hypertension. Am J Obstet Gynecol 154:806–813
26. Campbell S, Pearce JMF, Hackett G et al (1986) Qualitative assessment of uteroplacental blood flow: early screening test for high risk pregnancies. Obstet Gynecol 68:649–653
27. Arduini D, Rizzo G, Romanini C et al (1987) Uteroplacental blood flow velocity waveforms as predictors of pregnancy-induced hypertension. Eur J Obstet Gynecol Reprod Biol 26:335–341
28. Voigt J, Becker V (1992) Uteroplacental insufficiency: comparison of uteroplacental blood flow velocimetry and histomorphology of placental bed. J Matern Fetal Invest 2:251–255
29. Aardema MW, Oosterhof H, Timmer A, Van Rooy I, Aarnoudse JG (2001) Uterine artery Doppler flow and uteroplacental vascular pathology in normal pregnancies and pregnancies complicated by preeclampsia and small for gestational age fetuses. Placenta 22:405–411
30. Lin S, Shimuzu I, Suehara N, Nakayama M, Aono T (1995) Uterine artery Doppler velocimetry in relation to trophoblast migration into the myometrium of the placental bed. Obstet Gynecol 85:760–765
31. Ness RB, Roberts JM (1996) Heterogeneous causes constituting the single syndrome of preeclampsia; a hypothesis and its implications. Am J Obstet Gynecol 175:1365–1370
32. Walters WAW, Lim YL (1975) Blood volume and haemodynamics in pregnancy. Clin Obstet Gynecol 2:301–320
33. Christianson RE (1976) Studies of blood pressure during pregnancy. I. Influence of parity and age. Am J Obstet Gynecol 125:509–513
34. Clark SL, Cotton DB, Lee W et al (1989) Central hemodynamics of normal term pregnancy. Am J Obstet Gynecol 161:1439–1442
35. Weir RJ, Brown JJ, Fraser R et al (1975) Relationship between plasma renin, renin-substrate, angiotensin II, aldosterone and electrolytes in normal pregnancy. J Clin Endocrinol Metab 40:108–115
36. Taufield PA, Mueller FB, Edersheim TG et al (1988) Blood pressure regulation in normal pregnancy: unmasking the role of renin angiotensin system with captopril (abstract). Clin Res 36:433A
37. Gant NF, Daley GL, Chand S et al (1973) A study of angiotensin II pressor response throughout primigravid pregnancy. J Clin Invest 52:2682–2689
38. Rosenfeld CR (1989) Changes in uterine blood flow during pregnancy. In: Rosenfeld CR (ed) The uterine circulation. Perinatology Press, Ithaca, NY, pp 135–156
39. Massicotte G, St Louis T, Parent A et al (1987) Decreased in vitro response to vasoconstrictors during pregnancy in normotensive and spontaneously hypertensive pregnant rats. Can J Physiol Pharmacol 65: 2466–2471
40. Naden RP, Rosenfeld CR (1981) Effect of angiotensin II on uterine and systemic vasculature in pregnant sheep. J Clin Invest 68:468–474
41. Moncada S, Gryglewski R, Bunting S et al (1976) An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibit platelet aggregation. Nature 263:663–665
42. Furchgott RF, Zawadzki JV (1980) The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288:373–376

43. Furchgott RF, Vanhoutta PM (1989) Endothelium-derived relaxing and contracting factors. FASEB J 3:2007–2018
44. Palmer RMJ, Ferrig AG, Moncada S (1987) Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 327:524–526
45. Ignarro LJ (1989) Biological actions and properties of endothelium-derived nitric oxide formed and released from artery and vein. Circ Res 65:1–21
46. Gardiner SM, Compton AM, Bennett T et al (1990) Control of regional blood flow by endothelium-derived nitric oxide. Hypertension 15:486–492
47. Ahokas RA, Sibai BM, Mabie MD et al (1988) Nifedipine does not adversely affect uteroplacental blood flow in the hypertensive term-pregnant rat. Am J Obstet Gynecol 159:1440–1445
