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Accuracy of First Trimester Uterine Artery Doppler in Early Prediction of Preeclampsia in High-Risk Women

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Abstract

Preeclampsia is a complex hypertensive disorder of pregnancy and one of the leading causes of maternal and perinatal morbidity and mortality globally. Its pathophysiology is rooted in defective placentation and abnormal spiral artery remodeling, resulting in impaired uteroplacental perfusion, hypoxia, and the release of anti-angiogenic factors that trigger maternal endothelial dysfunction. Early and accurate prediction of preeclampsia has become a priority in modern obstetric care, as it allows targeted prophylactic measures such as low-dose aspirin, enhanced maternal surveillance, and optimized timing of delivery. Uterine artery Doppler assessment has emerged as a non-invasive and reproducible tool to evaluate uteroplacental blood flow. First-trimester Doppler parameters—including pulsatility index (PI), resistance index (RI), and early diastolic notching—provide valuable insights into abnormal vascular adaptation. When integrated with maternal characteristics, mean arterial pressure, and biochemical markers such as placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A), predictive accuracy improves significantly, particularly for early-onset disease. Despite its limitations related to population variability, technical challenges, and resource constraints, uterine artery Doppler represents a cornerstone of multiparametric screening strategies for preeclampsia and continues to evolve with the integration of advanced imaging and artificial intelligence approaches.

Keywords: Uterine artery Doppler, preeclampsia prediction, first trimester screening, pulsatility index, pregnancy complications

Introduction

Preeclampsia stands as one of the most formidable challenges in contemporary obstetric practice, representing a leading cause of maternal and perinatal mortality worldwide. This pregnancy-specific hypertensive disorder affects approximately 2-8% of pregnancies globally, with devastating consequences that extend far beyond the immediate pregnancy period. The condition contributes to 9-26% of maternal deaths in low-income countries and 16% in high-income countries, making it a critical public health concern that demands urgent attention and innovative approaches to early detection and prevention. The clinical definition of preeclampsia has evolved significantly over recent decades, moving from a triad of hypertension, proteinuria, and edema to a more nuanced understanding that emphasizes the multisystem nature of this disorder. Currently, preeclampsia is characterized by new-onset hypertension after 20 weeks of gestation, defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on two occasions at least 4 hours apart, accompanied by evidence of maternal organ dysfunction. This may manifest as proteinuria, maternal organ dysfunction including renal insufficiency, liver involvement, neurological complications, hematological complications, or uteroplacental dysfunction including fetal growth restriction. The recognition that preeclampsia can occur without proteinuria has broadened our diagnostic criteria and emphasized the importance of identifying early predictive markers (1).

The pathophysiological foundation of preeclampsia lies in the complex interplay between defective placentation and maternal vascular dysfunction, a process that begins in the earliest stages of pregnancy. During normal pregnancy, extravillous trophoblasts invade the maternal decidua and myometrium, transforming the spiral arteries from high-resistance, muscular vessels to high-capacity, low-resistance conduits capable of supporting the dramatic increase in

uteroplacental blood flow required for fetal development. The consequences of inadequate spiral artery remodeling extend far beyond simple mechanical obstruction to blood flow. The resulting placental hypoperfusion triggers a cascade of pathological events including chronic hypoxia, oxidative stress, inflammation, and cellular dysfunction within the placental tissue. These conditions lead to the excessive production and release of various bioactive factors into the maternal circulation, including anti-angiogenic proteins such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin, inflammatory cytokines, and placental debris. These circulating factors contribute to widespread maternal endothelial dysfunction, which manifests as the clinical syndrome of preeclampsia with its characteristic features of hypertension, proteinuria, and multiorgan involvement. The temporal relationship between defective placentation in early pregnancy and the later development of clinical symptoms provides a crucial window of opportunity for early detection and intervention. The clinical heterogeneity of preeclampsia has led to important distinctions between early-onset and late-onset disease, each with distinct pathophysiological mechanisms and clinical implications. Early-onset preeclampsia, typically defined as disease requiring delivery before 34 weeks of gestation, occurs in approximately 0.4-1% of pregnancies but accounts for a disproportionate burden of maternal and perinatal morbidity and mortality (2).

