REVIEW ARTICLE

Uterine Artery Doppler in the Prediction of Preeclampsia and Adverse Pregnancy Outcome

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Abstract

Preeclampsia and fetal growth restriction are major causes of perinatal mortality and morbidity. Several studies have shown that a generalized endothelial dysfunction is associated with these complications. Clinical trials have shown that pregnant women who demonstrate high resistance in uteroplacental blood flow are at higher risk for preeclampsia. Uterine artery Doppler studies both in the second and the first trimester can predict pregnancies at increased risk of the complications of impaired placentation. The sensitivity for predicting severe preeclampsia ranges between 80 and 90% for a false positive rate of 5 to 7%. Uterine artery Doppler screening at 20 to 24 weeks' gestation is superior to first trimester screening, and appears to fulfill the requirements for a worthwhile screening test. Further research is needed to better assess the value of various combinations of uterine artery Doppler and maternal serum markers, for the prediction of adverse pregnancy outcome.

Keywords: Preeclampsia, uterine artery Doppler, screening, ultrasound.

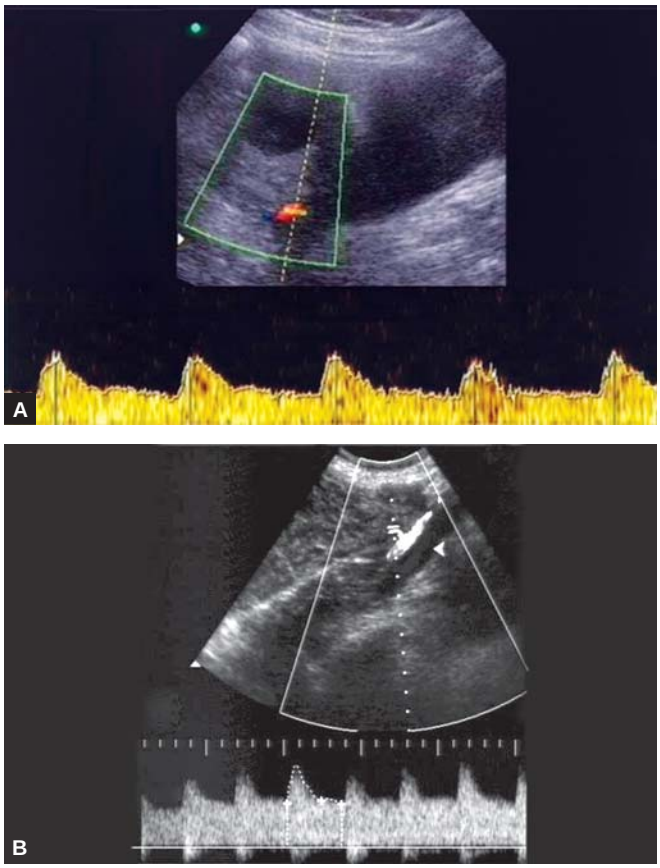
INTRODUCTION

Preeclampsia is a major cause of maternal and perinatal mortality and morbidity worldwide, particularly in developing countries.[1,2] Although, it is a heterogeneous disease, it is believed to result from impaired placentation. Current literature suggests that preeclampsia requires the interaction between placental abnormalities and genetically determined maternal factors that are modified by pregnancy-specific changes.[3,4] In preeclampsia there is insufficient invasion of maternal spiral arteries by the trophoblast early in gestation, so the transformation of these vessels from high resistance low volume to low resistance high volume non-responsive vessels does not take place.[5]

As there is no effective treatment for this complication, the identification of women who are at risk of developing preeclampsia would be of great value. Clinicians could then identify women who require closer antenatal surveillance and allow early referral for timely delivery, when signs or symptoms occur. The earliest efforts to predict preeclampsia focused on the detection of early signs of the disease, such as hypertension, proteinuria, edema, excessive weight gain and increased vascular resistance. Lately, many investigators focused on biochemical markers, primarily those suggesting endothelial dysfunction. Although, numerous tests have been proposed for the prediction of preeclampsia, their results have been inconsistent. Thus most deemed unreliable for routine use in clinical practice.[6] Persistence of high impedance to blood flow was observed in the uterine arteries of women with preeclampsia, which is another indirect evidence of abnormal placentation.[7] It is therefore logical that many studies had focused on uterine artery Doppler as a screening test of women at risk to develop preeclampsia.