48. Greiss FC (1966) Pressure-flow relationship in the gravid uterine vascular bed. Am J Obstet Gynecol 96:41–47
49. Venuto RC, Cox JW, Stein JH et al (1976) The effect of changes in perfusion pressure on uteroplacental blood flow in the pregnant rabbit. J Clin Invest 57:938–944
50. Lindow SW, Davies N, Davey DA et al (1988) The effects of sublingual nifedipine on uteroplacental blood flow in hypertensive pregnancy. Br J Obstet Gynaecol 95:1276–1281
51. Thaler I, Weiner Z, Manor D et al (1991) Effect of calcium channel blocker nifedipine on uterine artery flow velocity waveforms. J Ultrasound Med 10:301–304
52. Landauer M, Phernetton TM, Parisi VM et al (1985) Ovine placental vascular response to the local application of prostacyclin. Am J Obstet Gynecol 151:460–464
53. Husslein P, Gitch E, Pateisky N et al (1985) Prostacyclin does not influence placental blood flow in vivo. Gynecol Obstet Invest 19:78–81
54. Speroff L, Haning RV Jr, Levin RM (1977) The effect of angiotensin II and indomethacin on uterine artery blood flow in pregnant monkey. Obstet Gynecol 50: 611–614
55. Weiner CP, Liu KZ, Thompson L et al (1991) Effect of pregnancy on endothelium and smooth muscle: their role in reduced adrenergic sensitivity. Am J Physiol 261:H1275–H1283
56. Ylikorkala O, Makila UM (1985) Prostacyclin and thromboxane in gynecology and obstetrics. Am J Obstet Gynecol 152:318–329
57. Magness RR, Osei-Boaten K, Mitchell MD et al (1985) In vitro prostacyclin production by ovine uterine and systemic arteries. J Clin Invest 76:2206–2212
58. Rakoczi I, Tihanyi K, Gero G et al (1988) Release of prostacyclin (PGI_2) from trophoblast in tissue culture: the effect of glucose concentration. Acta Physiol Hung 71:545–549
59. Diss EM, Gabbe GS, Moore JW et al (1992) Study of thromboxane and prostacyclin metabolism in an in vitro model of first-trimester human trophoblast. Am J Obstet Gynecol 167:1046–1052
60. Blumenstein M, Keelan JA, Mitchell MD (2001) Hypoxia attenuates PGE(2) but increases prostacyclin and thromboxane production in human term villous trophoblast. Placenta 22:519–525
61. Weiner CP, Martinez E, Chestnut DH et al (1989) Effect of pregnancy upon the uterine and carotid artery response to norepinephrine, epinephrine and phenylephrine in vessels with documented functional endothelium. Am J Obstet Gynecol 161:1605–1610
62. Resnik R, Killman AP, Barton MD et al (1976) The effect of various vasoactive compounds upon the uterine vascular bed. Am J Obstet Gynecol 125:201–206
63. Greiss FC Jr, Gabbe FL Jr, Anderson SG et al (1967) Effect of acetylcholine on the uterine vascular bed. Am J Obstet Gynecol 99:1073–1077
64. Van Buren GA, Yang D, Clark KE (1992) Estrogen induced uterine vasodilation is antagonized by L-nitroarginine methyl ester, an inhibitor of nitric oxide synthesis. Am J Obstet Gynecol 167:828–833
65. Molnar M, Hertelendy F (1992) Nw-nitro-L-arginine, an inhibitor of nitric oxide synthesis, increases blood pressure in rats and reverses the pregnancy-induced refractoriness to vasopressor agents. Am J Obstet Gynecol 166:1560–1571
66. Luscher TF (1990) The endothelium: target and promoter of hypertension? Hypertension 15:482–485
67. Yanagisawa M, Kurihara H, Kimura S et al (1988) A novel potent vasoconstrictor-peptide produced by vascular endothelial cells. Nature 332:411–415
68. Katusie ZS, Vanhoutta PM (1989) Superoxide anion is an endothelium-derived contacting factor. Heart Circ Physiol 26:H33
69. Bodelsson G, Sjoberg NO, Stjernquist M (1992) Contactile effect of endothelium in human uterine artery and autoradiographic localization of its binding sites. Am J Obstet Gynecol 167:745–750
