Chapter 16

Doppler Velocimetry of the Uteroplacental Circulation

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Introduction

Since the last edition of this volume, interest has continued in uterine artery Doppler velocimetry (UADV) as a screening technique to predict adverse pregnancy outcomes such as preeclampsia, for pregnancy risk scoring, and as an entry criterion for randomized trials on medical therapies for the prevention of preeclampsia and intrauterine growth restriction. These areas have been updated and UADV for predicting pregnancy outcome in medical conditions other than preeclampsia has been added. The areas regarding non-Doppler assessment of uterine artery flow, physiology and development of uterine artery flow, and the development of uterine artery Doppler waveform remain essential and have been retained for historical purposes.

Non-Doppler Methods to Measure Uterine Artery Blood Flow

Methods developed to measure uteroplacental blood flow in humans, such as the nitrous oxide technique based on the Fick principle [1, 2], clearance of radioactive ^{24}N [3–6], and the flow probe technique [7], are obviously not suitable for human application. They suffer from various limitations, such as questionable accuracy, invasiveness, requirement for radiation, and being unsuitable for longitudinal observations. Once it was realized that the placenta must utilize maternal dehydroisoandrosterone sulfate, testosterone, and androstenedione in the intervillous space for the synthesis of estradiol, a technique that measured the rate of estradiol synthesis was developed to assess intervillous space perfusion in human pregnancies [8, 9]. This technique was tedious, required sophisticated laboratory equipment (which made it expensive), made use of isotope-labeled prehormone, and proved to be of questionable accuracy. Its clinical applicability is limited. Nonetheless, when all these techniques were applied to human pregnancies they had surprisingly similar results. Normal uterine blood flow at term was estimated at 500–700 ml/min with a two- to threefold decrease in uteroplacental perfusion noted in the presence of preeclampsia.

Uterine artery Doppler velocimetry was first reported by Campbell and colleagues in 1983 [10]. They showed that, compared to pregnancies with normal uterine artery waveforms, pregnancies with abnormal uterine artery Doppler waveforms were associated with more proteinuric hypertension, required more antihypertensive therapy, and resulted in lower birth weights and younger gestational ages at birth. Thus the capability for this potentially safe, noninvasive, prospective means of analyzing uterine artery blood flow during pregnancy was realized and set off a wave of interest and research that has continued until today.

Anatomy of Uterine Circulation

The uterine artery originates from the internal iliac artery and meets the uterus just above the cervix. The main uterine artery branches into the arcuate arteries, which arch anteriorly and posteriorly and extend inward for about one-third of the thickness of the myometrium (Fig. 16.1). They are tortuous and vary in thickness and in the area they supply. The arcuate artery network anastomoses near the midline [11]. The radial arteries arise from this network, are directed toward the uterine cavity, and become spiral arteries when they enter the endometrium.

There are a variety of arterial anastomoses of the human uterine circulation that have been demonstrated by anatomic and radiographic studies and uterine perfusion experiments [11–14]. Ipsilateral connections between uterine and ovarian arteries have been demonstrated. Also identified are contralateral anastomoses between the right and left uterine arteries and their branches. The uterine circulation is also connected to the systemic circulation, for example the inferior mesenteric, middle sacral, and inferior epigastric arteries. During pregnancy these anastomotic connections can increase in size and function after occlusion of major vessels.

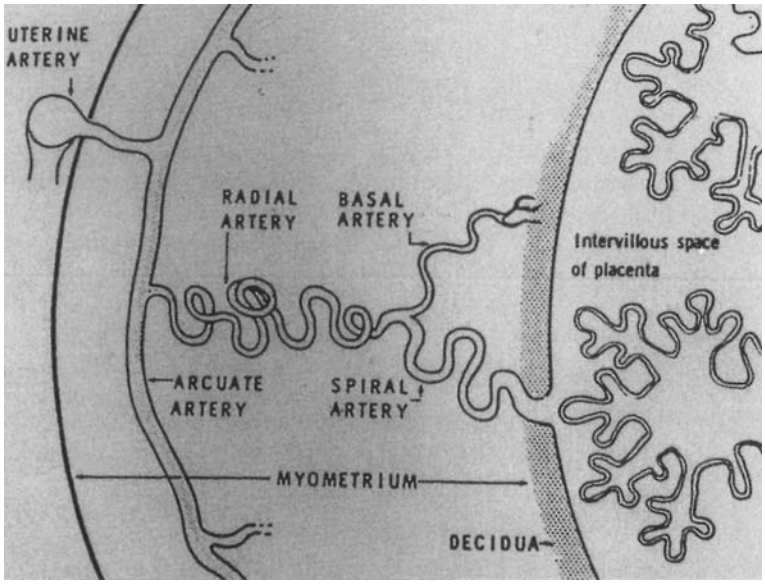

Fig. 16.1. Anatomy of the arcuate, radial, and spiral arteries during pregnancy. (From [112] with permission)

Normal Growth and Development of Uteroplacental Circulation During Pregnancy

During the first 12 weeks of pregnancy cytotrophoblasts invade the spiral arterial walls in the decidua and replace the endothelium and muscular media with a matrix of cytotrophoblasts and fibrinoid and fibrous tissue [15, 16]. The fibrinoid material is a complex of maternal fibrin and other plasma constituents plus proteinaceous material derived from the trophoblastic cells. Beginning at about 12 weeks' gestation and continuing throughout the remainder of the second trimester, the endovascular trophoblasts move into the myometrial segments of the spiral arteries. Once again the trophoblasts replace the endothelium and establish themselves in the muscular media. The elastic and muscular tissue of the myometrial segments of the spiral arteries is gradually lost and replaced with fibrinoid material (Fig. 16.2). This condition, along with the increase in blood flow and the associated hemodynamic forces, converts the entire length of the spiral arteries from small muscular arteries to dilated, tortuous uteroplacental vessels (Fig. 16.3). At term these changes can be seen at the distal portions of the radial arteries. The mean external diameter of the myometrial segments of the spiral arteries is approximately 500 μm, an increase from 200–300 μm in the nonpregnant state. The small muscular arteries that branch off the radial and spiral arteries, the basal arteries, do not undergo these

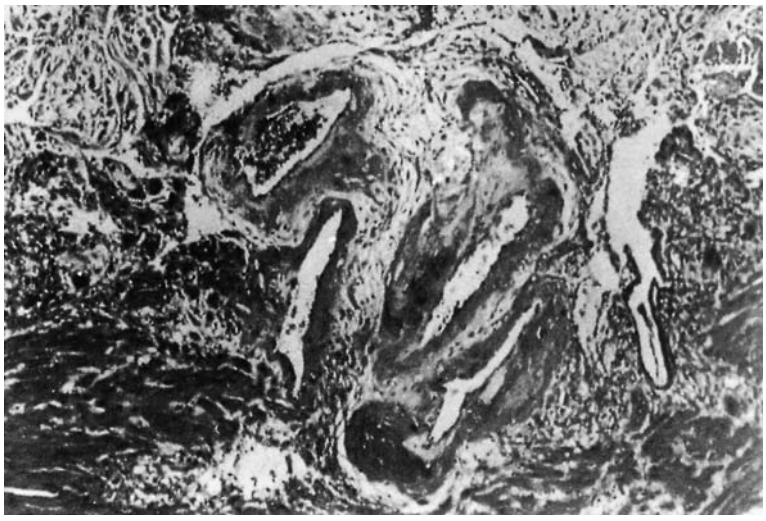

Fig. 16.2. Normal pregnancy. Spiral artery at the myometrial junction shows extensive structural alterations (physiologic changes). (Reprinted from [15] with permission)

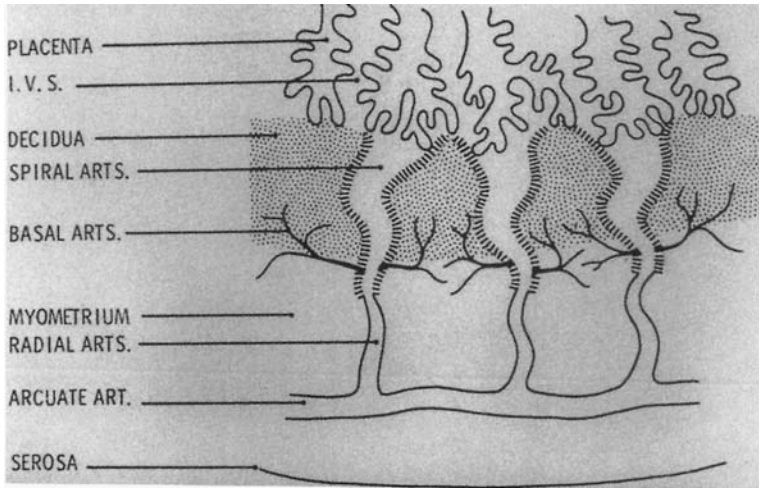

Fig. 16.3. Fully developed physiologic changes in the uteoplacental arteries during normal pregnancy. *Hatched portions* of the wall of these vessels indicate the extent of the physiologic changes. *I. V. S.* intrvillous space. (From [113] with permission)

changes. In all, approximately 100–150 converted spiral arteries supply the placental bed. It is believed that these uteroplacental vessels have lost their ability to respond to vasoactive substances.

The question arises whether this change from small muscular arteries to dilated tortuous vessels is entirely responsible for the increase in flow from 100 ml/min to 500–800 ml/min. All large vessels of the pregnant uterus, regardless of whether they supply the placental bed, undergo hyperplasia and hypertrophy [17]. Thus the increase in cross-sectional area leads to a reduction in resistance and further development of the uterine circulation. This increase in luminal diameter of the large vessels probably accounts for the increase in uteroplacental flow during the third trimester. In addition, the effects of the hormones estrogen and progesterone, the increased blood volume and cardiac output, the diminished blood viscosity, and the lowered peripheral resistance influence uterine flow.

Abnormal Development of the Uteroplacental Circulation in the Presence of Essential Hypertension, Preeclampsia, and Intrauterine Growth Restriction

According to Brosens et al. [15], Robertson et al. [16], and Khong et al. [18], a lack of endovascular infiltration by trophoblasts into the myometrial portion of the placental bed spiral arteries is a consistent finding in the presence of preeclampsia. The physiologic changes of the placental bed spiral arteries extend only to the deciduomyometrial junction (Fig. 16.4). With preeclampsia the spiral arteries may remain unconverted throughout their decidual and myometrial length (Fig. 16.5). Thus there is both an incompleteness in the degree of endovascular trophoblastic invasion of the spiral arteries, being confined to the decidual portion, and a reduction in the number of uteroplacental arteries formed. The diameter of the spiral arteries remains at 200–300 μm. Sheppard and Bonnar [19] reported the picture not to be so clear-cut, as they observed physiologic changes in the myometrial spiral arteries in preeclamptic pregnan-

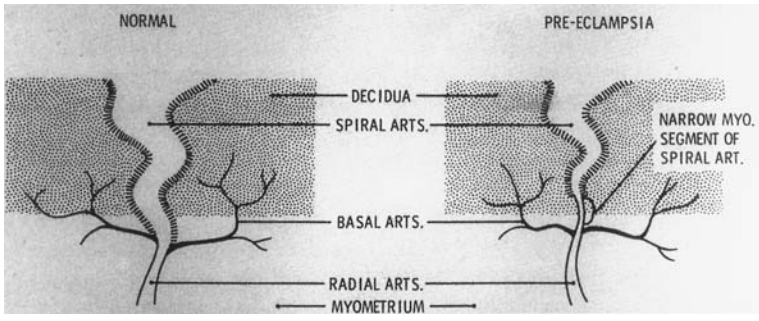

Fig. 16.4. Difference between normal and preeclamptic pregnancies regarding the extent of physiologic changes in the uteroplacental arteries. With preeclampsia these changes do not extent beyond the deciduomyometrial junction. (From [113] with permission)

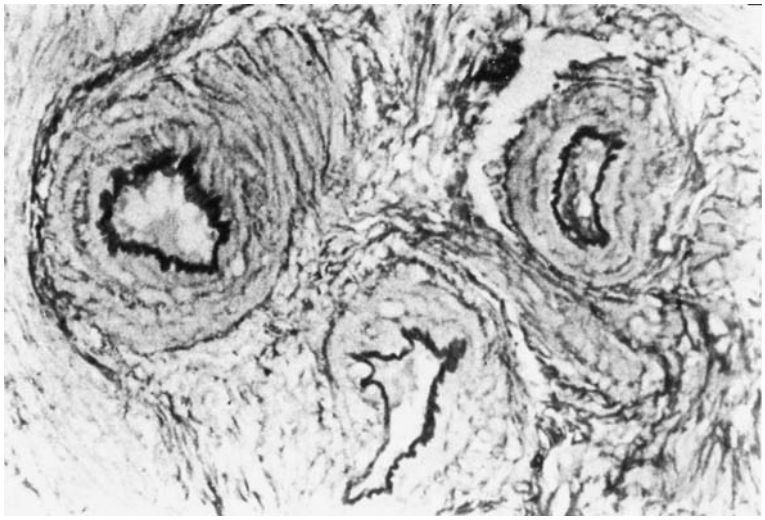

Fig. 16.5. Preeclampsia. Myometrial spiral artery is unaffected by physiologic changes and retains a normal internal elastic lamina. (Reprinted from [15] with permission)

cies. What has not been studied is whether the large vessels in the uterine artery circulation in the presence of preeclampsia undergo the same degree of hyperplasia as is seen in normotensive pregnancies.