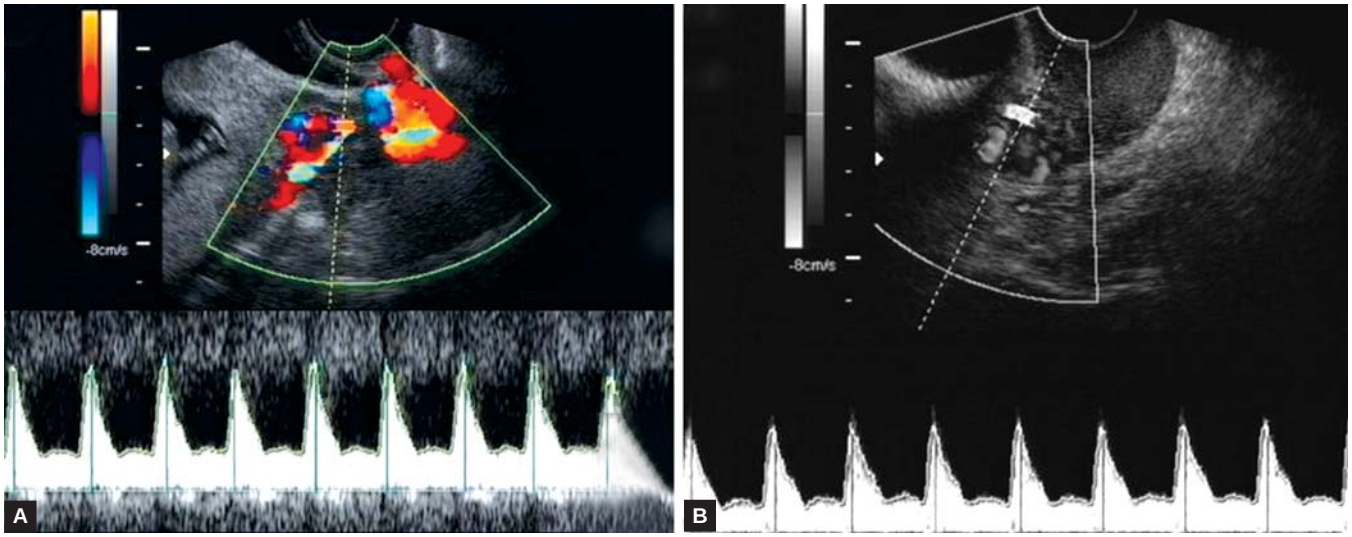
SECOND TRIMESTER UTERINE ARTERY DOPPLER

Studies in pregnancies with established preeclampsia or fetal growth restriction have shown that impedance of blood flow in uterine arteries is increased.[8-10] and this is also compatible with the histopathological findings of placentas from women with established preeclampsia. Placental perfusion and vascular resistance dysfunction have been evaluated with Doppler ultrasonography of uterine arteries. Color flow mapping has been used to identify vessels, either transabdominally at the apparent crossover with the external iliac artery (Figs 1A and B) or transvaginally lateral to the uterine cervix at the level of the internal cervical os (Figs 2A and B). Two important systematic reviews were conducted recently and were published in 2004.[11,12] These meta-analyses assessed the clinical usefulness of different tests in prediction of conditions associated with poor placental perfusion. Conde - Aguelo et al,[11] on behalf of WHO assessed the clinical usefulness of clinical, biophysical and biochemical tests in the prediction of preeclampsia. The authors concluded that there was no clinically useful screening test to predict the development of preeclampsia in either low-risk or high-risk population. They noted though that among women at low-risk of developing this disorder,