The ability to predict preeclampsia early in pregnancy represents a paradigm shift in obstetric care, moving from reactive management of established disease to proactive prevention and risk mitigation. Early identification of high-risk pregnancies enables several crucial interventions that can significantly improve maternal and perinatal outcomes. Low-dose aspirin prophylaxis, when initiated before 16 weeks of gestation in appropriately selected high-risk women, has been demonstrated to reduce the risk of preterm preeclampsia by approximately 62% and early-onset preeclampsia by up to 82%. This remarkable protective effect appears to be mediated through aspirin's ability to modulate the balance between vasoconstrictor and vasodilator prostaglandins, potentially improving placental vascularization and reducing inflammation. Beyond pharmacological intervention, early risk stratification allows for enhanced surveillance protocols, including more frequent antenatal visits, serial blood pressure monitoring, laboratory assessment of organ function, and fetal growth surveillance. The development of effective screening strategies for preeclampsia has been hampered by the complexity of the condition and the limitations of traditional risk factor-based approaches. Historical approaches relying solely on maternal characteristics and medical history, such as those recommended by the National Institute for Health and Care Excellence (NICE) and the American College of Obstetricians and Gynecologists (ACOG), achieve detection rates of only 30-40% for preterm preeclampsia. While these guidelines appropriately identify women with the highest baseline risks, including those with previous preeclampsia, chronic hypertension, chronic kidney disease, diabetes mellitus, or autoimmune disease, they fail to identify the majority of women who will develop the condition (3).

The recognition that preeclampsia originates from defective uteroplacental vascularization has naturally led to interest in Doppler ultrasound assessment of uterine artery blood flow as a potential screening tool. Uterine artery Doppler ultrasonography offers a non-invasive method to evaluate the hemodynamic consequences of inadequate spiral artery remodeling, providing insights into uteroplacental perfusion that may predict the later development of preeclampsia and other pregnancy complications. The technique involves measurement of blood flow velocity waveforms in the main uterine arteries, typically expressed as pulsatility index (PI) or resistance index (RI), along with qualitative assessment for the presence of early diastolic notching. Abnormal uterine artery Doppler findings, characterized by elevated resistance indices and persistent notching, reflect incomplete spiral artery transformation and inadequate uteroplacental blood flow (4).

The evolution of uterine artery Doppler assessment from a research tool to a clinically applicable screening method has been facilitated by advances in ultrasound technology, standardization of measurement techniques, and the development of population-specific reference ranges. The integration of uterine artery Doppler with other predictive parameters, including maternal characteristics, blood pressure measurements, and biochemical markers, has resulted in multiparametric screening algorithms that achieve detection rates of 75-85% for early-onset preeclampsia. These sophisticated approaches, exemplified by the competing risk model developed by the Fetal Medicine Foundation, treat preeclampsia as a time-to-event outcome and incorporate multiple likelihood ratios to provide individualized risk estimates for different gestational age cut-offs. The clinical validation of these algorithms in large prospective studies has demonstrated their superiority over traditional screening approaches and has led to their incorporation into international guidelines and clinical practice (5).

Normal Uterine Vascular Adaptation in Pregnancy

The uterine circulation undergoes dramatic physiological changes during pregnancy to accommodate the growing fetoplacental unit. Under normal circumstances, total uteroplacental blood flow increases from baseline values of 20-50 ml/min to 450-800 ml/min in singleton pregnancies, with values exceeding 1000 ml/min in twin pregnancies. This remarkable increase is achieved through several complementary mechanisms including circumferential structural enlargement of the uterine vascular tree, reduction in vascular tone through vasodilation, and creation of the placental circulation (4). The process involves extensive remodeling of spiral arteries, where maternal vessels are invaded by extravillous trophoblasts, replacing the muscular arterial wall with fibrinoid material and creating high-flow, low-resistance vessels essential for adequate placental perfusion (5).

Pathological Changes in Preeclampsia

In pregnancies destined to develop preeclampsia, this normal physiological transformation is impaired. Shallow trophoblast invasion results in incomplete remodeling of spiral arteries, maintaining their muscular walls and high-resistance characteristics. This leads to inadequate placental perfusion, chronic hypoxia, and placental oxidative stress. The resulting placental dysfunction triggers the release of anti-angiogenic factors including soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin, which contribute to maternal endothelial dysfunction and the clinical manifestations of preeclampsia (6). These pathological changes can be detected through Doppler assessment of uterine arteries, which demonstrate increased resistance to flow and persistent early diastolic notching reflecting incomplete spiral artery transformation (7).

First Trimester Uterine Artery Doppler Assessment

First-trimester uterine artery Doppler assessment is typically performed between 11-14 weeks of gestation using transvaginal or transabdominal ultrasound. The examination involves identification of the uterine arteries at the level of the internal cervical os, where they cross the external iliac vessels. Key parameters measured include the pulsatility index (PI), resistance index (RI), and presence of early diastolic notching. The mean PI of both uterine arteries is typically used for screening purposes, with values often expressed as multiples of the median (MoM) after adjustment for maternal characteristics (8). Standardized protocols, such as those developed by the Fetal Medicine Foundation, emphasize the importance of consistent methodology to ensure reproducible results and reliable risk assessment (9).