Another placental bed lesion seen with preclampsia is an acute arteriopathy, termed acute atherosis by Zeek and Assali [20]. Here the wall of the spiral artery shows fibrinoid necrosis with lipophages, and there is a mononuclear cellular infiltrate around the artery (Fig. 16.6). This lesion is seen in the decidual and myometrial segments of the placental bed spiral arteries that have not undergone physiologic changes.

In pregnancies complicated by essential hypertension, hyperplastic arteriosclerosis of the myometrial segments of the placental bed spiral arteries can be seen [15, 16]. Here there is proliferation of all coats of the vessel wall, collagenous sclerosis, and stenosis of the lumen. The breadth and severity of the lesions correlate with the severity and duration of the hypertension. This lesion is not seen with preeclampsia unless there is a history of essential hypertension (Fig. 16.7). When essential hypertension is complicated by superimposed preeclampsia, both acute atherosis and hyperplastic arteriosclerosis are seen [15, 16].

In normotensive pregnancies resulting in intrauterine growth-restricted (IUGR) fetuses, acute artherosis has been seen in the decidual spiral arteries, with the myometrial spiral arteries retaining their muscular coats [18, 19]. This finding implies that these lesions are not particular to preeclampsia.

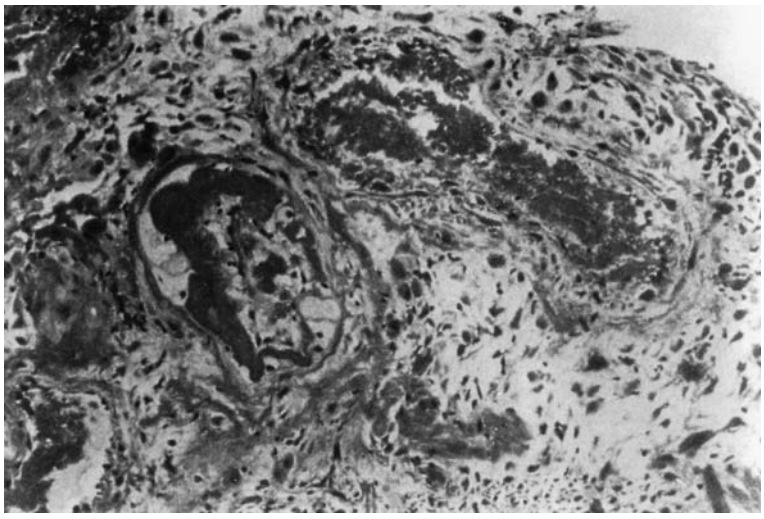

Fig. 16.6. Preeclampsia. Decidual portion of a spiral artery shows acute atherosis characterized by fibrinoid necrosis and infiltration of lipophages into the damaged vessel wall. (Reprinted from [15] with permission)

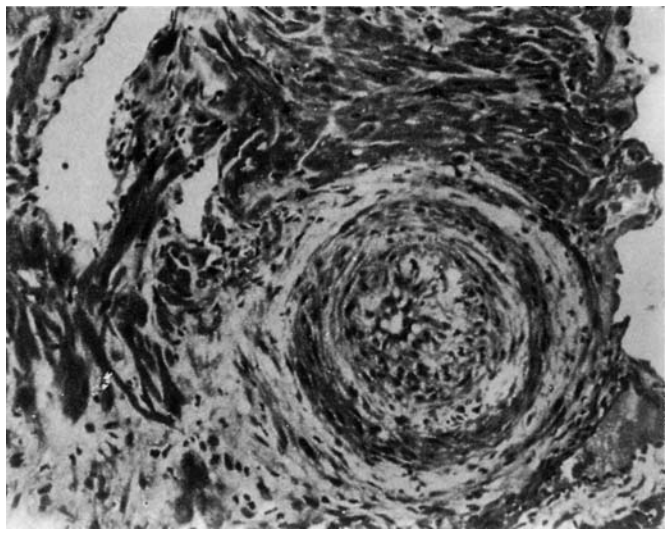

Fig. 16.7. Preeclampsia complicating essential hypertension. Myometrial spiral artery is unaffected by physiologic changes but shows hyperplastic changes in all layers of the vessel. (Reprinted from [15], with permission)

Indices of Uterine Artery Waveform Analysis

Uterine artery Doppler waveforms are most commonly analyzed by simple semiquantitative techniques based on analysis of the maximum Doppler shift frequencies of the time-velocity waveform, which varies during the cardiac cycle. Evaluation of the change in maximal Doppler shifts over time provides information on the impedance of the circulatory bed being fed. Time-velocity waveforms with high diastolic flow are seen when downstream resistance is low, and those with low or reverse diastolic flow are found when downstream resistance is high. The heart rate can significantly modify the waveform: high heart rates shorten the diastolic runoff time, producing high end-diastolic frequency shifts; low heart rates have an opposite effect. The Doppler shift frequencies are proportional to flow velocity. If the angle of insonation is kept constant over the course of the cardiac cycle, comparisons of Doppler frequency shifts from any point of the waveform are angle-independent.

There are three widely used semiquantitative techniques for analysis of uterine artery waveforms. The pulsatility index (PI) is the most complex of the three. The PI is equal to peak systole minus end diastole divided by the mean value of the area under the curve over one cardiac cycle: (S-D)/mean velocity. This index has an advantage when analyzing complex waveforms that have absent or reverse flow during parts of the diastole. However, it requires a computer program that can calculate the area under the curve. Whether the computer outlines the maximum frequency envelope or whether it is done manually, some degree of error is involved that is probably greater than that for other techniques. When uterine circulation resistance is high, the uterine artery waveform has shorter upstroke and downstroke times and an early diastolic notch. Infrequently, there is absent early diastolic flow or reverse flow of the main uterine artery. These characteristics can be incorporated in the waveform analysis if one uses the PI but not when other, simpler methods are utilized.

The other, simpler forms of uterine waveform analysis are the S/D ratio (or A/B ratio) and the resistance index (RI), or Pourcelot ratio [(S-D)/S]. All that is required here is measurements of peak systole and end diastole. The main problem with the S/D (A/B) ratio is that it becomes infinity when there is no or reversed end-diastolic velocity. The other obstacle is its nonparametric distribution at high values, which could be a problem because there are many occasions in the presence of severe preeclampsia where uterine artery S/D ratios are greater than 5.0. Nonparametric analysis is required when using the S/D (A/B) ratio [21]. To reiterate, these simple techniques would not be affected by the presence of a waveform early diastolic notch. Regardless of any peculiarities inherent in each type of waveform index, none has been proved to offer a clinical advantage over the other.

The general principles of Doppler indices are discussed in depth in Chap. 4.

Normal and Abnormal Development of Uterine Artery Doppler Waveform

In the nonpregnant state the uterine artery waveform exhibits high pulsatility with a rapid rise and fall in frequency shifts during systole, an early diastolic notch, and low diastolic shifts. Schulman et al. [22],

using transvaginal continuous-wave Doppler revealed high S/D ratios during the proliferative phase of the menstrual cycle (12.9 ± 4.4, mean ± standard deviation) that dropped significantly during the secretory phase (7.2 ± 3.2; $p = 0.003$) (Fig. 16.8). Scholtes et al. [23], using transvaginal pulsed Doppler found no significant difference in the PIs between the two uterine arteries, with mean PI values between 2.9 and 3.2. They found no correlation between the PI and stage of menstrual cycle. Long et al. [24], using transabdominal pulsed Doppler found similar results, with PI values of 3.25 ± 0.83. They also reported no difference between the uterine arteries and no correlation with the menstrual cycle. Thaler and colleagues [25], using transvaginal pulsed Doppler, obtained S/D ratios of 5.3 ± 1.1 in a group of 27 nonpregnant women (Fig. 16.9). The difference in the data of Schulman et al. and those of subsequent investigators is probably due to the problem of using continuous-wave Doppler sonography when trying to determine if a waveform showing the characteristics of high resistance is from the uterine artery.

Pregnancy results in marked changes in the uterine artery waveform. Schulman et al., using abdominal and vaginal continuous-wave Doppler ultrasonography, showed striking increases in uterine artery compliance between weeks 8 and 16 of gestation (Fig. 16.8) [22]. Increases in compliance continued until 26 weeks but in a less dramatic fashion. From 26 weeks onward the S/D ratios were similar, whether they were obtained abdominally or vaginally, and did not change in value throughout the remainder of pregnancy. The diastolic notch disappeared by 20–26 weeks' gestation. Thus the full evolution of the uterine artery waveform may not be complete until 26 weeks. These investigators defined abnormal uterine artery waveforms as those with S/D ratios greater than or equal to 2.7 (the average of the right and left uterine arteries) or persistence of the early diastolic notch.

Deutinger et al. [26] repeated Schulman's work using transvaginal pulsed Doppler ultrasonography and reported similar results except for a more gradual, smoother drop in S/D ratios during the first 14–16 weeks of gestation. Their mean averaged S/D values for each trimester were 5.5, 2.9, and 2.1. Deutinger et al. believed the S/D ratios plateaued at 24 weeks.

Thaler et al. [25] followed up using transvaginal pulsed Doppler (Fig. 16.9). Again, during the first 14–16 weeks the drop in S/D ratios was not as rapid as those obtained with continuous-wave Doppler ultrasound. During the first 26 weeks' gestation the S/D ratios were lower and had narrower standard deviations than did the continuous-wave data of Schulman et al. Thaler et al. also showed that the S/D values do

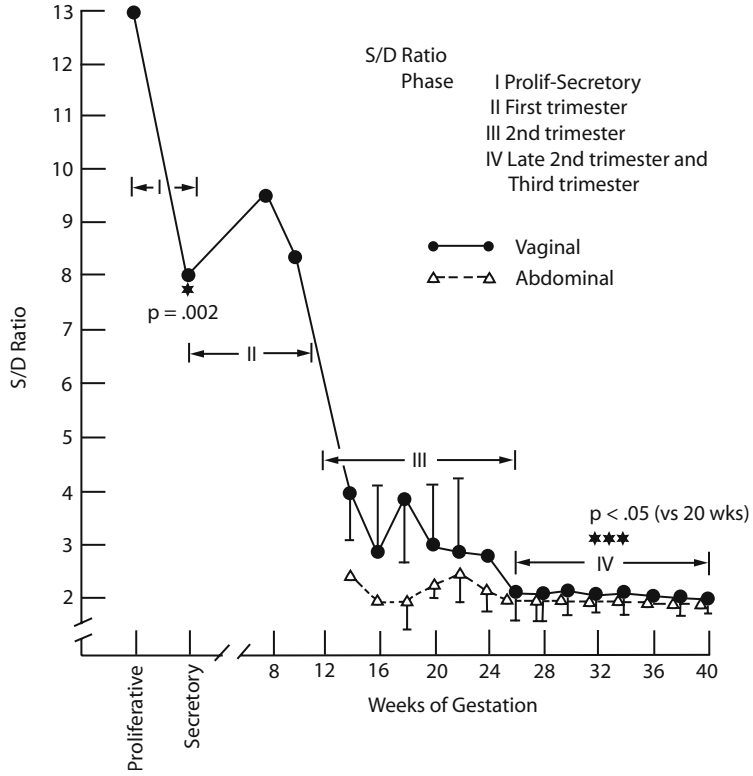

Fig. 16.8. Uterine artery complicance during the menstrual cycle and throughout pregnancy (means ± SD). *Circles* represent measurements through the vaginal fornices; *triangles* represent measurements across the abdomen. Each value represents the average between the left and right arteries. *S/D* systolic/diastolic. (Reprinted from [44] with permission)

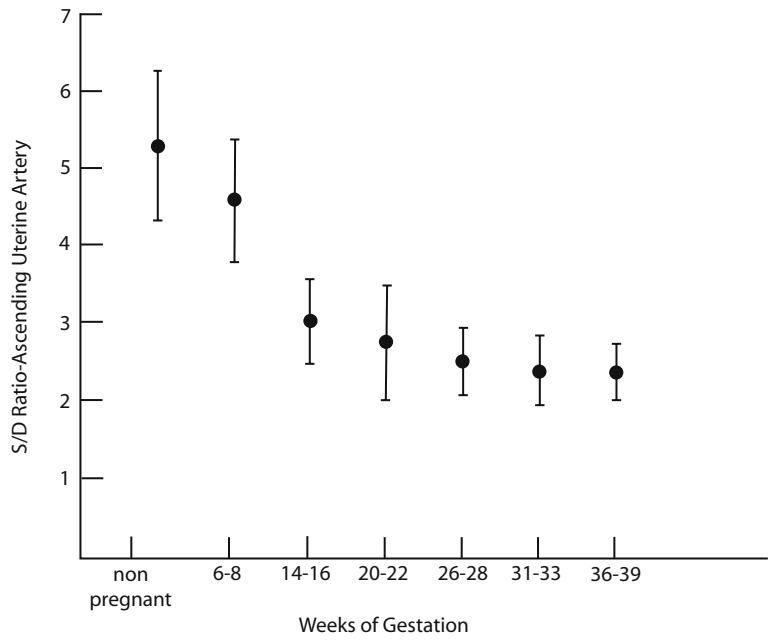

Fig. 16.9. Systolic/diastolic (*S/D*) flow velocity ratios in the uterine artery in the nonpregnant state and during weeks of gestation. (Reprinted from [28], with permission)

not plateau until 26 weeks. Thus the uterine artery waveform transforms rapidly to one of lower pulsatility during the first 16 weeks and shows continual but less dramatic increases in compliance until 26 weeks' gestation, by which time it should lose its diastolic notch. From 26 weeks onward the waveform has a stable appearance.