Figs 1A and B: Uterine artery flow measurement (transabdominal approach) (A) first trimester and (B) second trimester scan

there is a moderate predictive accuracy of bilateral diastolic notching at Doppler ultrasonography, anticardiolipin antibodies and urine kallikrein, although the increase in pre-test probability was minimal when the results were positive. Concerning the studies which assessed the accuracy of Doppler ultrasonography 43 of them, with a total of 42,261 cases met the reviewers' criteria. Twenty two studies provided data on low-risk populations, 18 on high-risk populations and three on both low- and high- risk populations. The artery Doppler velocity waveform analysis was performed using transabdominal ultrasonography in all but two studies in which transvaginal approach was used. In most cases the test was done during the second trimester of pregnancy. Studies were classified into 4 groups according to how the abnormal uterine artery flow velocimetry waveform was defined: (1) those that used flow waveform ratios (resistance index, pulsatility index, systolic/diastolic ratio, diastolic/systolic ratio); (2) those that used the presence or absence of any diastolic notch; (3) those that used the presence or absence of bilateral diastolic notches; and (4) those that used flow waveform ratios and presence of diastolic notches. Meta-analyses was restricted to studies that used a resistance index greater than 0.58 or greater than the 90-95th percentile or the presence of any diastolic notch or bilateral diastolic notches to indicate an abnormal test result. Overall, the level of prediction of preeclampsia in both low-risk and high-risk populations was moderate to minimal, irrespective of the criteria used. Papageorgiou et al,[12] contacted another review on the findings of 15 second trimester screening Doppler studies in unselected population with a total number of 20000 women. In the pooled data from all studies, the likelihood ratio (LR) for the subsequent development of preeclampsia in women with increased impedance to flow was 6, whereas



Figs 2A and B: Uterine artery flow measurement transvaginally lateral to the uterine cervix at the level of the internal cervical (first trimester)

for those with normal Doppler the likelihood ratio was about 0.5. An important observation of both reviews was that uterine artery Doppler is better in predicting severe than mild disease. Steel et al,[13] in their study show that the sensitivity of increased impedence in the uterine arteries was 39% for gestational hypertension and 63% for preeclampsia. Papageorgiou et al,[14] in their study concluded that sensitivity for preeclampsia with fetal growth restriction (FGR) was 69% whereas for preeclampsia without FGR was 24%. An additional index for severity of disease reported in some studies is the gestational age at which delivery is undertaken. Harrington et al[15] found that bilateral notching at 24 weeks identified 55% of women who later developed preeclampsia and this rose to 81% for preeclampsia requiring delivery before 34 weeks. Similarly, Albaiges et al showed that the sensitivity in increased PI or bilateral notches in the second trimester, in predicting preeclampsia was 45% whereas for preeclampsia requiring delivery before 34 weeks the sensitivity was 90%.[16] Finally Papageorgiou et al,[14] reported that the sensitivities for preeclampsia requiring delivery before 36, 34 and 32 weeks were 70%, 81% and 90% respectively. Hafner et al, compared the value of 3D placental volume in the first trimester and uterine artery Doppler in the second trimester and found that they had similar sensitivities for the prediction of preeclampsia and fetal growth restriction.[17] More recently, Toal et al, examined the usefulness of a second trimester placental profile (maternal serum screening, uterine artery Doppler and placental morphology) in high-risk pregnancies and found that a normal profile reduced significantly the odds ratio for adverse perinatal outcome.[18] The sensitivity of uterine artery Doppler may also be improved by the addition of certain risk factors of maternal history. Papageorgiou et al,[19] studied 16806 unselected women who were attended for routine antenatal care and concluded that combining risk factors from maternal history such as race, smoking habit, essential hypertension, previous preeclampsia, family history, body mass index and parity with uterine artery Doppler could estimate the patient's specific risk for development preeclampsia. Yu et al,[20] studied 32,157 unselected pregnant women and found that the combination of second trimester uterine arteries Doppler and risk factors such as history of preeclampsia, ethnicity, previous term birth and smoking habit provided better estimation of the risk for preeclampsia than ultrasound alone.