70. Svane D, Larsson B, Alm P et al (1993) Endothelin-1: immunocytochemistry, localization of binding sites, and contractile effects in human uteroplacental smooth muscle. Am J Obstet Gynecol 168:233–241
71. Taylor RN, Varma M, Nelson NHT et al (1990) Women with preeclampsia have higher plasma endothelin levels than women with normal pregnancies. J Clin Endocrinol Metab 71:1675–1677
72. Burns PN (1993) The physics of Doppler. In: Chervenak FA, Isaacson GC, Campbell S (eds) Ultrasound in obstetrics and gynecology. Little, Brown, Boston, pp 33–54
73. Thaler I, Bruck A (1991) Transvaginal sonography and Doppler measurements: physical considerations. In: Timor-Tritsch IE, Rottem S (eds) Transvaginal sonography. Elsevier, New York, pp 1–27
74. Thaler I, Manor D (1990) Transvaginal imaging: applied physical principles and terms. J Clin Ultrasound 18:235–238
75. Thaler I, Manor D, Rottem S et al (1990) Hemodynamic evaluation of the female pelvic vessels using a high-frequency transvaginal image-directed Doppler system. J Clin Ultrasound 18:364–369
76. Kurjak A, Jurkovic D, Alfirevic Z et al (1990) Transvaginal color Doppler imaging. J Clin Ultrasound 18:227–234
77. Thaler I, Manor D, Rottem S (1993) Transvaginal Doppler duplex system. In: Chervenak FA, Isaacson GC, Campbell S (eds) Ultrasound in obstetrics and gynecology. Little, Brown, Boston, pp 141–148
78. Bowere SJ, Campbell S (1993) Doppler velocimetry of the uterine artery as a screening test in pregnancy. In: Chervenak FA, Isaacson GC, Campbell S (eds) Ultrasound in obstetrics and gynecology. Little, Brown, Boston, pp 579–586

79. McCowan LM, Ritchie K, Mo LY et al (1988) Uterine artery flow velocity waveforms in normal and growth-retarded pregnancies. Am J Obstet Gynecol 158:499–504
80. Pearce JM, Campbell S, Cohen-Overbeek TE et al (1988) Reference ranges and sources of variation for indices used to characterize flow velocity waveforms obtained by duplex, pulsed Doppler ultrasound from the uteroplacental and fetal circulation. Br J Obstet Gynaecol 95:248–256
81. Hanretty KP, Primrose M, Neilson JP et al (1989) Pregnancy screening by Doppler uteroplacental and umbilical artery waveforms. Br J Obstet Gynaecol 96:1163–1167
82. Juaniaux E, Jurkovic D, Campbell S et al (1991) Investigation of the placental circulation by color Doppler. Am J Obstet Gynecol 164:486–488
83. Thaler I, Weiner Z, Itskovitz J (1992) Systolic and diastolic notch in uterine artery blood flow velocity waveforms in hypertensive pregnant patients: relationship to outcome. Obstet Gynecol 80:277–282
84. Bewley S, Campbell S, Cooper D (1989) Uteroplacental Doppler flow velocity waveforms in the second trimester: a complex circulation. Br J Obstet Gynaecol 90: 1040–1046
85. Deutinger J, Rudelstorfer R, Bernaschek G (1988) Vaginosonographic velocimetry of both uterine arteries by visual vessel recognition and pulsed Doppler method during pregnancy. Am J Obstet Gynecol 159:1072–1076
86. Konje JC, Kaufmann P, Bell SC, Taylor DJ (2001) A longitudinal study of the quantification of uterine blood volume flow using colour power angiography in appropriate for gestational age pregnancies. Am J Obstet Gynecol 185:608–613
87. Arduini D, Rizzo G, Romanini C (1991) Doppler ultrasonography in early pregnancy does not predict adverse pregnancy outcome. Ultrasound Obstet Gynecol 1:180–185
88. Jurkovic D, Jauniaux E, Kurjak A et al (1991) Transvaginal color Doppler assessment of uteroplacental blood flow in early pregnancy. Obstet Gynecol 77:365–369
89. Jaffe R, Warsof SL (1991) Transvaginal color Doppler imaging in the assessment of uteroplacental blood flow in normal first-trimester pregnancy. Am J Obstet Gynecol 164:781–785
