Uterine Artery Doppler and Its Value in Predicting Preeclampsia

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Abstract

Background: Most pregnancies, labours, and deliveries are normal biological processes that result in a healthy outcome for mothers and babies. Those that are not normal, however, can result in maternal and/or perinatal mortality or substantial morbidity. In the latest Centre for Maternal and Child Enquiries (CEMACE) report on maternal deaths ("Saving Mothers' Lives" 2006–2008), preeclampsia/eclampsia was the second commonest cause of direct maternal deaths in the United Kingdom (0.83 per 100,000 maternities). Preeclampsia and fetal growth restriction (FGR) have also been identified as antecedent causes in 6% and 10% of perinatal deaths, respectively. Modern antenatal care provision is focused on a risk-based approach to monitoring for adverse pregnancy outcomes such as preeclampsia, fetal growth restriction, placental abruption, and stillbirth. Increasingly, research is geared toward early identification of risks, thereby allowing early commencement of management strategies to minimise the risk of adverse outcome, including facilitation of an appropriate level of pregnancy monitoring. In this review, the technique of uterine artery Doppler interrogation in the first trimester is outlined, and its role in the prediction of pregnancy complications is discussed

Keywords: Doppler, Preeclampsia

Introduction

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I. Changes in Uterine Artery Doppler Waveform in Pregnancy

In the nonpregnant state and in early pregnancy, Doppler interrogation of the uterine artery typically demonstrates low end- diastolic velocities and an early diastolic notch. Uterine artery impedance can be affected by various factors such as maternal heart rate, antihypertensive use, hormonal changes in the menstrual cycle, and chronic hyperandrogenism in the polycystic ovarian syndrome. Resistance to blood flow within the uteroplacental circulation is transmitted upstream to the uterine arteries and can be measured as an increased pulsatility index (PI) or resistance index (RI). Uterine artery PI values are affected by ethnicity and are lower in women with a high body mass index (BMI). Researchers have determined reference ranges for uterine artery Doppler parameters from 11–14 weeks' gestation to 41 weeks' gestation in various populations **(3).**

Uterine artery PI and RI values decrease with increasing gestational age, a change that is thought to be secondary to a fall in impedance in uterine vessels following trophoblastic invasion. In a prospective crosssectional the mean uterine artery PI continued to fall ´ in the third trimester until week 34. "Notching" appears to be a common feature of the uterine artery Doppler waveform in pregnancy, as it is present in 46–64% of normal gestations in the first trimester. In pregnancies after 20 weeks, a diastolic notch has been defined as a fall of at least 50 cm/s from the maximum diastolic velocity, but most studies have utilized subjective criteria. Similar to uterine artery PI, the prevalence of notching decreases with increasing gestational age until 25 weeks' gestation and thereafter remains stable. Early diastolic notching in the uterine artery represents reduced diastolic velocities compared with those in later diastole and reflects vessel elasticity. Persistent early diastolic notching is thought to reflect abnormal maternal vascular tone, while defective placentation results in persistently raised uterine artery impedance **(4).**

Overall, notching demonstrates a low positive predictive value for preeclampsia and FGR, in contrast to its 97% negative predictive value for these conditions in a high-risk study population. The poor reproducibility of uterine artery notching has led to its omission from recent research in this field, with a trend instead toward inclusion of more objective measures of vascular impedance, favouring PI. As the formula for the calculation of the PI includes the area below the waveform [(peak systolic − end-diastolic velocity)/mean velocity], the PI indirectly includes the presence or absence of an early diastolic notch **(5).**
Uterine artery Doppler analysis has the potential to predict pregnancy complications associated with uteroplacental insufficiency before the onset of clinical features. For almost 30 years, uterine artery

Doppler studies have been utilized as a screening tool for uteroplacental insufficiency, mostly in the second trimester (from 18–23 + 6 weeks' gestation). Just as aneuploidy screening in the first trimester has become the accepted standard of care, so too is there an increasing impetus for the earlier prediction of other pregnancy complications, in the belief that doing so will facilitate appropriate monitoring and timely intervention to reduce maternal and/or fetal morbidity and mortality **(6).**

1. Measurement of Uterine Artery Doppler Parameters

Doppler assessment of uterine artery impedance can be performed between 11 + 0 and 13 + 6 weeks' gestation via a transabdominal or transvaginal approach. The transabdominal approach is the preferred method as it is less invasive with good interobserver reproducibility **(7).**

1. **Transabdominal Ultrasound Technique**.