Pearce et al. [27], using a pulsed duplex Doppler technique, portrayed similar evolutions in the RI from 16 weeks onward. They noted that there was increased compliance in the placental (versus nonplacental) uterine artery. Trudinger et al. [28] studied the subplacental vascular bed with continuous-wave Doppler ultrasound. They were probably insonating the arcuate and radial arteries, and they reported a progressive drop in S/D ratios. Their values were lower than those of other investigators, however, because they were interrogating distal branches of the uterine circulation whereas the configuration of the main uterine artery waveform is affected by the summation of resistances of the entire vascular tree. They did not report a notch in any subplacental waveform.

A lesson learned from these studies is that continuous-wave Doppler ultrasound is probably unreliable for studying the uterine artery in the nonpregnant state and up to 14–16 weeks' pregnancy, as pattern recognition is used to identify the uterine artery. It is not until 14–16 weeks' gestation that there is a generous diastolic component to the waveform, thereby clearly distinguishing it from waveforms of other pelvic vessels.

A number of other investigators have looked at the early development of the uterine artery (during the first 18 weeks' gestation) using continuous-wave, pulsed-wave, and color Doppler techniques [29–32]. Regardless of the equipment or waveform index used, all showed a significant, smooth, progressive decrease in waveform indices (Fig. 16.10). Using transvaginal color Doppler sonography, Jurkovic et al. [30] and Juaniaux et al. [31] showed uterine artery mean RIs decreasing from 0.80 at 8 weeks to around 0.63 at 17 weeks; and the mean PI of 2.0 at 8 weeks dropped to nearly 1.3 at 18 weeks' gestation. Their variation around the mean was narrower than those of other investigators, probably because they used color Doppler ultrasonography as the method of vessel identification.

Uterine Artery Diameter and Volume Flow

Estimations of volume flow of the uterine arteries would be an ideal method to determine the state of this circulation. However, to determine volume flow, knowledge of the angle of incidence and vessel diameter is required. Any error when estimating vessel diameter becomes squared, and small errors when determining the angle of incidence result in even larger errors in the velocity calculations. Estimates of volume flow are accurate when the angle of incidence is zero and the vessel of interest is straight. Such conditions are difficult to achieve when studying the main uterine arteries. Volume flow assessments of the uterine artery are confounded further by the abundant collateral circulation.

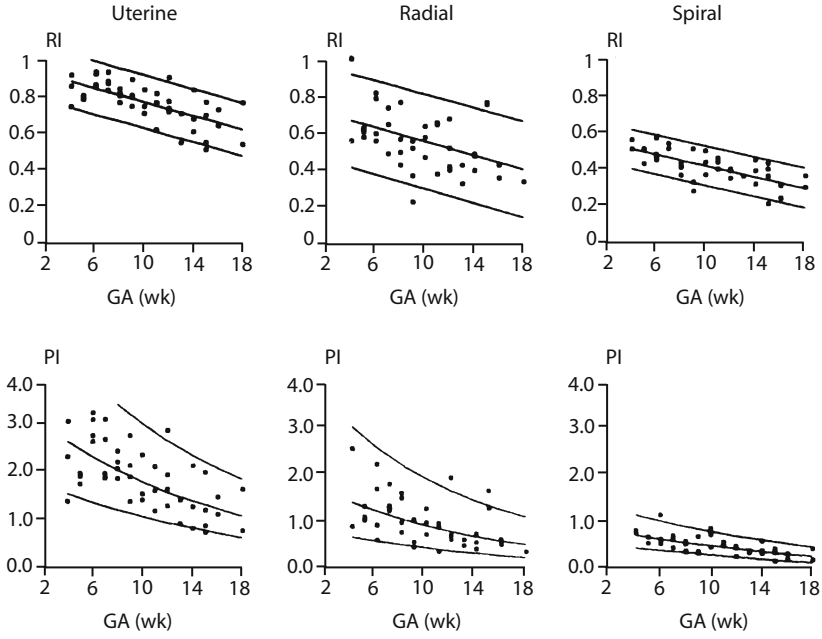

Fig. 16.10. Individual values and reference ranges (mean and 90% confidence interval) of the resistance index (*RI*) and pulsatility index (*PI*) in the uteroplacental circulation with gestational age (*GA*). Both indices decreased significantly with gestation in all three arteries. (Reprinted from [30] with permission)

Three investigative groups have reported their data on uterine volume flow. Thaler et al. [25] used the transvaginal approach to study the left ascending uterine artery. They reported a mean volume flow rate of 94.5 ml/min before pregnancy, which increased to a mean of 342 ml/min during late pregnancy (Fig. 16.11); it represented a 3.5-fold increase. The standard deviation about the mean volume flow during the last trimester was reasonable at ± 50 ml/min. The mean diameter was 1.6 mm before pregnancy and increased to 3.7 mm at term, which represented more than a twofold increase (Fig. 16.12). Thaler et al. did not see a significant difference in volume flow between the two uterine arteries in a group of 32 women who were studied up to 26 weeks' gestation.

Palmer et al. [33], with transabdominal pulsed Doppler ultrasonography and without the color Doppler technique, reported remarkably similar results for vessel diameter and volume flow measurements. The uterine artery diameter doubled by week 21 (from 1.4 ± 0.1 to 2.8 ± 0.2 mm; $p < 0.05$), did not change between weeks 21 and 30 (2.9 ± 0.1 mm), and increased between weeks 30 and 36 (to 3.4 ± 0.2 mm). Uterine artery volume flow was approximately 312 ml/min by 36 weeks' gestation. These investigations showed that increases in uterine artery flow during the first 21 weeks of pregnancy were due equally to changes in uterine artery diameter and mean velocity, whereas the rise during late pregnancy (30–36 weeks) was mainly due to increases in mean flow velocity. Their use of two pulsed Doppler devices to separately measure uterine artery diameter and mean velocity and then combine the measurements to determine volume flow is not technically sound.

Bower and Campbell [34] estimated uterine volume flow using the transabdominal approach. They found marked differences in volume flow between the placental and nonplacental uterine arteries, with values of approximately 400 ml/min and 290 ml/min, respectively, at 42 weeks' gestation. Although their

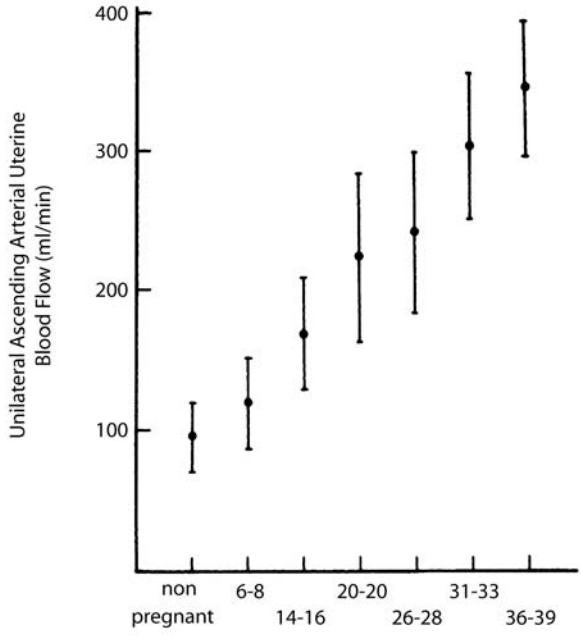

Fig. 16.11. Changes in uterine blood flow during pregnancy. (Reprinted from [28] with permission)

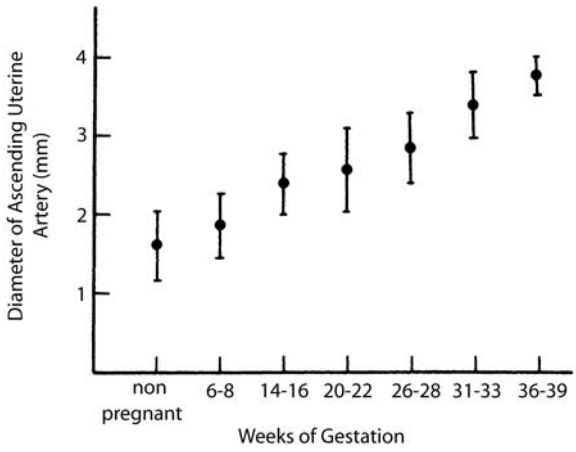

Fig. 16.12. Diameter of ascending uterine artery at various gestational ages. (Reprinted from [28] with permission)

mean volume flow values were similar to those of Thaler et al. and Palmer et al., there was great variation around the mean, and their measurements were skewed. Some of their volume recordings of the placental uterine were greater than or equal to 1 l/min – readings that were not seen in the studies of Thaler et al. or Palmer et al.

These data show that changes in the placental spiral arteries do not solely explain the development of the uterine circulation, and that the increase in flow is in part due to hypertrophy of the larger uterine vessels. Moreover, the preliminary data show that volume flow estimates of the uterine artery may be more reproducible with the transvaginal approach. Additional work is requested to assess its association with perinatal outcome and the potential for clinical usefulness.

Uterine Artery Maximum and Mean Flow Velocity

Maximum and mean velocities of the uterine artery in the nonpregnant and pregnant state have been studied. Jurkovic et al. [30], using transvaginal color Doppler sonography, showed a significant increase in maximum peak systolic velocity, from approximately 53 cm/s at 6 weeks' to 140 cm/s at 18 weeks' gestation. Jauniaux et al. [31], using the same technique, found almost identical changes in peak systolic velocities. At 10 weeks' the peak velocity of 68.0 ± 8.5 cm/s increased to 74.0 ± 6.5 cm/s at 13 weeks' gestation. At 14 weeks gestation there was an abrupt significant increase to 117 ± 7 cm/s ($p = 0.005$). A slow increase continued until 17 weeks (127.0 ± 9.3 cm/s). During these time periods both investigators noted decreasing impedance in the uterine, radial, and spiral arteries (Fig. 16.10). They believed that it supported the hypothesis that endovascular trophoblastic invasion of the spiral arteries reduces resistance. Also, the progressive fall in resistance from the uterine artery to the radial and spiral arteries was due to an increase in branching and cross-sectional area of the circulation.

Palmer et al. [33], using transabdominal pulsed Doppler sonography without color flow mapping, was able to insonate the uterine artery as it branched off the internal iliac artery. They recorded a mean flow velocity of 8.4 ± 2.2 cm/s in the nonpregnant state. At 21 weeks of pregnancy the mean flow velocity rose to 38.5 ± 4.9 cm/s and continued to increase to 46.6 ± 3.4 cm/s at 30 weeks and 61.4 ± 3.0 cm/s at 36 weeks of pregnancy. Bower and Campbell [34], using transabdominal pulsed Doppler sonography with color flow mapping, obtained signals from the uterine artery as it crossed medially to the external iliac artery. Their measurements of mean flow velocity at similar gestational ages were lower, with large variation around the means. Mean velocities in the placental uterine artery were greater than those in the nonplacental uterine artery. Their data were also markedly skewed.

These data show that maximal and mean flow velocities of the uterine artery increase throughout gestation. The velocity data during early pregnancy [30, 31] were remarkably similar, showed reasonable variation, and were obtained by the technique that should be best suited for these measurements (transvaginal pulsed Doppler sonography with color flow mapping). However, the data need to be reproduced by others. Mean and maximal velocities from midpregnancy onward must be studied with the same technique. The method Palmer et al. used to detect signals from the uterine artery as it branches off the internal iliac artery deep in the pelvis (transabdominal approach with color flow mapping) is difficult, and the transabdominal approach of Bower and Campbell results in considerable variation. The clinical usefulness of such data must also be explored.

Uterine Artery Waveform Notch

The uterine artery Doppler waveform has an early diastolic notch in the nonpregnant state, and it often persists in the pregnant state until weeks 20–26. What constitutes an early diastolic notch during pregnancy has never been defined. Campbell et al. [35] defined a "true" abnormal notch during pregnancy as a deceleration of at least 50 Hz below the maximum diastolic velocities after 20 weeks. They believed that it is rarely seen on the placental side beyond that point of pregnancy. Fleischer et al. [36] thought that it is a

normal finding until week 26 of gestation. Later, Thaler et al. [37] identified a group of women who had both systolic and diastolic notches in the uterine artery waveform and demonstrated that perinatal outcome was worse than when there was a diastolic notch only (Fig. 16.13). Retention of the early diastolic notch is thought to represent persistence of the inherent total high impedance of the uterine artery circulation. It has been identified in waveforms of the main uterine artery and its most proximal branches.