90. Stabile I, Bilardo C, Panella M et al (1988) Doppler assessed uterine blood flow in the first trimester of pregnancy. Trophoblast Res 3:301–308
91. Den Ouden M, Cohen-Overbeek TE, Wladimiroff JW (1990) Uterine and fetal umbilical artery flow velocity waveforms in normal first trimester pregnancies. Br J Obstet Gynaecol 97:716–719
92. Stabile I, Grudzinskas J, Campbell S (1990) Doppler ultrasonographic evaluation of abnormal pregnancies in the first trimester. J Clin Ultrasound 18:497–501
93. Thaler I, Tessler M, Itskovitz J (1991) Systolic and diastolic notch in uterine artery FVW in the first trimester of pregnancy: clinical significance. Presented at the 4th Congress of the International Perinatal Doppler Society, Malmö
94. Alfirevic Z, Kurjak A (1990) Transvaginal colour Doppler ultrasound in normal and abnormal early pregnancy. J Perinat Med 18:173–180
95. Makikallio K, Tekay A, Jouppila P (2001) Effects of bleeding on uteroplacental, umbilicoplacental and yolk-sac hemodynamics in early pregnancy. Ultrasound Obstet Gynecol 18:352–356
96. Kurjak A, Zalud I, Predanic M, Kupesic S (1994) Transvaginal color and pulsed Doppler study of uterine blood flow in the first and early second trimesters of pregnancy: normal versus abnormal. J Ultrasound Med 13:43–47
97. Pellizzari P, Pozzan C, Marchiory S, Zen T, Gangemi M (2002) Assessment of uterine artery blood flow in normal first-trimester pregnancies and in those complicated by uterine bleeding. Ultrasound Obstet Gynecol 19:366–370
98. Jauniaux E, Zaidi J, Jurkovic D, Campbell S, Hustin J (1994) Comparison of colour Doppler features and pathological findings in complicated early pregnancy. Hum Reprod 9:2432–2437
99. Coppens M, Loquet P, Kollen M, De Neubourg F, Buytaert P (1996) Longitudinal evaluation of uteroplacental and umbilical blood flow changes in normal early pregnancy. Ultrasound Obstet Gynecol 7:114–121
100. Jaffe R, Jauniaux E, Hustin J (1997) Maternal circulation in the first-trimester human placenta – myth or reality? Am J Obstet Gynecol 176:695–705
101. Simpson NA, Nimrod C, De Vermette R, Fournier J (1997) Determination of intervillous flow in early pregnancy. Placenta 18:287–293
102. Simpson NA, Nimrod C, De Vermette R, Leblanc C, Fournier J (1998) Sonographic evaluation of intervillous flow in early pregnancy: use of echo-enhancement agents. Ultrasound Obstet Gynecol 11:204–208
103. Kurjak A, Kupesic S (1998) Parallel Doppler assessment of yolk sac and intervillous circulation in normal pregnancy and missed abortion. Placenta 19:619–623
104. Bude RO, van de Ven CJ, Rubin JM (1999) Transabdominal power Doppler sonography of the normal early placenta. Can Assoc Radiol J 50:255–259
105. Alouini S, Carbillon L, Perrot N, Uzan S, Uzan M (2002) Intervillous and spiral artery flows in normal pregnancies between 5 and 10 weeks of amenorrhea using color Doppler ultrasonography. Fetal Diagn Ther 17:163–166
106. Jauniaux E, Hempstock J, Greenwold N, Burton GJ (2003) Trophoblastic oxidative stress in relation to temporal and regional differences in maternal placental blood flow in normal and abnormal early pregnancies. Am J Pathol 162:115–125
107. Giacobbe M, Zeferino LC, Franzin CM, Faundes A (2002) Uteroplacental circulation during the first trimester of normal and abnormal pregnancy. Reprod Biomed Online 4:62–67
108. Chesley LC (1978) Hypertensive disorders in pregnancy. Appleton-Century-Crofts, Norwalk, CT, p 225
109. Turnbull AC (1987) Maternal mortality and present trends. In: Sharp F, Symonds EM (eds) Hypertension in pregnancy. Perinatology Press, Ithaca, NY, p 135
110. MacGillivray I (1983) Preeclampsia: the hypertensive disease of pregnancy. Saunders, Philadelphia, p 17