A 5 or 3.5-MHz curvilinear transabdominal transducer is used. A midsagittal section of the uterus and cervical canal is obtained and the transducer is moved laterally until the paracervical vessels are visualized. Color flow Doppler is applied. The uterine arteries are seen as aliasing vessels along the side of the cervix. Using pulsed wave Doppler, flow velocity waveforms from the ascending branch of the uterine artery at the point closest to the internal os are obtained, with the Doppler sampling gate set at 2 mm. Care is taken to use the smallest angle of insonation **(4).**

Another site for Doppler insonation of the uterine artery is at the level of its apparent crossover with the external iliac artery. Using this method, the probe is positioned approximately 2-3 cm inside the iliac crests and then directed toward the pelvis and the lateral side of the uterus. Color flow Doppler is used to identify each uterine artery. Pulsed wave Doppler is applied approximately 1 cm above the point at which the uterine artery crosses over the external iliac artery. This ensures that Doppler velocities are obtained from the main uterine artery trunk. This is similar to the technique commonly adopted for measurement of the uterine artery Doppler waveform in the second trimester **(8).**

Figure 1: Transabdominal Doppler interrogation of the uterine artery at the level of the internal cervical os. Uterine artery waveform demonstrating raised PI with an early diastolic notch (arrow) **(6).**

2. Transvaginal Ultrasound Technique.

A 4.6–8 MHz transvaginal transducer is used. The transducer is placed in the anterior vaginal fornix and a sagittal section of the cervix is obtained. The vaginal probe is then moved laterally until the paracervical vascular plexus is seen. Color flow Doppler is applied and the uterine artery is identified at the level of the cervicocorporeal junction. Measurements are taken at this point before the uterine artery branches into the arcuate arteries **(9).**

It Was found that the mean uterine artery PI at 11–13 + 6 weeks' gestation measured transabdominally was lower than that measured transvaginally: 1.83 (95% CI: 1.78–1.89) as against 1.98 (95% CI 1.93– 2.08) ($p <$ 0.05). Appropriate reference charts should thus be used. **(6).**

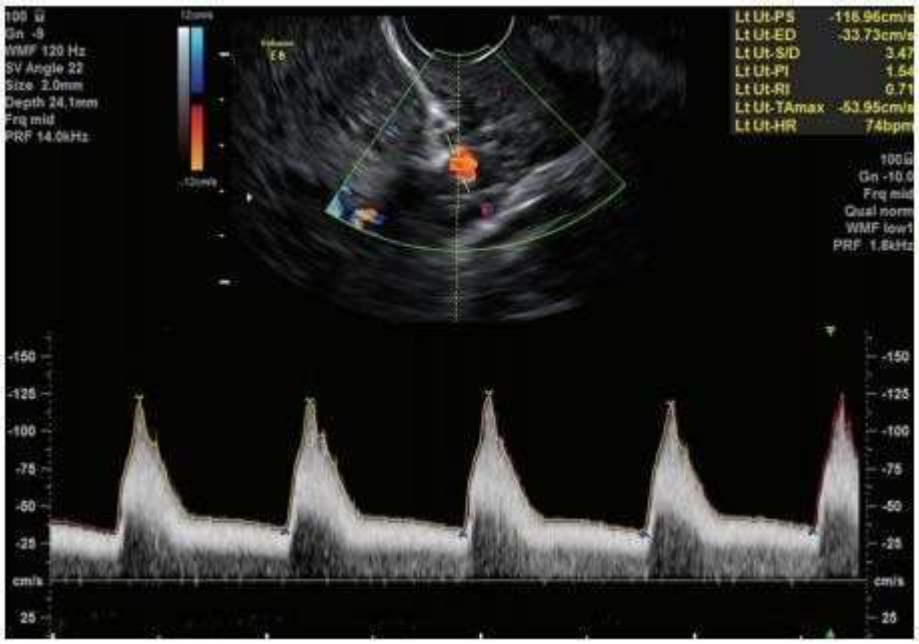

Figure 2: Transvaginal Doppler interrogation of the uterine artery at the cervicocorporeal junction. Normal uterine artery waveforms **(6).**