FIRST TRIMESTER UTERINE ARTERY DOPPLER

There is also evidence that uterine artery Doppler can be used for assessment of trophoblast invasion in early pregnancy. In 1995, van den Elzen et al,[21] reported on 352 women aged 35 years and older. Using Doptek, the pulsatility index was measured at 12 to 13 weeks of gestation, and this was associated with the development of hypertensive disorders and fetal growth restriction (FGR). When the pulsatility index was in the upper quartile the risk of preeclampsia was increased by a factor of four and the risk of FGR (birth weight below the 5th percentile) was doubled when compared with women in which the pulsatility index was in the lower quartile. More recent studies have demonstrated the feasibility of uterine artery Doppler in the first trimester (11-14 weeks). These studies have shown that Doppler ultrasonography can identify women who will subsequently develop preeclampsia and intrauterine growth restriction.

Martin et al,[22] conducted the largest screening multicenter study to date. Transabdominal examination of the uterine arteries was carried out at 11 to 14 weeks in unselected population. The sensitivity of mean uterine artery pulsatility index above the 95th percentile (2.35) was 27.0% for preeclampsia. The study showed that early diastolic notches were present in 55% of cases, limiting their use for screening at this gestation. Gomez et al, reported a progressive decrease in the prevalence of bilateral notching with gestation.[23] In this study 999 pregnancies were examined between 11 to 14 weeks during routine scan using transvaginal color and pulsed Doppler. The authors found a significant change in the 95th percentile of mean uterine artery pulsatility index with advancing gestation. There were 22 cases of preeclampsia, and using a cut-off of pulsatility index above the 95th percentile, the sensitivity for predicting preeclampsia was 24%, with a positive predictive value of 11%. The authors of the study acknowledged the potential advantages of early screening for preeclampsia and associated complications, but concluded that there is a limited clinical role for uterine Doppler velocimetry in identifying pregnancies with increased risk of developing hypertensive disorders. Pilalis et al,[24] reported that the sensitivity and the positive predictive value of mean uterine artery PI $\geq$ 95th centile at 11 to 14 weeks was 23% and 6.7% respectively. The writers also noted that uterine artery Doppler was the only independent factor in predicting preeclampsia in nulliparous women. Plasencia et al,[25] investigated the performance of screening for preeclampsia using maternal characteristics such as body mass index, age, ethnic origin, smoking status, medical and obstetric history and uterine artery pulsatility index (PI) in the first trimester. They concluded that in unaffected individuals log MoM PI was influenced by maternal ethnic origin, body mass index, previous history of PET and fetal crown-rump length. In the prediction of PET significant contributions were provided by log MoM PI, ethnic origin, body mass index

and previous and family history of PET. They also added that for a false-positive rate of 10% the predicted detection rate of PET requiring delivery before 34 weeks was 82%, compared to 31% for late PET, 12% for gestational hypertension and 18% for small for gestational age. In all studies there was a stepwise increase in sensitivity with the severity of preeclampsia, as expressed by gestational age at delivery. Pilalis et al,[24] showed that the combination of maternal history with abnormal uterine artery Doppler at 11 to 14 weeks achieves better results than does either test alone in the prediction of preeclampsia. The same observation was also confirmed by Plasencia et al.[25] In contrast, in a review article Detti et al, concluded that first trimester Doppler investigation of the uterine circulation cannot predict second or third trimester pregnancy complications.[26] In an observational study Khaw et al examined nulliparous women with singleton pregnancies and found that there were alterations in maternal cardiac function and uterine artery Doppler in those women who subsequently developed preeclampsia and/or fetal growth restriction.[27] Rizzo et al, combined first trimester uterine artery Doppler and 3D ultrasound placental volume calculation and observed better results in the prediction of preeclampsia than either test alone.[28]