Fleischer et al. [36] were the first to note the importance of the uterine notch in their study of 71 women with hypertensive disorders of pregnancy. Ninety percent (27 of 30) of women who developed preeclampsia or chronic hypertension with superimposed preeclampsia had a uterine waveform notch. When normal pregnancy outcome was defined as delivery at 37 weeks or later or a birth weight of 2500 g or more, the uterine artery notch had better sensitivity (93%), specificity (91%), positive predictive value (87%), and negative predictive value (95%) compared to the mean arterial blood pressure, creatine clearance, uric acid level, and uterine S/D ratios.

Thaler et al. [37] evaluated a group of 140 hypertensive pregnant women. Of 39 women with diastolic or systolic notches (or both) in the uterine artery waveform, 82% (32 of 39) had pregnancy-related hypertensive complications. Hypertensive women with uterine systolic and diastolic notches had higher waveform indices of both uterine and umbilical arteries, higher diastolic and systolic blood pressures, and worse perinatal outcomes than those without notches (Tables 16.1 and 16.2). When umbilical artery resistance was normal and both uterine arteries had elevated resistance indices, the group with the uterine waveform notch had worse perinatal outcomes (Table 16.3). When the uterine artery and umbilical artery waveforms were abnormal, the presence of the

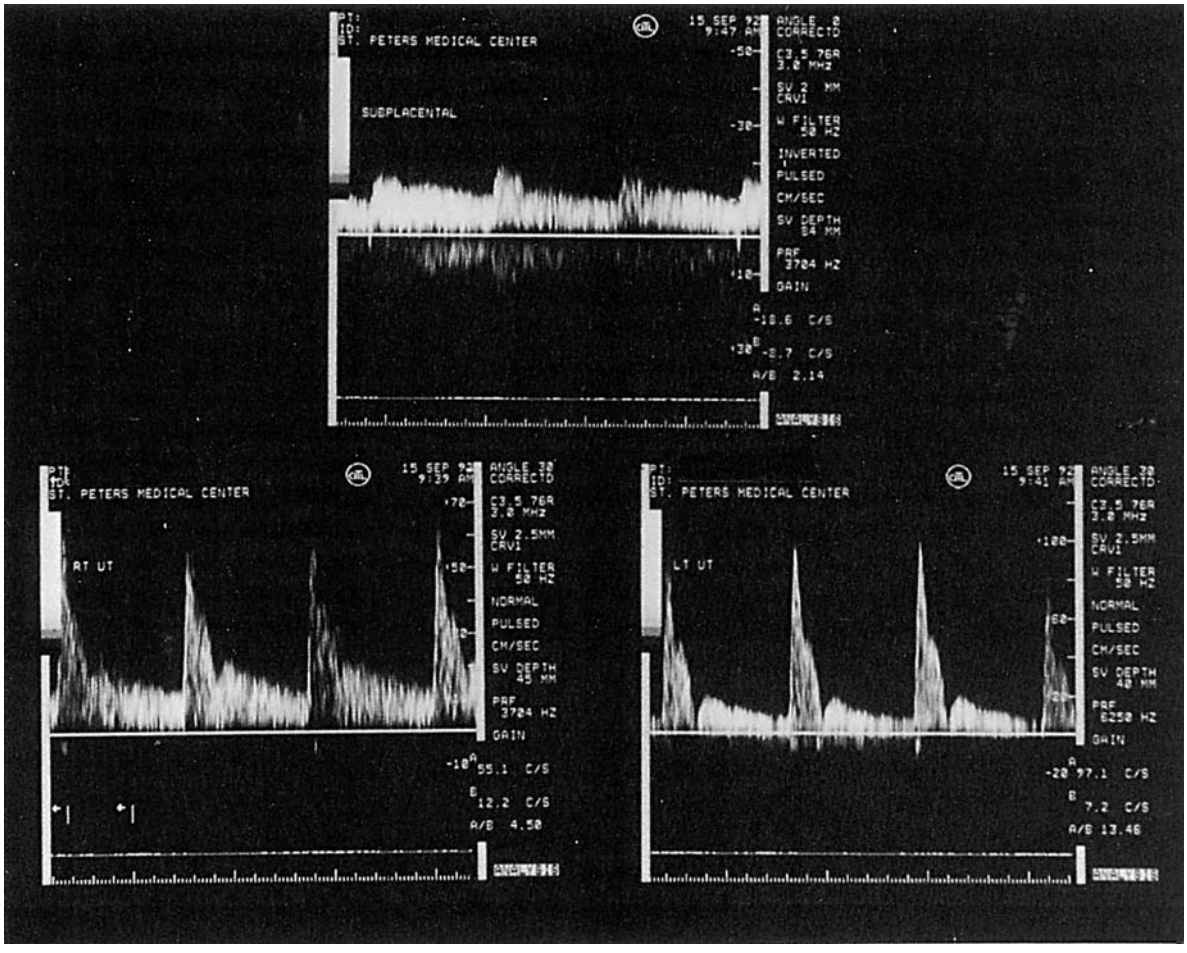

Fig. 16.13. Subplacental (*top*), right uterine (*bottom left*), and left uterine (*bottom right*) waveforms in a chronically hypertensive pregnant woman at 22 weeks' gestation. Both uterine arteries have systolic and diastolic notches. The placenta was central and posterior. At 26 weeks' gestation she presented with a fetal demise after an arrest of fetal growth at 19 weeks

Table 16.1. Resistance indexes and blood pressures in hypertensive pregnant patients with and without a systolic or diastolic notch (from [37] with permission)

Parameter	Notch absent ($n=101$)	Diastolic notch ($n=25$)	p	Systolic notch ($n=14$)	p
Resistance index					
Left uterine artery	0.64 ± 0.1	0.77 ± 0.1	< 0.0001	0.78 ± 0.07	< 0.0001
Right uterine artery	0.65 ± 0.1	0.75 ± 0.09	< 0.01	0.78 ± 0.07	< 0.0001
Umbilical artery	0.66 ± 0.1	0.74 ± 0.1	< 0.01	0.78 ± 0.1	< 0.0001
Blood pressure (mmHg)					
Systolic	140.3 ± 14.8	146 ± 17.7	NS	153 ± 20	< 0.003
Diastolic	91.4 ± 9.3	99.0 ± 8.9	< 0.006	98 ± 7.9	< 0.004

NS, not significant. Data are presented as means ± SD.

Table 16.2. Pregnancy outcomes in hypertensive pregnant patients with and without a systolic or diastolic notch in the uterine artery flow velocity waveform (from [37] with permission)

Parameter	Notch absent ($n=101$)	Diastolic notch ($n=25$)	p	Systolic notch ($n=14$)	p
Delivery (weeks)	37.6 ± 2.48	34 ± 3.5	< 0.001	33.4 ± 2.8	< 0.001
Perinatal mortality (%)	5	12		14.3	
Fetal growth retardation (%)	12.9	64	< 0.00001	64.3	< 0.00003
Abnormal FHR in labor (%)	13.9	28		42.9	< 0.025
Cesarean for fetal distress (%)	29.7	56	< 0.03	64.3	< 0.025
Apgar score < 7 at 5 min (%)	6.9	16		25.6	< 0.04
NICU > 48 h (%)	16.8	52	< 0.0006	71.5	< 0.00003

FHR, fetal heart rate; NICU, neonatal intensive care unit.

Table 16.3. Pregnancy outcomes in hypertensive pregnant patients with an abnormally elevated resistance index in both uterine arteries[a] (from [37], with permission)

Parameter	Normal umbilical artery RI		Abnormal umbilical artery RI	
	Notch absent ($n=11$)	Notch present ($n=8$)	Notch absent ($n=13$)	Notch present ($n=19$)
Delivery (weeks)	38.2 ± 1.4	35.7 ± 2	36.3 ± 3	33.4 ± 2.8
Perinatal mortality (%)	0	12.5	0	21.1
Fetal growth retardation (%)	0	62.5*	15.4	73.7**
Abnormal FHR during labor (%)	0	37.5	23.1	36.8
Cesarean for fetal distress (%)	27.3	50	46.2	52.6
Apgar score < 7 at 5 min (%)	0	37.5	7.7	21.2
NICU > 48 h (%)	0	62.5*	30.8	63.2
Resistance index				
Left uterine artery	0.72 ± 0.05	0.76 ± 0.09	0.72 ± 0.08	0.79 ± 0.07
Right uterine artery	0.72 ± 0.04	0.78 ± 0.07	0.72 ± 0.04	0.76 ± 0.06
Umbilical artery	0.57 ± 0.06	0.60 ± 0.04	0.75 ± 0.06	0.78 ± 0.09

FHR, fetal heart rate; NICU, neonatal intensive care unit; RI, resistance index.
[a] Based on resistance index in the umbilical artery and presence or absence of notch in the uterine artery.
* $p < 0.005$; ** $p < 0.002$.

uterine notch portended a worse perinatal outcome (Table 16.3). When the umbilical RI was normal and there was no notch in the uterine artery waveform, perinatal outcome was similar whether the uterine artery RI was normal or abnormal (Table 16.4). Thaler et al. clearly showed that the uterine artery systolic and diastolic notches were the better predictor of perinatal outcome than the RI alone. Aristidou et al. [38] undertook uterine artery screening in women with elevated maternal serum α-fetoprotein levels, and they too noted that the uterine artery notch was a good predictor of poor perinatal outcome.

Table 16.4. Pregnancy outcomes in women with normal resistance indexes in umbilical artery flow velocity waveforms and no notch in uterine artery waveforms (from [37], with permission)

Parameter	Normal uterine artery RI ($n=30$)	Abnormal uterine artery RI ($n=11$)
Delivery (weeks)	38.5 ± 1.55	38.2 ± 1.4
Birth weight (g)	3,184 ± 738	3,104 ± 544
Perinatal mortality (%)	0	0
Fetal growth retardation (%)	3.3	0
Abnormal FHR during labor (%)	3.3	0
Cesarean for fetal distress (%)	3.3	27.3
Apgar score < 7 at 5 min (%)	0	0
NICU > 48 h (%)	3.3	0

FHR, fetal heart rate; NICU, neonatal intensive care unit; RI, resistance index.

It is of interest that when Trudinger and Cook [39], using continuous-wave Doppler ultrasonography, studied the subplacental arteries in pregnant women with severe proteinuric hypertension they did not report a diastolic notch. As in the study of Thaler et al. [37], regardless of whether there was normal or increased impedance in the subplacental vessels, there was no correlation with fetal or neonatal outcome.

Rarely, absent early diastolic flow and reverse flow of the uteine artery waveform are seen (Figs. 16.14, 16.15).

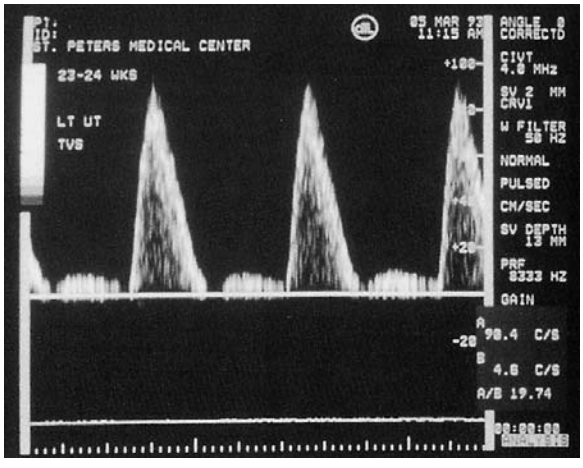

Fig. 16.14. Absent early-diastolic velocities in the uterine artery velocity wave with pulsed Doppler

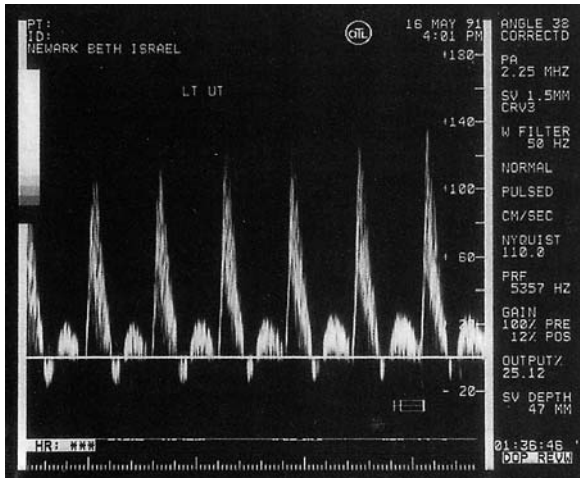

Fig. 16.15. Reverse flow of the uterine artery of a severely preeclamptic woman

Influence of Placental Location on Uterine Artery Waveforms

It has been observed that placental location influences the uterine and arcuate artery waveform [22, 40–43]. In the case of a lateral placenta, the placental uterine and arcuate artery waveform frequently shows low resistance (Fig. 16.16). Nomograms for placental and nonplacental uterine and arcuate artery waveforms using transabdominal color and pulsed Doppler techniques have been constructed (Fig. 16.17) [34].

Campbell et al. [40] were the first to report that the RI of the placental uterine artery was significantly lower than that of the nonplacental uterine artery. This difference increased when the waveforms were abnormal.