2. Prediction of Adverse Pregnancy Outcome in patients with preeclampsia

Around 2–8% of pregnancies are affected by preeclampsia. This condition is commonly divided into earlyonset (diagnosed and requiring delivery < 34 weeks' gestation) and late-onset disease. Early-onset preeclampsia occurs less frequently (0.4–1%) than late-onset preeclampsia but is responsible for a more significant burden of disease, with its associated prematurity and fetal growth restriction (FGR), in addition to increased long-term maternal cardiovascular morbidity. Early- onset preeclampsia or results from impaired trophoblast invasion into the spiral arteries, causing placental ischemia and oxidative stress. Placental histology in early-onset preeclampsia or FGR often demonstrates thrombotic changes in the villous trees, lending support to this theory. On the other hand, late-onset preeclampsia or "maternal PE" is thought to be secondary to maternal cardiovascular and metabolic predisposition for endothelial dysfunction and shares similar risk factors for adult cardiac disease such as hypertension, obesity, impaired glucose tolerance, and dyslipidemia. The placenta in such cases may appear normal or have minimal abnormalities histopathologically. Consequently, the uterine artery Doppler parameters may remain within the normal range **(10).**

1. Doppler Studies in Unselected and High-Risk Pregnant Women.

The predictive accuracy of second-trimester uterine artery Doppler analysis outperforms its utility in the first trimester. Studies in the first trimester vary in their reported results due to heterogeneity of vascular impedance measures, gestational age at screening, and in the prevalence and definition of preeclampsia and FGR. In addition, the performance of uterine artery Doppler velocimetry as a screening test is dependent on the pretest probability that the disease will be present in the target population **(11)**

2. Sequential Testing in the First and Second Trimester of Pregnancy.

It Was examined That the uterine artery PI in 3107 pregnancies at 11 + 0 to 13 + 6 weeks and compared the measurements with those at a later gestation (21 + 0 to 23 + 6 weeks). Consistent with previous research, the uterine artery PI was above the 90th centile in 77% of cases of early preeclampsia and in 27% of the late preeclampsia cases. An elevated uterine artery PI above the 90th centile persisted at 21 + 0 to 24 + 6 weeks in 94% of the early preeclampsia cases, 74% of the late preeclampsia cases, and 37% of those who did not develop preeclampsia. A predictive testing model incorporating maternal factors, uterine artery PI in the first trimester, and the change in uterine artery PI between the first and second trimesters achieved a detection rate for early preeclampsia of 90.9% at a false positive rate of 5%. The authors concluded that reserving secondtrimester testing for the 20% of women with the highest risk from first-trimester screening would achieve the same detection rate.This method of contingency screening resulted in three quarters of women initially screened as high risk being reassigned to the low risk group and streamlined the remaining high risk women for increased surveillance **(12).**

3. Multiple Gestations

Although the risk of preeclampsia is increased twofold in twin gestations, the majority of studies to date have been conducted on singleton pregnancies. It Was sought to compare the distribution of mean arterial pressure (MAP) and uterine artery Doppler PI in the first trimester in 147 twin pregnancies. There was no significant difference in MAP levels between twins and singletons in women who did not go on to develop preeclampsia. Chorionicity did not affect MAP levels. The uterine Doppler PI values were statistically significantly lower in twins than in singletons, and dichorionic twins had lower PI compared with monochorionic twins. Women with twin pregnancies complicated by preeclampsia had a significantly higher MAP than women who were unaffected, but, in general, the uterine artery PI levels were significantly lower, contrary to findings from singleton studies. The authors postulated that this is due to overcompensation of blood flow to the placenta. Second-trimester studies on uterine artery Doppler in twins confirm lower PI values during the course of the pregnancy, which decrease with advancing gestational age. Uterine artery Doppler PI reference ranges for twin pregnancies should be validated in larger studies before incorporation into clinical practice **(13).**