COMBINATION OF UTERINE ARTERY DOPPLER AND MATERNAL SERUM MARKERS

There is growing interest in the use of combinations of uterine Doppler and different markers of placental dysfunction and oxidant stress for the prediction of preeclampsia. In a study by Aquilina et al, improved predictive efficacy for preeclampsia was found by combining second trimester maternal serum inhibin-A and uterine artery Doppler.[29] A prospective case– control study demonstrated that 3 types of combination of markers of placental insufficiency and endothelial function (plasminogen activator inhibitor-PAI-1/PAI-2- ratio, leptin, and placental growth factor were highly predictive of the development of preeclampsia when measured at 20 and 24 weeks of gestation in women at high-risk for this disorder.[30] Two recently published nested case-control studies using the same population showed that reduced first trimester serum levels of placental growth factor, a potent angiogenic factor, and increased levels of its soluble inhibitor, fms-like tyrosine kinase 1, predicted the subsequent development of preeclampsia.[31,32] Parra et al,[33] also showed that markers of impaired placentation and oxidative stress such as abnormal PAI-1/PAI-2, increased plasma concentration of 8-epi-prostanglandin F2a, increased circulating anti-angiogenic factor (sFlt1) and reduced PIGF can be found in women before clinical onset of preeclampsia. In this study, it is noted though that the best predictive factor for preeclampsia is uterine artery Doppler and that further investigation is needed for the biochemical factors. In women with early onset gestational hypertension the determination of maternal plasma factor II:C (FII:C) and mean uterine artery resistance index at mid-trimester, may improve the prediction of preeclampsia.[34] Ay et al, resulted that maternal serum inhibin A, activin A levels and uterine artery Doppler appear to be useful screening tests during the second trimester for preeclampsia.[35] However, the authors noted that the addition of these hormonal markers to Doppler velocimetry slightly improves the predictive efficacy, thus their clinical significance is limited. This result was confirmed by the study of Spencer et al,[36] who have shown that screening for preeclampsia by uterine artery pulsatility index at 22 + 0 to 24 + 6 weeks' gestation can be improved by measurement of activin A and inhibin A levels. Espinoza et al,[37] examined the relationship between abnormal uterine artery Doppler velocimetry and plasma concentrations of placental growth factor (PIGF) and soluble endothelial growth factor receptor-1(sVEGFR-1) in maternal blood before the clinical onset of preeclampsia. The conclusion was that the combination of abnormal UADV and maternal plasma PIGF concentration of 280 pg/mL in the second trimester is associated with a high-risk for preeclampsia and early onset and/or severe preeclampsia in a low-risk population. Among those with abnormal UADV, a maternal plasma concentration of PIGF of 280 pg/mL identifies most patients who will experience early onset and/or severe preeclampsia. Two other factors have been evaluated in the first trimester as predictors of preeclampsia. Yaron et al,[38] examined whether low levels of maternal pregnancy associated plasma protein-A (PAPP-A) are predictive of adverse pregnancy outcomes. They concluded that decreased PAPP-A was associated with higher rates of preeclampsia (RR = 6.09). Spencer et al,[39] studied the combination of second trimester uterine arteries' Doppler and first trimester PAPP-A concentration in maternal blood in 4390 unselected women. They found that the detection rate for preeclampsia (5% false positive rate) was 14.1% for maternal PAPP-A , 54.7% for Doppler and 62.1% for the combination. Pilalis et al,[24] showed that the combination of low PAPP-A level, maternal history and abnormal uterine artery Doppler at 11 to 14 weeks achieves better results than does either test alone in the prediction of preeclampsia. Nikolaides et al,[40] investigated the value of serum placental protein 13 (PP-13) and concluded that PP-13 in combination with uterine artery Doppler might be useful in predicting preeclampsia.

Recently Anastasakis et al, evaluated the relationship between increased resistance at the Doppler assessment of the uterine arteries in the second trimester and biochemical markers of oxidative stress (malondialdehyde and uric acid) and the development of preeclampsia.[41] They found that women with increased malondialdehyde levels and abnormal uterine artery Doppler were at increased risk of developing preeclampsia. Prospective, longitudinal studies are needed to better assess the real predictive value of all these markers.

CONCLUSION

Uterine artery Doppler screening meets all the requirements for a worthwhile screening program in prediction of Preeclampsia. The sensitivity for predicting severe preeclampsia was between 80 and 90% for a false positive rate of 5 to 7%. The detection rate could be better if we would set a higher screen-positive rate. In terms of performance, uterine artery screening at 20 to 24 weeks' gestation is superior to first trimester screening, and appears to fulfill all the requirements for a worthwhile screening test. Despite these impressive results few hospitals have established uterine artery screening programs in the second trimester, possibly because there is no effective preventive therapy when treatment is commenced around 20 to 24 weeks.

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