111. Chiswick ML (1985) Intrauterine growth retardation. BMJ 291:845–848
112. Allen MC (1984) Developmental outcome and followup of the small for gestational age infant. Semin Perinatol 8:123–156

113. Resnik R (1978) Maternal disease with abnormal, fetal growth. J Reprod Med 21:315
114. Beaufils M, Uzan S, Donsimoni R et al (1985) Prevention of preeclampsia by early antiplatelet therapy. Lancet 1:840–842
115. Andersen HG, Andersen LF, Fuchs AR (1989) Diet, preeclampsia and intrauterine growth retardation. Lancet 1:1146
116. Kaar K, Jouppila P, Kuikka J et al (1980) Intervillous blood flow in normal and complicated late pregnancy measured by means of an intravenous ^{133}Xe method. Acta Obstet Gynecol Scand 59:7–10
117. Nylund L, Lunell NO, Lewander R et al (1983) Uteroplacental blood flow index in intrauterine growth retardation of fetal and maternal origin. Br J Obstet Gynaecol 90:16–20
118. Sheppard BL, Bonnar J (1976) The ultrastructure of the arterial supply of the human placenta in pregnancy complicated by fetal growth retardation. Br J Obstet Gynaecol 83:948–959
119. McFayden IR, Price AB, Geirsson RT (1986) The relation of birthweight to histological appearance in vessels of the placental bed. Br J Obstet Gynaecol 93:476–481
120. Newnham JP, Patterson LL, James IR et al (1990) An evaluation of the efficacy of Doppler flow velocity waveform analysis as a screening test in pregnancy. Am J Obstet Gynecol 162:403–410
121. Jacobson S-L, Imhof R, Manning N et al (1990) The value of Doppler assessment of the uteroplacental circulation in predicting preeclampsia or intrauterine growth retardation. Am J Obstet Gynecol 162:110–114
122. Steel SA, Pearce JM, McFarland P et al (1990) Early Doppler ultrasound screening in prediction of hypertensive disorders of pregnancy. Lancet 1:1548–1551
123. Bewley S, Cooper D, Campbell S (1991) Doppler investigation of uteroplacental blood flow resistance in the second trimester: a screening study for preeclampsia and intrauterine growth retardation. Br J Obstet Gynaecol 98:871–879
124. Zimmermann P, Eirio V, Koskinen J, Kujansuu E, Harrington K (1997) Doppler assessment of the uterine and uteroplacental circulation in the second trimester in pregnancies at risk for pre-eclampsia and/or intrauterine growth retardation: comparison and correlation between different Doppler parameters. Ultrasound Obstet Gynecol 9:330–338
125. Papageorghiou AT, Yu CKH, Bindra R, Pandis G, Nicolaides KH (2001) Multicenter screening for preeclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. Ultrasound Obstet Gynecol 18:441–449
126. Chien PF, Arnott N, Gordon A, Owen P, Khan SK (2000) How useful is uterine artery Doppler flow velocimetry in the prediction of preeclampsia, intrauterine growth retardation and perinatal death? An overview. Br J Obstet Gynaecol 107:196–208
127. Martin A, Bindra R, Curcio P, Cicero S, Nicolaides KH (2001) Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11–14 weeks of gestation. Ultrasound Obstet Gynecol 18:583–586
128. Schuchter K, Metzenbauer M, Hafner E, Philipp K (2001) Uterine artery Doppler and placental volume in the first trimester in the prediction of pregnancy complications. Ultrasound Obstet Gynecol 18:590–592
129. Gant NF, Worley RJ (1980) Hypertension in pregnancy. Appleton-Lange, Norfolk, CT, p 29
130. Zeeman GC, Dekker GA (1992) Pathogenesis of preeclampsia: a hypothesis. Chr Obstet Gynecol 35:317
131. Thaler I, Manor D, Brandes JM et al (1990) Basic principles and clinical applications of the transvaginal Doppler duplex system in reproductive medicine. J In Vitro Fertil Embryo Transfer 7:74