4. Multifactorial Approach with Biophysical and Biochemical Markers *I.*
Preeclampsia.

Women at risk of adverse pregnancy outcomes are generally identified based on their clinical history. Screening by maternal history alone will detect a third of women who will develop preeclampsia but is ineffective in nulliparous women, who are at particular risk of this complication. In a prospective study involving 8366 singleton pregnancies, It Was investigated That the role of uterine artery Doppler in the development of a predictive model for prediction of early preeclampsia. The detection rates for early preeclampsia, late preeclampsia, and gestational hypertension achieved by a model incorporating clinical history (history of preeclampsia, chronic hypertension, and method of conception) and maternal demographics (age, BMI, and ethnicity) alone were 47%, 41%, and 31%, respectively, at a 10% false positive rate. In women who subsequently developed preeclampsia or gestational hypertension, the lowest, mean, and highest uterine artery PI were significantly higher **(14).**

I. Preeclampsia and Uterine Artery Assessment

A prevalent theory for the development of preeclampsia relates to abnormal vasculature maturation of the arteries within the placenta. Normally, the spiral arteries of the placenta are formed from the myometrial

radial arteries during a process known as placentation. This is thought to occur from trophoblast cells as they move through the placental bed in the first trimester and a subsequent wave in the second trimester. Without proper trophoblast invasion, inadequate vascular formation may occur. This defect in placentation has been shown to increase the incidence of spontaneous preterm delivery **(15).**
During pregnancy, the normal uterine artery Doppler waveform shows low-resistance flow during diastole with the peak end diastolic flow increasing as gestational age increases. Assessment of the uterine artery waveform can give indirect evidence of abnormal placentation by displaying a persistently high-resistance flow pattern in the uterine arteries **(16).**

A resistive index (RI) of the uterine artery can be calculated by taking the peak systolic measurement and dividing it by the sum of the systolic and diastolic measurements. A value of greater than 0.58 is considered abnormal and a risk indicator for preeclampsia. Sometimes, the RI measurement has a high false-positive rate, so a classification method has been used to help in the diagnosis. An abnormal uterine artery waveform can be classified into three categories. Type I indicates an RI that is above the range of normal. Type II is a waveform that demonstrates a notch at the beginning of diastole, and this represents increased resistance of blood flow into the placenta, usually as a result of the blood vessels in the placenta not enlarging or dilating as they should. Type III waveform shows both an RI above normal as well as notching in early diastole. It is considered to have the highest risk for adverse outcomes **(17).**

II. Comparison between maternal risk factor and Doppler assessment in identification of Preeclampsia

The recognition of maternal risk factors has been used in clinic practice to help physicians identify patients at risk for preeclampsia. Combining the maternal risk factors with uterine artery Doppler may improve identification. In one study, low-risk patients were asked to fill out a maternal history evaluation and undergo a Doppler assessment of the uterine arteries. When using the maternal history alone, the detection rate for preeclampsia was 46.5%. Using uterine artery Doppler alone, the detection rate was 64.6%. When the two were combined, the detection rate was 69.4%. **(18).**

One value that can be assessed in the first trimester is pregnancy- associated plasma protein– A (PAPP-A), which is an insulin-like growth factor found in maternal blood cultures. Women who developed mild to moderate preeclampsia often have lower PAPP-A values than those in a control group. Those who developed severe preeclampsia had PAPP-A values even lower. Studies have noted an association between low PAPP- A values in the first trimester and abnormal uterine artery Doppler measurements. When this measure was assessed in the second trimester, an additional finding was noted relating to pulastility indexes (PIs). Low PIs were noted for women who developed mild to moderate preeclampsia and even lower PI values for those with severe preeclampsia, which corresponds with the values of the PAPP-A. This preliminary research needs further evaluation, but the results show a strong correlation between first-trimester PAPP-A values and second-trimester uterine artery PIs as a valid assessment for preeclampsia **(19).**

Further investigation studied the timing of these two tests— specifically, whether both PAPP-A values and uterine artery Doppler performed in the first trimester would increase the rate of detection compared to the detection rates of the two screenings individually. Uterine artery Doppler has a sensitivity of 50% for the detection of preeclampsia, which is higher than PAPP-A sensitivity alone. However, the Doppler sensitivity improves to 62% when first-trimester PAPP-A is added to the screening. Further investigation on this correlation may help predict the potential risk for developing the various types of preeclampsia or mild, moderate, or severe preeclampsia **(17).**