Schulman et al. [44] developed the concept of divergent uterine arteries. They thought that uterine levorotation or dextrorotation made ultrasonic placental localization difficult. Also, most lateral placentas are not pure lateral placentas. Another confounding variable is the development of a collateral circulation, and that the right and left uterine circulations may or may not have functioning anastomoses. These authors therefore thought it was more important to look at the difference between the right and left S/D ratios. They found that normal pregnancies were associated with more or less equal contributions from each uterine artery, and that the normal S/D ratio difference between the uterine arteries was 0.3 ± 0.3. Accordingly, divergent uterine arteries were defined as those with S/D ratio differences of greater than or equal to 1.0. They found that 81% of women with abnormal S/D ratios had significant divergence. When there was an abnormal S/D ratio the outcome was worse when there was divergence.

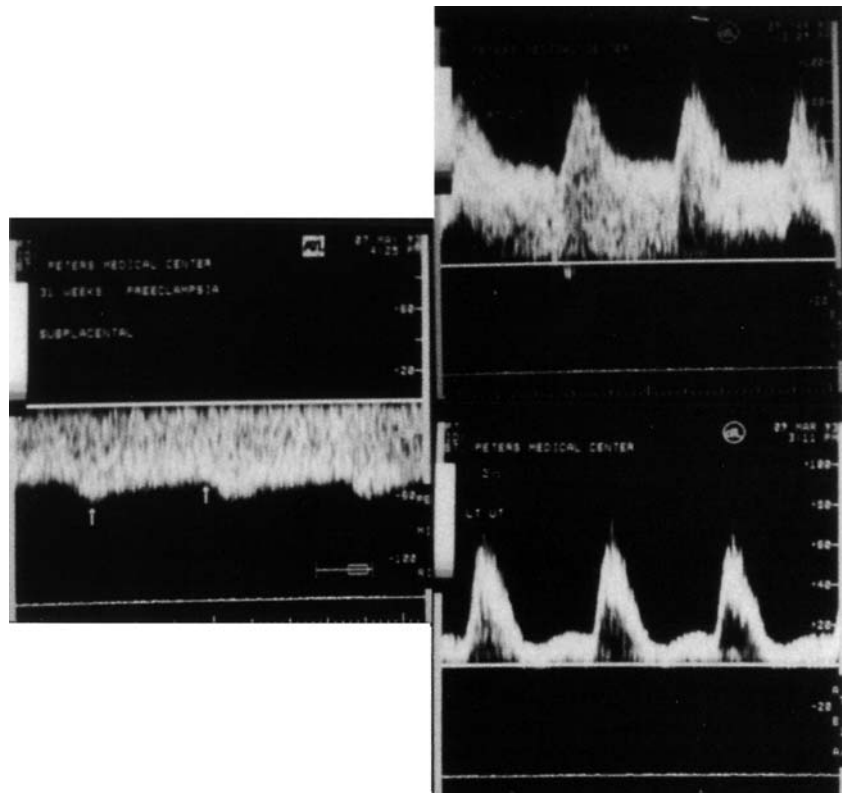

Fig. 16.16. Spiral (*left*), right uterine (*top right*), and left uterine (*bottom right*) artery velocity waveforms in a pre-eclamptic woman at 31 weeks' gestation. The right lateral placentation resulted in divergent uterine velocity waveforms, with the right uterine artery circulation much more compliant than that on the left

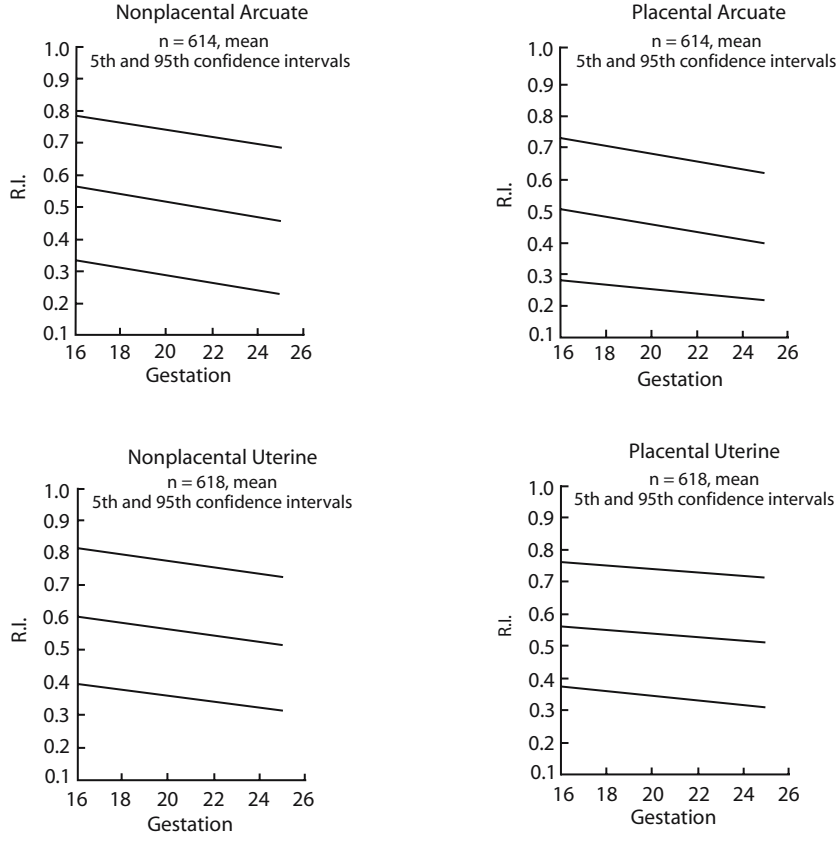

Fig. 16.17. Reference ranes of the uterine and arcuate resistance index, demonstrating the effect of placental site. (Reprinted from [34] with permission)

Kofinas et al. [41] believed that they could define placental location by ultrasonography. They found that in both normal and hypertensive pregnancies with unilateral placentas the S/D ratio of the placental uterine artery was significantly lower than that of the contralateral artery (1.73 ± 0.35 versus 2.46 ± 0.73; $p < 0.001$, and 2.38 ± 1.01 versus 4.04 ± 1.77, $p = 0.0012$). Ito et al. [42] and Oosterhof and Aarnoudse [43] found the same placental effect on the ipsilateral uterine artery, but in addition Ito et al. [41] observed that the lower the placental site, the lower the uterine waveform index.

Kofinas et al. [45] reexamined the relation between placental location and uterine artery velocimetry and found that perinatal outcome correlated best with the placental uterine artery; the mean index using both uterine arteries had the next best condition, and the nonplacental uterine artery was the poorest predictor. As they pointed out, the placental uterine artery perfuses most of the placental bed and the nonplacental uterine artery primarily perfuses nonplacental myometrial vessels.

It is clear from these studies that the unilateral placenta results in greater erosion and recruitment of the subplacental spiral arteries of the ipsilateral uterine circulation. The question is whether placental location is essential when evaluating uterine artery Doppler waveforms.

Doppler Waveforms of the Arcuate, Radial, and Spiral Arteries

Color flow mapping has allowed us to interrogate specific sites of the uterine circulation. Several investigators have demonstrated a progressive drop in impedance in all aspects of the uterine circulation, from the main uterine arteries to the spiral arteries, as pregnancy advances (Fig. 16.10) [30–32, 46]. Also, there is a drop in resistance from the proximal to the distal branches of the uterine circulation, the uterine artery having the highest impedance and the spiral arteries the least (Fig. 16.18). These studies are important physiologic observations whose clinical value has yet to be realized.

If one considers the subplacental spiral artery lesions identified in the presence of preeclampsia, essential hypertension, or fetal intrauterine growth restriction (IUGR), the subplacental vessels seem to be the ideal site of Doppler sampling to detect abnormal resistance in the uteroplacental circulation. Trudinger et al. [28], using continuous-wave Doppler sonography, was the first to obtain signals from the arcuate and radial arteries. However, they detected increases in the S/D (A/B) ratios in some but not all high-risk pregnancies. Some subplacental radial and arcuate arteries are normal in the face of significant pathology in others.

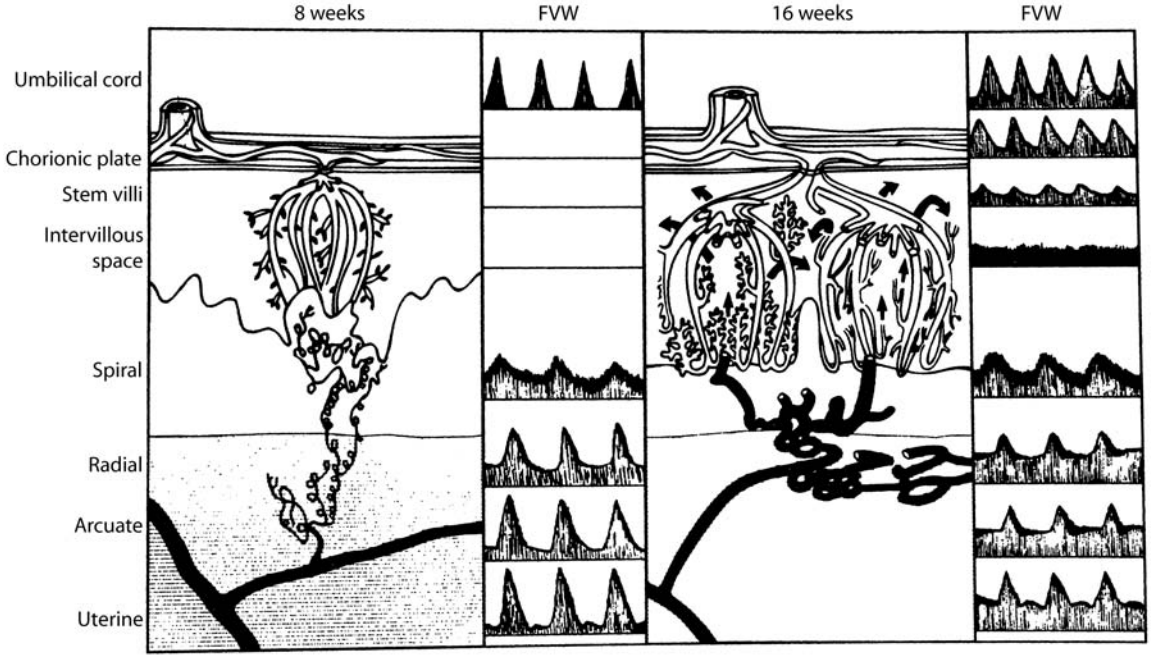

Fig. 16.18. Flow velocity waveforms (*FVW*) obtained from both placental circulations at 8 and 16 weeks' gestation, respectively. Note the progressive increase in diastolic flow of the uteroplacental waveforms from the uterine artery to the spiral artery and as gestational age advances. (From [31] with permission)

Voigt and Becker [47] studied 58 women with pregnancy-induced hypertension ($n=49$) or fetal IUGR using pulsed Doppler sonography of the subplacental arcuate arteries. They correlated the arcuate artery PI with placental bed biopsy findings. There were marked increases in the subplacental arcuate artery PI when the placental bed biopsies were pathologic.

Judging from these studies it appears that using information from sites other than the main uterine artery for clinical purposes requires color and pulsed Doppler sonography. Even with this technology it remains difficult to differentiate the radial, arcuate, and spiral artery waveforms. The difference in the main uterine waveform indices between normal and pathologic pregnancies is probably greater than at other sites. This difference allows clearer distinction between normal and abnormal waveform index values. Measurement of the main uterine artery may be more reproducible and allow standardized longitudinal follow-up. It seems that studying the main uterine artery waveform, a reflector of total subplacental resistance, remains the most clinically important parameter.

Effect of Pharmacologic Agents and Epidural Anesthesia on Uterine Artery Waveforms

Uterine Doppler velocimetry has been used to study the effects of drugs on the uterine circulation. Nifedipine [48], dihydralazine [49], indomethacin [50], oxymetazoline [51], pseudoephedrine [52], smoking [53], and nicotine gum [53] have not been shown to alter uterine waveform indices during pregnancy. Estrogen and progesterone hormonal replacement therapy after 6–10 weeks or on a chronic basis and magnesium sulfate therapy for tocolysis have been shown to lower uterine artery resistance [54]. Magnesium sulfate was found either to have no effect [55] or to lower [56] resistance. Methyldopa had no effect on the uterine artery PI [57]. The effects of several β-blockers have been looked at with varying results. In one study propranolol had no effect, but pindolol decreased resistance [58]. Atenolol was found to increase the arcuate artery PI [59]. The latter study must be reproduced, as it has important implications for management of the pregnant hypertensive woman.

There is evidence that preeclampsia is associated with a deficiency of prostacyclin, which could lead to generalized vasoconstriction. Therefore prostacyclin infusion seems to be a potential form of treatment for preeclampsia. Jouppila et al. [60] intravenously infused prostacyclin in 13 preeclamptic women. It resulted in significant decreases in maternal blood pressure and a rise in maternal plasma 6-ketoprostaglandin $F_{1\alpha}$. However, there was no effect on uterine artery flow when studied with the intravenous xenon 133 isotope clearance method. This study would be worth repeating using Doppler technology.