Predictive Performance in High-Risk Populations

Studies examining first-trimester uterine artery Doppler in high-risk populations have demonstrated variable but promising results. A prospective study of 120 Caucasian women with high-risk factors for preeclampsia found that uterine artery PI had a sensitivity of 61.5% and specificity of 63.8% for predicting preeclampsia. The addition of bilateral notching improved performance to 65.4% sensitivity and 66% specificity, suggesting the complementary value of these parameters (10). However, the predictive accuracy varies significantly across different populations and risk categories, with some studies reporting sensitivities as low as 23.9% in low-risk populations, highlighting the importance of appropriate patient selection for screening programs (11).

Integration with Maternal Factors

The predictive performance of first-trimester uterine artery Doppler is significantly enhanced when combined with maternal characteristics and risk factors. The competing risk model developed by the Fetal Medicine Foundation incorporates maternal age, weight, height, race, medical history, and pregnancy characteristics to establish baseline risk before applying likelihood ratios from biophysical and biochemical markers. This approach recognizes that preeclampsia screening should be viewed as predicting the timing of delivery in pregnancies where the condition will eventually develop, rather than simply identifying affected cases (12). The integration of multiple parameters allows for more accurate risk stratification and targeted intervention strategies (13).

Biochemical Markers and Multiparametric Screening

Placental Growth Factor and PAPP-A

The combination of uterine artery Doppler with biochemical markers has revolutionized first-trimester preeclampsia screening. Placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A) are key biomarkers that

reflect placental function and development. PlGF, a member of the vascular endothelial growth factor family, plays crucial roles in angiogenesis and vasculogenesis. Reduced PlGF levels in the first trimester are associated with impaired placentation and increased preeclampsia risk. When combined with uterine artery Doppler and maternal factors, PlGF significantly improves detection rates for preterm preeclampsia (14). Similarly, low PAPP-A levels, while less specific than PlGF, contribute to multiparametric screening algorithms by reflecting inadequate trophoblast function and placental development (15).

Mean Arterial Pressure Integration

Maternal mean arterial pressure (MAP) measured at 11-13 weeks represents another crucial component of multiparametric screening. Blood pressure is typically elevated in pregnancies that will subsequently develop preeclampsia, with particularly marked increases in those developing early-onset disease. The systematic measurement of MAP using standardized protocols, including appropriate rest periods and validated devices, ensures reliable risk assessment. When combined with uterine artery Doppler PI and PlGF, MAP contributes to screening algorithms that can detect 82% of preterm preeclampsia cases, substantially improving upon clinical risk factor-based approaches (16). This multiparametric approach forms the basis of several international screening guidelines and has demonstrated clinical utility in preventing preeclampsia through targeted aspirin prophylaxis (17).

Special Populations and Clinical Scenarios

Twin Pregnancies

Twin pregnancies present unique challenges for uterine artery Doppler screening due to different hemodynamic adaptations compared to singleton pregnancies. Studies have consistently shown that twin pregnancies have lower uterine artery PI values in the first and second trimesters, reflecting increased placental mass and altered maternal cardiovascular adaptation. However, the predictive accuracy of uterine artery Doppler for preeclampsia in twins appears reduced compared to singletons, with lower sensitivity and negative predictive values. This suggests that the etiology of preeclampsia in multiple pregnancies may involve factors beyond simple placental dysfunction, limiting the utility of Doppler-based screening in this population (22). Current evidence suggests that twin-specific reference ranges and modified screening algorithms may be necessary for optimal risk assessment (23).

Pregnancies with Medical Comorbidities

Women with pre-existing medical conditions such as chronic hypertension, diabetes mellitus, renal disease, or autoimmune disorders face elevated baseline risks for preeclampsia. In these populations, uterine artery Doppler assessment may provide additional risk stratification beyond clinical factors alone. Studies in women with systemic lupus erythematosus have shown that abnormal first-trimester uterine artery Doppler parameters are associated with increased preeclampsia risk, potentially helping identify the highest-risk patients who might benefit from enhanced surveillance or prophylactic interventions (24). However, the interpretation of Doppler parameters in the context of underlying vascular disease requires careful consideration of baseline abnormalities and disease-specific factors (25).