III. Identification of early onset preeclampsia in pregnancy

Not only is identifying those who are at risk for preeclampsia important, but identifying those who will develop it early in pregnancy is essential to improving long-term outcomes. This finding is significant because early onset of preeclampsia has a worse prognosis as compared to late onset. A woman who is diagnosed early would have the benefit of high-risk obstetric care before an adverse event occurs, which could lead to preterm labor and delivery. When patients with early onset of preeclampsia were assessed with a combination of maternal history and uterine artery Doppler in the second trimester, a detection rate of 93.1% was found. This is above the 51.4% for maternal history only and the 91.7% for uterine artery Doppler only in the same study. A further study assessed the uterine artery blood flow between 11 and 14 weeks' gestation to establish if this assessment could accurately predict preeclampsia early in pregnancy. The results showed that pregnancies that ended with adverse complications had a significantly higher mean PI, 2.04, as opposed to 1.75 for normal pregnancies. The high-risk pregnancies also showed a greater rate of bilateral notching of the waveform, 58% versus 41% for normal pregnancies. Although these results may help predict preeclampsia in the presence of specific waveform characteristics, further investigation needs to be performed in the first trimester of pregnancy to suggest a strong correlation between the two **(20).**

Predicting Severity Preeclampsia can be classified as mild, moderate, or severe, and the treatment is based on the severity of the condition. There is potential for uterine artery Doppler to predict which classification the disease may progress. Second-trimester gestations that underwent uterine artery Doppler assessment have demonstrated that Doppler assessment may not be as helpful in predicting milder forms of preeclampsia as more severe forms. In one study, an abnormal uterine artery was described as one with an RI above the 95th percentile and/or the presence of a dicrotic notch in either of the arteries. The sensitivity for mild preeclampsia was only 29% compared to 82% with moderate to severe preeclampsia. In a similar study, women with firsttrimester gestations underwent Doppler evaluation of the uterine arteries. The sensitivity of predicting milder forms of preeclampsia was only 27% compared to 60% in the more severe forms. The severe forms were classified as requiring delivery before 32 weeks' gestation **(21).**

Transvaginal sonograms have been assessed to see how their accuracy compares to the transabdominal approach when screening for preeclampsia. Similar to the transabdominal approach, transvaginal sonography in the second trimester was more accurate in detecting more severe forms of preeclampsia than the milder forms. Although these results are not as good for patients who may develop mild preeclampsia, women who develop severe forms are the more clinically relevant cases, and sonography can provide information to help diagnose **(22).**

IV. One-Stage vs. Two-Stage Screening

Some studies have used uterine artery waveform characteristics in the second trimester to benchmark predictive values, whereas others have attempted to assess the waveform earlier in pregnancy. Another approach is to provide a one-stage versus two-stage screening where the Doppler waveform is assessed and compared later in the pregnancy. The hope is that comparing the arterial signal in the same patient would show subtle changes that may occur over time. The one-stage screening is a single evaluation of the uterine arteries typically during the second trimester of pregnancy. At 23 weeks' gestation, an increased PI was observed in 35.3% of women who later developed preeclampsia and in 80% of women with preeclampsia who required delivery before 34 weeks' gestation. The findings showed that the one-stage screening in the second trimester identified most women who would go on to develop adverse outcomes requiring delivery before 34 weeks **(23).**

Another study using a two-stage approach that evaluated the uterine artery at 18 weeks' and again at 24 weeks' gestation assessed the difference of impedance between the uterine artery when comparing the second waveform with the earlier one. This method showed a sensitivity of 63% for preeclampsia based on a persistent increase in impedance between the two waveforms. Because a two-step approach has not been shown to improve predictive values, it has not been widely recommended as a diagnostic protocol **(20).**

V. Third-Trimester Implications

A new finding is reversed diastolic flow in the uterine artery that seems to be related to placental insufficiency during the third trimester. The physiologic basis for an abnormal uterine artery in the first or second trimester of pregnancy is failure of the terminal villous and spiral arteries to form properly. Current theory is that in the third trimester, an abnormal uterine artery will demonstrate reversed diastolic flow, and this reversed flow is the end result of placental vasculature deterioration, leading to placental insufficiency. Two case studies have been found in the literature, one involving severe preeclampsia that developed into eclampsia and the other with intrauterine growth restriction with an abnormal fetal heart rate. With both, reversed diastolic flow in the uterine artery was noticed in the third trimester. These cases obviously have limitations— the sample size was only two patients— but further research could focus on these findings to note the implications **(24).**

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