Uterine artery waveforms have been studied after infusion of angiotensin II. Erkkola and Pirhonen [61] used color and pulsed Doppler sonography to study the uterine artery between 24 and 26 weeks' gestation and found increases in the S/D ratio after angiotensin II infusion (1.6 ± 0.1 versus 2.09 ± 0.29, $p < 0.001$). This increase was not affected by placental location. Interestingly, the increases in uterine artery resistance followed the increases in blood pressure, providing evidence of a differential response in the uterine circulation versus the systemic vasculature. In a follow-up report they compared the uterine artery response to angiotensin II infusion in normotensive and hypertensive pregnant women [62]. The uterine S/D ratios increased equally in the two groups but the increase was faster and recovery slower in the hypertensive group. Jones and Sanchez-Ramos [63] reported no changes in uterine artery S/D ratios using continuous-wave Doppler ultrasonography in nine normotensive pregnant women.

The effects of epidural anesthesia on uterine artery resistance have been studied using Doppler velocimetry. Four studies using anesthetic agents with and without epinephrine showed no change in uterine artery resistance in normal, term, laboring patients or in those prior to elective cesarean section [64–67].

Ramos-Santos et al. [68] evaluated the effects of epidural anesthesia in normal and hypertensive patients in active term labor. The mean uterine artery S/D ratios did not change in normotensive and chronically hypertensive patients but fell significantly in the term mildly preeclamptic patients – to values similar to those of the normotensive group. Both placental and nonplacental uterine artery S/D ratios fell to values seen in the normotensive group. The uterine S/D ratios in the chronic hypertensive group, which were similar to those of the preeclamptic group, did not change after administration of epidural anesthesia. The authors accepted this finding as evidence of underlying vascular disease. This study demonstrates the benefits of epidural anesthesia in the presence of mild preeclampsia at term. The study must be reproduced and involve women with preeclampsia of varying severity.

Effects of Exercise on Uterine Velocimetry

Studies that examine the effect of exercise during pregnancy on uterine artery velocimetry are difficult to compare, as they have differences in (1) the degree of exercise employed, (2) the Doppler equipment used, (3) the maternal position during exercise, and (4) the maternal position and time of recording after exercise.

Three studies performed on healthy pregnant women showed no changes in uterine artery waveform indices [69–71]. These findings are not in line with previous studies in animals. The fact that there were no changes in waveform indices despite significant increases in maternal heart rate may be evidence of increased uterine resistance.

Morrow et al. [72] studied healthy, term, pregnant women after 5 min of bicycling at a continuous power of 20 watts. This moderate level of exercise was associated with an increase in uterine artery resistance at 2 min after exercise. There was no evidence of deleterious fetal effects. Erkkola et al. [73] studied the responses of eight healthy women at term to increasing levels of exercise on a stationary bicycle. Maternal heart rate and blood pressure rose during each workload period, as did the uterine S/D ratios. Therefore impedance in the uterine artery rose with increasing degrees of exertion. As in the study of Morrow et al., there were no apparent ill effects on the fetus. One explanation for the lack of adverse fetal effects is that the increases in uterine resistance are counteracted by increases in mean arterial pressure. This situation may not lead to changes in volume flow, as volume flow equals pressure divided by resistance.

Hackett et al. [74] were the first to look at the effects of exercise on uterine Doppler velocimetry in pregnancies complicated by hypertension or small-for-gestational-age (SGA) fetuses. Uncomplicated and complicated pregnancies with and without abnormal uterine artery waveforms comprised the three groups. All three groups showed an increase in uterine artery RI after exercise that rapidly returned to normal within 5 min of rest. The mean change in RI was greater in complicated pregnancies with abnormal waveforms than in complicated pregnancies with normal uterine waveforms. The RI in all complicated pregnancies increased more than those of the normal pregnancies.

The studies of Morrow et al. [72], Erkkola et al. [73], and Hackett et al. [74], which show increased uterine artery resistance during exercise, have important implications for physical activities of pregnant women with uterine or umbilical artery vasculopathy. One must question the validity of uterine velocimetry in the presence of changes of heart rate and blood pressure.

Effects of Uterine Contractions on Uterine Waveforms

The effects of the contractions of active labor and Braxton-Hicks contractions on uterine artery velocity waveforms has been studied. Fleischer et al. [75] studied 12 pregnant women in labor at term and found that the uterine artery end-diastolic velocity fell progressively during contractions. End-diastolic velocities reached zero when intrauterine pressures exceeded 35 mmHg. An early diastolic notch did not appear. Janbu and Nesheim [76] found that flow velocity begins to drop immediately as the intrauterine pressure rises, and it falls linearly with increasing intrauterine pressures up to 60 mmHg.

Bower et al. [77] studied the effects of Braxton-Hicks contractions on normal and abnormal uterine artery Doppler waveforms. The PI increased in all cases during spontaneous contractions. In some cases where the uterine waveforms were normal, there was an absence of end-diastolic velocities. However, when the uterine artery waveforms were abnormal and had an early diastolic notch, there was an absence of end-diastolic velocities during contractions in all cases (Fig. 16.19).

Kofinas et al. [78] studied the effects of Braxton-Hicks contractions on the uterine arteries and the arcuate arteries supplying the placental and nonplacental myometrium. When the contractions were localized in the placental myometrium, there was no increase in the subplacental arcuate artery resistance or the main uterine artery resistance. When the contraction involved the nonplacental myometrium, the resistance in the nonplacental arcuate artery and the uterine artery increased. Thus they showed that the human myometrium manifests functional asymmetry, with the subplacental and nonplacental myometrium showing different degrees of contractility.

Uterine Artery Circulation with Uterine Anomalies

Stege et al. [79] reported a case of severe preeclampsia and fetal growth restriction at 34 weeks' gestation in a woman with a bicornuate uterus. The placenta was in the left uterine horn. There was a marked difference in uterine artery waveforms with the right and left uterine artery PIs being 4.27 and 0.80, respectively. The right uterine waveform had an early diastolic notch, and the authors took it as evidence of a lack of anastomosis between the right and left uterine circulations.

These uterine malformation cases exemplify the complexities of the effects of placentation on the uter-

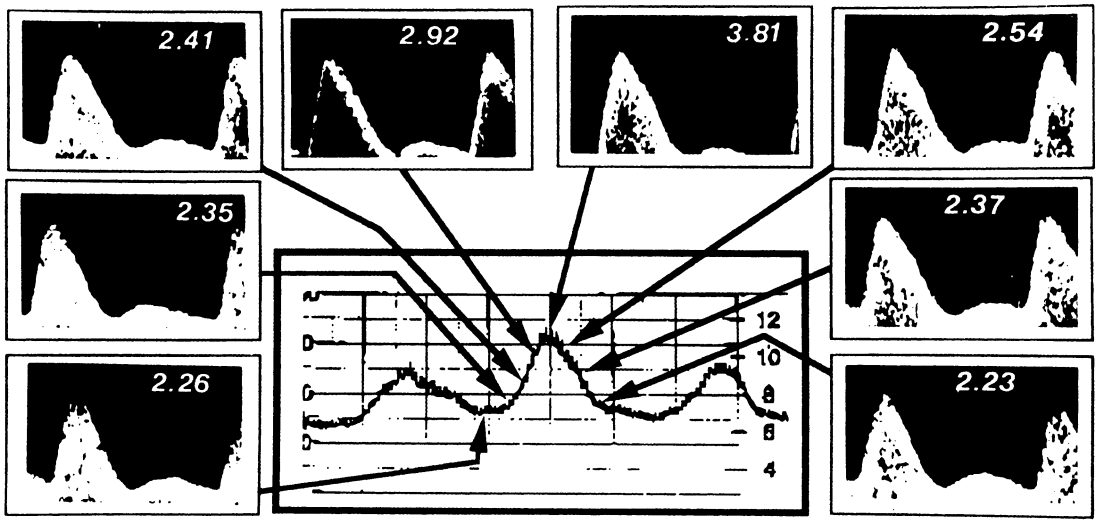

Fig. 16.19. Tocography demonstrating uterine contractions. Alterations of uterine artery flow velocity waveforms in temporal association with a contraction are also shown. The *number* in each frame indicates the pulsatility index of individual flow velocity waveforms. (Reprinted from [77] with permission)

ine circulation and the potential of each uterine artery to develop collateral branches. Also, extrauterine collateral circulation may help compensate when the nonplacental uterine circulation is not recruited or available.

Uterine Velocimetry and Umbilical Vein Gases

Soothill et al. [80] performed funicentesis and uterine velocimetry in 32 pregnancies complicated by IUGR to see if there was a correlation between the uterine circulation and fetal umbilical vein blood gases. A significant negative correlation was found between uteroplacental RI and fetal pH ($r=-0.37$, $n=32$, $p<0.05$). Significant positive correlations were found between the uteroplacental RI and fetal hypoxia ($r=0.55$, $n=32$, $p<0.001$) and gestation-adjusted PCO_2 ($r=0.36$, $n=32$, $p<0.05$). In addition, there was a significant positive correlation between gestation-adjusted lactate ($r=0.41$, $n=26$, $p<0.05$) and erythroblast count ($r=0.37$, $n=32$, $p<0.05$). These findings demonstrated that abnormal uterine velocimetry can be associated with inadequate maternal delivery of oxygen and nutrition to the intervillous space. The findings may have been confounded by alterations in umbilical-placental flow and the fetal hemoglobin content, which were not measured.

Uterine Artery Screening During Pregnancy

There have been several uterine artery screening studies, and the results have varied (Table 16.5) [40, 81–85]. Several factors make comparisons difficult. The timing of the screening affects results. For example, the uterine artery waveform does not complete its evolution until approximately 26 weeks. Also, the uterine notch, which correlates well with adverse pregnancy outcome, can persist until 26 weeks. Thus screening too early leads to false-positive rates and lower positive predictive values because what appear to be abnormal uterine arteries at 18 weeks' gestation may fully develop and normalize by 24–26 weeks. Screening at 24–26 weeks leads to improvement in the false-positive rates and positive predictive values, but it allows pathologic changes to progress and so steps to modify or prevent disease are less effective. Screening pregnancies at risk yields a high sensitivity because of a high incidence of disease, in contrast to screening unselected low-risk pregnancies. Other factors that influence results are the definition of the abnormal uterine artery waveform index used and whether one takes into account the early diastolic notch. The equipment results in variations in sampling sites depending on whether continuous-wave or color with pulsed-wave Doppler sonography is used. These studies have varied in their definition of adverse outcome, including clinical classifications or definitions of hypertensive disorders. Given the same clinical situation, physician management and the decision-making process may vary and so influence the outcome.

Table 16.5. Uterine Doppler velocimetry screening studies

Study: first author	Population	Equipment	No.	Time of screening (weeks)	Outcome measure	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Prev (%)
Arduini [81]	High risk for PIH	PD	60	18–20	PIH with or without proteinuria	63.6	84.2	70	80	36.6
Jacobson [82]	High risk for preeclampsia and IUGR	PD	91	24	Proteinuric preeclampsia	66.7	–	16.7	–	9.7
–	–	–	–	–	IUGR	70.6	–	33.3	–	18.3
Campbell [40]	Consecutive patients	PD	126	16–20	PIH, IUGR, and fetal asphyxia[a]	68	69	42	87	25
–	–	–	–	–	PIH	67	64	20	–	12
Harrington [83]	Unselected	CWD, CD, PD	2,437	20	Proteinuric PIH	76	86	13	99	2.4
–	–	–	–	24	–	76	96	35	99	–
–	–	–	–	26	–	74	97	44	99	–
Valensise [84]	Low risk, primiparous	CD, PD	272	22	Total GH	74	97	76	97	9.9
–	–	–	–	–	IUGR	66	95	53	97	7.7
–	–	–	–	–	GH alone	50	92	23	97	4.4
–	–	–	–	–	GH with proteinuria	88	93	30	99	3.3
–		–	–	–	GH and IUGR	100	93	38	100	3.7
–	–	–	–	–	Onset of GH					
–	–	–	–	–	<34 weeks	88	93	30	99	3.3
–	–	–	–	–	<37 weeks	88	96	61	99	6.6
–	–	–	–	–	Maximum systolic BP >160 mmHg	100	94	50	100	4.8
–	–	–	–	–	Maximum diastolic BP >110 mmHg	88	95	57	95	6.3
					90 mmHg	44	91	18	97	3.3
Bower [85]	Unselected	CWD, CD, PD	2,058	18–22	Preeclampsia	82	86.9	12	99.5	2.2
–	–	–	–	–	PIH	15.7	85	7	93	6.5
–	–	–	2,026	24	Preeclampsia	78	96	28	99.5	1.8
–	–	–	–	–	PIH	4.5	95	5.7	94	6.4

PIH, pregnancy-induced hypertension; IUGR, intrauterine growth restriction; SGA, small-for-gestational age; HTN, hypertension; IUD, intrauterine death; GH, gestational hypertension; PD, pulsed Doppler; CWD, continuous-wave Doppler; CD, color Doppler; BP, blood pressure; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; Prev, prevalence.

[a] Taken together to define outcome measures.