Recurrent Pregnancy Loss

Emerging evidence suggests a role for uterine artery Doppler assessment in women with recurrent pregnancy loss (RPL), particularly unexplained cases. Studies have demonstrated that women with recurrent pregnancy loss often have increased uterine artery resistance and decreased endometrial blood flow, which may contribute to implantation failure and early pregnancy loss. The assessment of uterine artery blood flow in early pregnancy may help predict pregnancy viability and guide management decisions in this challenging population (26). However, the optimal timing and methodology for Doppler assessment in RPL cases remain areas of active investigation (27).

International Recommendations

Several international organizations have incorporated uterine artery Doppler assessment into their preeclampsia screening recommendations. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) has published practice guidelines emphasizing the role of first-trimester multiparametric screening including uterine artery Doppler for high-risk women. The International Federation of Gynecology and Obstetrics (FIGO) has endorsed similar approaches, particularly in resource-limited settings where comprehensive biochemical screening may not be available (28). These guidelines

emphasize the importance of standardized protocols, appropriate training, and quality assurance measures to ensure reliable implementation of Doppler-based screening programs (29).

Cost-Effectiveness Considerations

The implementation of uterine artery Doppler screening requires consideration of cost-effectiveness and resource allocation. While the individual costs of preterm preeclampsia are substantial, the relatively low prevalence of early-onset disease means that screening programs must demonstrate clear clinical and economic benefits. Studies have shown that multiparametric screening incorporating uterine artery Doppler can be cost-effective when implemented in appropriately selected populations, particularly when combined with aspirin prophylaxis for high-risk women (30). However, the requirement for trained sonographers and specialized equipment may limit implementation in some healthcare settings (31).

Technical and Interpretive Issues

Despite its clinical utility, uterine artery Doppler assessment faces several technical and interpretive challenges. Inter-observer variability in Doppler waveform analysis can affect reproducibility, particularly in less experienced hands. The presence of maternal obesity, fetal position, and technical factors can compromise image quality and measurement accuracy. Additionally, the interpretation of Doppler parameters requires consideration of gestational age, maternal characteristics, and population-specific reference ranges (32). Standardized training programs and quality assurance measures are essential for maintaining consistent performance across different centers and operators (33).

Population-Specific Variations

The predictive performance of uterine artery Doppler varies significantly across different ethnic populations and geographical regions. Studies have demonstrated that reference ranges and cut-off values established in one population may not be directly applicable to others, necessitating population-specific validation studies. Factors such as genetic background, environmental influences, and baseline disease prevalence can all affect the utility of Doppler-based screening (34). This highlights the importance of local validation and adaptation of screening protocols to ensure optimal performance in diverse clinical settings (35).

Advanced Doppler Techniques

Emerging ultrasound technologies are expanding the possibilities for uterine vascular assessment. Three-dimensional power Doppler and contrast-enhanced ultrasound offer new approaches to evaluating uteroplacental circulation. These techniques may provide more comprehensive assessment of placental vascularization and blood flow distribution, potentially improving the detection of subtle perfusion abnormalities associated with preeclampsia risk (36). However, these advanced techniques require specialized equipment and expertise, limiting their immediate clinical applicability (37).

Integration with Artificial Intelligence

The integration of artificial intelligence and machine learning approaches with Doppler assessment represents a promising frontier for preeclampsia prediction. Advanced algorithms can potentially identify subtle patterns in Doppler waveforms and integrate multiple parameters more effectively than traditional approaches. Machine learning models incorporating clinical data, Doppler parameters, and other biomarkers may achieve superior predictive performance while reducing operator dependency (38). However, the development and validation of such systems require large datasets and careful attention to generalizability across different populations (39).

Patient Selection and Timing

Current evidence supports the use of first-trimester multiparametric screening including uterine artery Doppler for women at increased risk of preeclampsia. This includes women with previous preeclampsia, chronic hypertension, diabetes mellitus, renal disease, autoimmune conditions, or multiple moderate risk factors. The optimal timing appears to be between 11-13 weeks of gestation, when crown-rump length measurements confirm gestational age and other first-trimester assessments are typically performed (40). For women not assessed in the first trimester, second-trimester uterine artery Doppler at 18-24 weeks can provide valuable risk stratification information (41).

Quality Assurance and Training

Successful implementation of uterine artery Doppler screening requires comprehensive training programs and ongoing quality assurance measures. Sonographers should receive standardized training in Doppler technique, waveform analysis, and measurement protocols. Regular audits of technique and inter-observer agreement studies help maintain consistency and identify areas for improvement. The establishment of reference ranges appropriate for the local population and equipment is essential for accurate risk assessment (42). Continuous education and updates on evolving guidelines ensure that practitioners remain current with best practices and emerging evidence (43).

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