Abnormal outcomes can occur with normal uterine artery screening, as there could be abnormalities in umbilical flow. In Ducey et al.'s [86] population of hypertensive pregnant women, 44% with preeclampsia, 74% with pregnancy-induced hypertension, and 88% with chronic hypertension had normal uterine artery Doppler studies and would be missed on screening. In their study pregnancy-related hypertension occurred with normal uterine and umbilical velocimetry. This population consisted of many white middle-class women, and so these findings may not pertain to all populations.

The screening studies involved both high- and low-risk patients. The incidence of abnormal uterine artery screening in 11 of the screening programs [40, 82–87] averaged 15.4% ± 14.6% with a range of 2.7%–42.0%. There is a hint that there is more uterine artery disease in the black versus the white population.

The uterine artery screening programs of Harrington [83], Valensise [84], and Bower [85] should serve as the ideal models. Harrington [83] used continuous-wave Doppler sonography for screening at 19–20 weeks; and those women who were abnormal were rescreened at 24 and 26 weeks with color and pulsed Doppler sonography of the main uteine artery. This method standardized the sample site and allowed sampling at the same location during longitudinal studies. Also, they defined abnormal uterine artery waveforms as an averaged RI from both uterine arteries that was above the 95th percentile for gestational age or a diastolic notch (or both). Using proteinuric pregnancy-induced hypertension and IUGR as their endpoints, they achieved good results.

Valensise and colleagues [84] screened 272 low-risk primiparous women at 22 weeks' gestation with color and pulsed Doppler ultrasonography. The average RI of both uterine arteries was considered abnormal when it was more than 0.58. Abnormal testing occurred in 9.5%, but the figure fell to approximately 7.0% at 24 weeks' gestation. These authors reported the best sensivitites for pregnancies with the worse outcomes, such as early onset of hypertension, proteinuric hypertension, and hypertension associated with IUGR.

Bower et al. [85] screened 2,058 unselected women at 18–22 weeks of pregnancy with continuous-wave Doppler sonography. Color and pulsed Doppler sonography was used at 24 weeks to rescreen the 273 women with a high RI or early diastolic notch. On rescreening, 104 remained abnormal (5.1%). The presence of the diastolic notch was a better predictor of preeclampsia than the RI. All cases of delivery before 34 weeks due to preeclampsia were predicted by the early diastolic notch.

Biochemical Serum Markers and Uterine Artery Doppler Velocimetry

Unexplained elevated maternal serum alpha-feto protein (MSAFP) is associated with an increased risk of perinatal death, preterm delivery, and IUGR. Cuckle et al. [88] demonstrated that inhibin-A levels in the second trimester were significantly elevated in women who developed preeclampsia versus those who did not. Aquilina et al. [89] combined inhibin-A levels with uterine artery Doppler velocimetry at 15 and 19 weeks' gestation to determine their efficacy in predicting preeclampsia and preeclampsia at less than 37 weeks' gestation. The found that combining inhibin-A and uterine artery Doppler velocimetry improved the sensitivity and positive predictive value for predicting preeclampsia above either parameter alone. The sensitivity and positive predictive value of combined inhibin-A and uterine artery Doppler velocimetry for predicting preeclampsia and preterm preeclampsia was 71.4% and 38.5%, and 60% and 32%, respectively. Therefore, this study proves that combining biochemical testing with uterine artery Doppler velocimetry can lead to a better screening test. The biochemical studies reviewed here provide incentive to perform larger studies with the potential to define effective screening tests for randomized controlled trials of therapies to prevent or modify fetal and maternal adverse outcomes.

Medical Attempts at Modification of Pregnancy Outcome in Women with Abnormal Uterine Artery Doppler Velocimetry

The first study on the prevention of preeclampsia in women with abnormal uterine artery Doppler velocimetry was performed by McParland et al. in 1990 [90]. They identified 100 women at 24 weeks' gestation with abnormal uterine artery Doppler velocimetry and randomly gave them either 75 mg of aspirin ($n = 48$) or placebo ($n = 52$). There was no significant difference between the aspirin and placebo groups in the frequency of pregnancy-induced hypertension (13% vs 25%), but there were significant differences in the frequencies of proteinuric hypertension (2% vs 19%) and hypertension occurring before 37 weeks' gestation (0% vs 17%) (Table 16.6). Fewer aspirin-treated than placebo-treated women had low-birthweight babies (15% vs 25%), but this difference was not significant.

The CLASP multicenter randomized clinical trial [91] involving 9,374 women was one of the many studies designed to determine whether aspirin thera-

Table 16.6. Pregnancy outcomes in placebo and aspirin groups

Parameter	Placebo group	Aspirin group	95% CL (%)	*p*
Hypertension (no.)				
Pregnancy-induced	13 (25%)	6 (13%)	–3 to 28	NS
Proteinuric	10 (19%)	1 (2%)	6 to 29	<0.02
Onset before 37 weeks	9 (17%)	0	7 to 27	<0.01
Gestation at delivery (weeks)[a]	38.7±3.9	39.5±2.1	–	NS
Birth weight (g)[a]	2,954±852	3,068±555	–	NS
<2,500 g	13 (25%)	7 (15%)	–5 to 25	NS
<1,500 g	4 (8%)	0	0 to 15	NS
Below 5th percentile	7 (14%)	7 (14%)	–	NS
Blood loss at delivery (ml)[a]	358 (228)	289 (188)	–	NS
Perinatal deaths (no.)	3	1	–	NS

95% CL, 95% confidence limits for difference in proportions; NS, not significant.
[a] Mean±SD.

py can prevent preeclampsia and/or IUGR. An inclusion criteria for this study was a risk for preeclampsia. This study revealed no overall decrease in proteinuric hypertension, IUGR, stillbirths, or neonatal deaths attributable to aspirin use. However, there was a significant reduction in the incidence of early-onset proteinuric preeclampsia (<37 weeks) in women who were exposed to aspirin therapy. During the performance of the CLASP trial, Bower et al. [92] were performing two-stage Doppler screening studies of the uterine arteries at 18–20 and 24 weeks' gestation. They identified 60 women with persistently abnormal uterine artery Doppler velocimetry at 24 weeks' gestation and entered them into the CLASP study. There was no significant difference in the incidence of preeclampsia and IUGR between the aspirin and placebo groups. However, there was a significant difference between the two groups (aspirin 13%, placebo 38%, $p=0.03$) regarding the development of severe preeclampsia (defined as diastolic blood pressure ≥110 mmHg, with proteinuria of >300 mg/24 h or preeclampsia requiring intravenous antihypertensive therapy). These results imply a possible role of aspirin in modifying the severity of preeclampsia (Table 16.7).

In the same year of the Bower et al. [92] study, Morris et al. [93] showed a statistically significant increase in the rates of preeclampsia (4% vs 11%) and

Table 16.7. Randomized studies examining the effects of aspirin versus placebo in the prevention of preeclampsia and IUGR in high-risk populations

Study	Time of screening	Definition of abnormal UAV	Population	*n*	Aspirin dose/timing	Outcomes	Aspirin (%)	Placebo (%)	Sig.
Bower et al. 1996 [92]	24 weeks	■ RI>95% or ■ diastolic notch	CLASP trial subset	60	60 mg/day 24 weeks	Preeclampsia	29	41	NS
						Severe preeclampsia	13	38	$p=0.03$
						IUGR (<3%)	26	41	NS
Morris et al. 1996 [93]	18 weeks	■ S/D>3.3 or ■ S/D>3.0 with ipsilateral diastolic notch	Nulliparous	100	100 mg/day 24 weeks	Preeclampsia	8	14	NS
						IUGR (<100%)	27	22	NS
Harrington et al. 2000 [94]	20 weeks	■ RI>50% (0.55) with bilateral diastolic notch or ■ RI>90% (0.65) with unilateral notch or ■ RI>95% (0.70) with no notch	Unselected	113	100 mg/day 20 weeks	Preeclampsia	6.5	8.4	NS
						IUGR (<3%)	8.4	14.0	NS
						IUGR (<10%)	29.9	33.0	NS

UAV, uterine artery velocimetry; Sig., significance; NS, not significant; RI, resistance index; S/D, systolic/diastolic ratio; IUGR, intrauterine growth restriction.

SGA weight less than 10% (11% vs 28%) for patients with abnormal uterine waveforms; however, there was no benefit from the use of aspirin. One of the concerns of using uterine artery screening at 18 weeks' gestation is the high rate of false-positive testing. In past studies approximately 70% of positive tests at 18 weeks will normalize by 22–24 weeks' gestation. Therefore, using abnormal 18-weeks' test results as entry criteria will require a greater number of participants to produce a study population with a sufficient frequency rate of severe early preeclampsia in order to demonstrate a treatment effect. This is confirmed by the 11% versus 35% incidence of preeclampsia in the Morris et al. and Bower et al. studies, respectively.

A recent randomized prospective study by Harrington et al. [94] also failed to show a reduction in preeclampsia and SGA under the 3rd percentile. However, when these investigators pooled the individual events into the two outcome measures, "severe complications" (preeclampsia < 34 weeks, SGA < 3rd percentile, placental abruption, Apgar score < 7 at 5 min, neonatal intensive care unit admission, stillborn or neonatal death) and "any complications" (severe complications and preeclampsia > 34 weeks' gestation and SGA < 10th percentile), there was a significant reduction in the treatment versus control group (Table 16.8). There were other interesting findings in this study. The incidence of early-onset preeclampsia was zero and 2.8% in the aspirin and placebo groups, respectively. This represents the lowest incidence of early-onset preeclampsia in women with abnormal screening uterine artery Doppler velocimetry in publication, which may explain the negative results. Another unique finding occurred in the group receiving aspirin therapy. The complication rates in the women who experienced normalization of uterine artery Doppler velocimetry at 24 weeks' gestation was equal to or slightly greater than those who had persistently abnormal velocimetry. This is an observation never published previously and must be taken into account in future studies.

In summary, the studies do not support the use of low-dose aspirin in women with abnormal uterine artery Doppler velocimetry. However, we agree with Harrington et al. [94] that the overall study results are encouraging and our impression is that women with abnormal uterine artery Doppler velocimetry may represent a group of patients uniquely sensitive to the effects of aspirin. The primary endpoint that may be modifiable or reducible appears to be the incidence of severe early-onset preeclampsia, which is the most serious of hypertensive disorders in pregnancy. One of the reasons for the negative results, with the exception of the Bower et al. [92] study, is the lack of sufficient numbers of patients with severe early-onset preeclampsia. Another reason is the varying definitions of abnormal uterine artery Doppler velocimetry. We would recommend that any trials performed today use the entry criteria of bilateral

Table 16.8. Obstetric/perinatal complications (with permission from [94])

	Normal*	Treatment (aspirin)**			
		Aspirin stopped at 24 weeks (n = 49)	Aspirin continued until delivery (n = 58)	Total % (n = 107)	Control (no aspirin)***
Preeclampsia (all)	0.8 (6)	2 (1)	10.3 (6)	6.5 (7)	8.4 (9)
Preeclampsia < 34 weeks	None	None	None	None	2.8 (3)
SGA < 10th percentile	11.8 (87)	32.7 (16)	27.6 (16)	29.9 (32)	33 (35)
SGA < 3rd percentile	4 (29)	8.2 (4)	8.6 (5)	8.4 (9)	14 (15)
Abruption	0.27 (2)	2.0 (1)	None	0.9 (1)	None
Apgar at 5 min < 7	1.0 (7)	4.1 (2)	None	1.9 (2)	4.9 (5)
NICU admission	2.9 (21)	None	3.2 (2)	1.9 (2)	3.7 (4)
SB/NND	0.13 (1)[c]	4.1 (2)	None	1.9 (2)[d]	2.9 (3)[e]
Any complication[a]	20.9 (153(	53.1 (26)	50 (29)	51.4 (55)	71.8 (74)
Severe complications[b]	8.1 (60)	18.4 (9)	12.1 (7)	15.0 (16)	29.1 (30)

* $n = 730$; ** $n = 107$; *** $n = 103$.

SGA, small-for-gestational age; PE < 34 weeks, preeclampsia requiring delivery before 34 weeks' gestation; NICU, neonatal intensive care unit; SB/NND, stillbirth/neonatal death.

[a] Any complication included all the severe complications, as well as preeclampsia delivered after 34 weeks and SGA < 10th percentile.

[b] Severe complications: preeclampsia requiring delivery before 34 weeks, SGA < 3rd percentile or placental abruption or an Apgar score < 7 at 5 min or NICU admission, or SB/NND.

[c] Case of Trisomy 13.

[d] Two terminations of pregnancy (TOP) at 22 and 23 weeks for severe preeclampsia not included.

[e] One TOP at 23 weeks for severe IUGR not included.

uterine artery notching which may result in the highest positive predictive value for early-onset preeclampsia. However, as pointed out by Harrington et al., these trials may have to await further refinements in uterine artery Doppler waveform analysis or combining uterine artery Doppler results with biochemical testing to improve screening efficacy. Other variables were differences in patient medical background, parity, socio-economic background, race, prior hypertensive medication use, and timing of screening and initiation of aspirin therapy.

We propose that studies performed in the immediate future should involve multiple centers, to achieve appropriate numbers of outcome events, with screening performed at 18–20 weeks' gestation and bilateral uterine artery notching as the definition of abnormal testing. Doppler reevaluation at 22–24 weeks' gestation should be performed and as in the Harrington et al. trial, aspirin therapy should be terminated if the results are normal. This would leave us with four groups to analyze based on the Doppler results at 22–24 weeks' gestation: aspirin therapy terminated secondary to normal Doppler results, aspirin with abnormal Doppler studies, and placebo with normal and abnormal Doppler studies. Proposed outcomes would be the early onset of preeclampsia (< 34 weeks), gestational age at delivery when preeclampsia was the indication for delivery, the degree of severity of preeclampsia, and the incidence and severity (< 10th percentile or < 3rd percentile) of IUGR. Survival analysis of gestational age at birth would be interesting to determine whether, regardless of indications for delivery, aspirin therapy results in significantly greater pregnancy duration.

Part of the pathophysiology of preeclampsia is endothelial dysfunction, which increases the sensitivity to vasoconstricting agents leading to vasospasm [95]. Free radicals are thought to injure the maternal vascular endothelium and promote endothelial cell dysfunction. Therefore, antioxidant therapy has the potential to prevent and/or modify preeclampsia. Chambers et al. [96] recently showed *in vivo* reversal of endothelial dysfunction in preeclampsia with ascorbic acid. These results require confirmation from larger randomized clinical trials.

Nitric oxide is produced by the endothelium of vessels and is a well-known vasodilator and platelet aggregation inhibitor. In preeclamptic women, inhibition of nitric oxide synthase and cyclooxygenase attenuates endothelial-derived relaxation. It has been suggested by several investigators that since preeclampsia is associated with decreased function of nitric oxide, introducing a nitric oxide agent, such as glyceryl dinitrate, would reduce the severity or prevalence of preeclampsia. Grunewald et al. [97] performed intravenous infusions of nitroglycerin in 12 severe preeclamptics. This resulted in a significant reduction in maternal blood pressure; however, the PI of the uterine arteries did not change significantly [1.23 (95% CI 1.01–1.61) versus 1.30 (95% CI 1.01–1.88)]. Thaler et al. [98] studied 18 women with low-risk pregnancy at 17–24 weeks' gestation, who were given a single 5 mg dose of sublingual isosorbide dinitrate. Blood flow velocity waveforms in the ascending uterine artery were measured by pulsed color Doppler ultrasound before and after the medication was administered. Maternal blood pressure and heart rate were also monitored. The S/D ratio in the uterine artery decreased from 4.83 (95% CI 3.99–5.56) to a nadir of 4.02 at 10 min (95% CI 3.41–4.63, $p < 0.001$). This study suggests a potential benefit of nitric oxide therapy.

Lees et al. [99] identified 40 healthy normotensive women with bilateral uterine artery Doppler waveform notching at 24–26 weeks' gestation and randomized them to transdermal glyceryl trinitrate (GTN) 5 mg/day patch versus placebo patch for 10 weeks or until delivery. There was no statistically significant difference in maternal systolic and diastolic blood pressure, mean uteine artery RI, or the rates of preeclampsia or IUGR. However, there was a significant increase in women who delivered at term an AGA infant without evidence of preeclampsia in the GTN group in comparison to the placebo group [15/21 (71%) vs 5/19 (26%), $p = 0.004$, hazard ratio 0.267 (95% CI 0.102, 0.701), 73% reduction in hazard]. Taken collectively these studies suggest that nitric oxide donor therapy needs further investigation.

Medical Conditions and Uterine Artery Doppler Velocimetry

Uterine Artery Doppler Velocimetry in IUGR Fetuses and Hypertensive Disorders of Pregnancy

The findings reported in the original article of Campbell et al. [10] in 1983 on uteroplacental Doppler velocimetry – that women with abnormal uterine waveforms had a higher frequency of proteinuric hypertension, poor fetal growth, and fetal hypoxia – inspired a wave of observational studies [28, 35–37, 39, 44, 45, 87, 100–107]. In addition to confirming the work of Campbell et al., these studies found that a significant number of women with hypertension or IUGR fetuses could also have abnormal umbilical artery Doppler waveforms alone or in combination with abnormal uterine artery waveforms. It became clear that a thorough investigation of hypertension during pregnancy and IUGR would require analysis of both uterine and umbilical circulations.

The results of these studies are best summarized by the work of Ducey and colleagues [86], who classified hypertension according to four vascular patterns (Table 16.9). The most common vascular pattern in hypertensive pregnancies is defined by normal uterine and umbilical velocimetry. Although most of these women had chronic hypertension, preeclampsia and pregnancy-induced hypertension also occurred with this pattern. Regardless of the clinical diagnosis, the perinatal outcome was similar to that of a normal obstetric population. These data support optimal medical management of hypertensive women who display this velocimetry pattern rather than aggressive intervention for fear of fetal risk.

The next most common category was abnormal uterine and umbilical artery velocimetry. The authors hypothesized that this group lacks endovascular trophoblastic invasion of the myometrial portion of the subplacental spiral arteries. The women had the worst perinatal outcome and accounted for all the perinatal deaths in the study. They and their fetuses experienced severe early disease. Most of the preeclamptic women and a significant number of the women with pregnancy-induced hypertension had this vasculopathy. For optimal outcome these patients must be identified early, and both mother and fetus require intensive surveillance. The potential for early delivery is great, with many requiring operative delivery. Consideration should be given to using preventive or modifying medication, such as aspirin.

The next two categories consisted of women with isolated deficiencies of either the uterine arteries or umbilical arteries. Surprisingly, the less common of the two was abnormal uterine artery flow only. The Doppler pattern of abnormal umbilical flow belies the popular concept that the placental ischemia seen with pregnancy hypertension is the result of poor maternal perfusion. The perinatal outcome is poorer than when there is abnormal uterine flow only. The fetus is protected by the umbilical artery circulation, and it adapts well to reductions in uterine artery flow. Guzman et al. [108] also described pregnancy-induced hypertension associated with abnormal umbilical flow, only with greater consequences to the fetus than the mother.

When viewing the results of all the observational studies, a pattern emerges wherein abnormalities in uterine artery flow correlate best with maternal complications. Moreover, the state of the umbilical artery circulation is more predictive than that of the uterine artery circulation in terms of fetal-neonatal outcome.

Uterine artery Doppler velocimetry has been shown to correlate very well with pregnancy outcome in women with chronic hypertension. Caruso et al. [109] studied 42 women with chronic hypertension and showed increased incidences of preeclampsia

Table 16.9. Velocimetry for hypertension and pregnancy (reproduced from [86] with permission)

Parameter	Normal flow velocity in uterine artery		Abnormal flow velocity in uterine arery	
	Nl. umb. ($n=66$)	Abnl. umb. (n=27)	Nl. umb. ($n=12$)	Abnl. umb. (m=31
Maternal data				
Age (years)	29±7	27±6	24±7	27±6
Nullipara (%)	57	52	80	63
MAP, 2nd trimester (mmHg)	97±12	95±13	105±21	96±21
Abnormal platelets (%)	0	26*	13	0
Uric acid (mg/dl)	5.6±1.1	6.5±2.2	6.0±1.4	6.5±1.5*
Proteinuria (%)	24	71**	75**	86***
Uterine artery S/D ratio	2±0.3	2.1±0.3	3.4±9.0***	4.1±1.5***
Fetal/neonatal data				
Birth weight (g)	3,261±522	2,098±811***	2,464±722***	1,627±697***
Gestational age (weeks)	39±2	35.7±3.2***	36.3±3.0**	33.3±2.7***
Delivery <37 weeks (%)	11	61***	67***	84***
SGA (%)	2	29**	17	51***
C/S fetal distress (%)	8	39**	8	62***
NICU (%)	12	68***	50*	89***
Umbilical artery S/D ratio	2.4±0.3	4.2±1.1***	2.5±0.3	4.6±1.1***
Clinical diagnosis (%)				
Chronic hypertension ($n=43$)	65***	23	5	7
PIH ($n=34$)	59***	15	6	21
Preeclampsia ($n=51$)	20	24	16	41

MAP, mean arterial pressure; Nl. umb., normal flow velocity in umbilical artery; Abnl. umb., abnormal flow velocity in umbilical artery; S/D, systolic/diastolic; SGA, small for gestational age; C/S, cesarean section; NICU, neonatal intensive care unit; PIH, pregnancy-induced hypertension.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$.

(60% vs 0%), IUGR (26% vs 0%), and perinatal mortality (46% vs 0%) in women with abnormal uterine RI compared to those with normal RI.

Kofinas et al. [106] studied 65 pregnant diabetics with 34 having pregestational insulin-dependent diabetes and 31 with diet-controlled gestational diabetes. They did not demonstrate a correlation between glycemic control and uterine artery S/D ratios; however, there were S/D ratio elevations when diabetes was complicated by preeclampsia.

Several studies have been performed using both uterine and umbilical artery Doppler studies in women with systemic lupus erythematosus (SLE). Guzman et al. [110] studied 27 pregnancies in 26 women with SLE. The 18 women with normal Doppler studies of both vessels had a normal outcome. Five women had abnormal umbilical artery Doppler studies and the pregnancies were of shorter duration and lower birth weight with two cases of SGA births. Four pregnancies had abnormal Doppler studies for both vessels and they resulted in three perinatal losses and all were SGA births. There was a greater incidence of lupus nephritis, preeclampsia, and chronic hypertension in those with abnormal uterine and/or umbilical studies. Umbilical and uterine artery Doppler studies were better at predicting abnormal antepartum fetal heart rate tracings and SGA fetuses than the presence of lupus nephritis, anticardiolipin antibodies, and lupus anticoagulant. In this study the umbilical-placental circulation was more adversely affected than the uterine circulation.

Uterine artery Doppler velocimetry has been performed in women with antiphospholipid syndrome. Caroll et al. [111] studied 28 women with antiphospholipid dyndrome. Of the six cases associated with IUGR, five demonstrated increased impedance to flow in the umbilical artery waveforms, while of those only two had abnormally increased impedance in the uterine arteries. Overall, for patients with autoimmune diseases, more studies need to be completed in order to determine if the development of IUGR and preeclampsia is preceded by abnormal waveforms in the umbilical and the uterine vessels.

Caruso et al. [109] studied 24 women with antiphospholipid syndrome who were treated with prednisone and aspirin during 28 pregnancies. An abnormal RI of the uterine arteries at 18–24 weeks' gestation correlated with reduced gestational age at birth, birth weight, and birth percentile, and predicted four of five cases of preeclampsia.

Thrombophilias can impair the anticoagulation process and lead to an increased tendency toward clot formation in pregnancy. Evidence is building for a strong association between the thrombophilias and adverse pregnancy outcomes, including fetal loss in the late-first, second, and third trimesters, severe IUGR, placental abruption, and severe and early-onset preeclampsia.

Conclusions

Uterine artery velocimetry has undergone a remarkable evolution, with present-day color and pulsed Doppler technology allowing the study of each component of the uterine artery circulation. Exceptional observations have been made of its transformation during pregnancy. Reliable reproducible relations between the results of waveform analysis and perinatal outcome have been firmly established by many centers worldwide. The ability to predict early-onset preeclampsia appears to be its strong point, but its exact role in modern obstetrics has yet to be established.

The findings of uterine artery screening studies show that it is an effective means of predicting preeclampsia associated with delivery before 34 weeks' gestation. The ideal time for screening appears to be between 22 and 26 weeks' gestation; the site for screening is the main uterine artery; and the equipment is color with pulsed Doppler technology. Our observations tell us that uterine velocimetry does not predict all forms of hypertensive disorders of pregnancy, as some are associated with normal studies. Those disorders missed do not dramatically affect overall perinatal outcome, as they are associated with near-term deliveries. The screening programs show excellent specificity and negative predictive value and identify a pool of women who require standard care. What needs to be improved is the positive predictive value of the test. The prevalence of the outcome measured will have the biggest impact as will the definition of abnormal uterine Doppler velocimetry. Also important is what percentage of women with abnormal uterine velocimetry will have an abnormal outcome.

We can begin to improve its positive predictive value by concentrating on the definition of an abnormal test. By defining abnormal uterine velocimetry, should we use the abnormal waveform index of one uterine artery or the average of both? Or a unilateral or bilateral early diastolic notch? Or the degree of divergence between the waveform indices of each uterine artery? The data suggest that the presence of the notch is the most important criterion. The early diastolic notch has not been objectively defined, and we could begin by measuring its depth and determining if there is a difference between the persistent notch and the intermittent notch. The volume and velocity of uterine flow should be examined further despite the expected variation in measurements.

Of all the hypertensive disorders associated with pregnancy, early-onset preeclampsia has the most

dramatic impact on perinatal outcome. The low rate of abnormal uterine velocimetry testing (2.6%–12.0%) in unselected populations, the low prevalence and implications of early-onset preeclampsia, and the potential to modify or prevent it favor a screening test with high sensitivity. At worst, the small number of women with false-positive tests would be inappropriately subjected to increased visits to health care providers and to modifying or preventive therapy. This occurrence would be greatly offset by adjustments in the care of women with normal screening. Finally, the impact of uterine artery velocimetry screening depends on the effectiveness of therapeutic regimens designed to alter the course of events of preeclamptic pregnancies.

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