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Review Article

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Prediction of Preeclampsia and Intrauterine Growth Restriction in Low-risk Pregnancies in East Avenue Medical Center using Uterine Artery Doppler Velocimetry

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Abstract
Preeclampsia, which is defined as elevated blood pressure after 20 weeks of pregnancy in a woman whose blood pressure had been normal, remains the second most common cause of direct maternal deaths (0.83 per 100,000 cases) worldwide. At present, no effective prophylactic measures have been identified in the prevention of preeclampsia and other pregnancy complications such as intrauterine growth restriction. Therefore, proper antenatal care remains the most important part of prevention. Identifying each woman's individualized risk can allow further antenatal surveillance to be directed to those women who are most likely to develop preeclampsia. Such care leads to early diagnosis and intervention, both in terms of maternal/ fetal monitoring and timing of delivery. In this study, uterine artery Doppler velocimetry in the mid-trimester will be analyzed, and its role in the prediction of later pregnancy complications (preeclampsia and intrauterine growth restriction) will be discussed. The aim of this study is to predict the risk for the development of adverse pregnancy outcomes on the basis of mid-trimester uterine artery Doppler velocimetry. Statistical analysis showed that preeclampsia occurred significantly more commonly in the group with an abnormal doppler result at 16-22 weeks of gestation, compared to pregnancies with normal doppler findings. That is 42.9% (3 out of 7) for abnormal doppler result versus 7.2% (2 out of 27) for those with normal doppler findings. However, none of the 34 evaluated cases developed intrauterine growth restriction. Abnormal uterine artery Doppler result at 16-22 weeks is associated with adverse pregnancy outcomes. In this study, it was well correlated with the development of preeclampsia. Hence, uterine artery Doppler can be used as a useful method for identifying high-risk pregnancies. Uterine artery pulsatility index (PI >1.45) can provide further information for the prediction of preeclampsia in order to conduct appropriate clinical interventions to avoid perinatal morbidity.

Keywords: Uterine Artery Doppler Velocimetry, Preeclampsia, Intrauterine Growth Restriction

Introduction
In most pregnancies, labor and delivery are normal biological processes that result in healthy outcomes for both the mother and the baby. 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, preeclampsia which is defined as elevated blood pressure after 20 weeks of pregnancy in a woman whose blood pressure had been normal, still remains the second most common cause of direct maternal deaths (0.83 per 100,000 cases) [1]. Although the incidence of preeclampsia in the general obstetric population is only 5%, there is a potential for serious adverse complications that include the HELLP syndrome (hemolytic anemia, elevated liver enzymes, low platelet count), eclampsia, coagulopathy, stroke and death. Newborns affected by intrauterine growth restriction (IUGR) are at increased risk for hypertension, cardiovascular disease and diabetes later in life [2]. Preeclampsia and intrauterine growth restriction have been identified as antecedent causes in 5% and 10% of perinatal deaths, respectively.

At present, no effective prophylactic measures have been identified in the prevention of preeclampsia and intrauterine growth restriction. Therefore, proper antenatal care remains the most important part of prevention [3]. Identifying each woman's individualized risk can allow further antenatal surveillance to be directed to those women who are most likely to develop preeclampsia. Such care leads to early diagnosis and intervention, both in terms of maternal/ fetal monitoring and timing of delivery.

The addition of Doppler flow studies of maternal and fetal vessels has provided a tool where the physiology of the maternal - fetal unit can be evaluated [4]. The relationship between abnormal uterine artery Doppler velocimetry and preeclampsia, intrauterine growth restriction and adverse pregnancy outcomes are well-established. Zemel et al., has demonstrated that changes occur in the maternal circulation as early as the first trimester in women who develop pre-eclampsia and IUGR [5]. Second trimester uterine artery pulsatility index (PI) may add more information to the prediction process of preeclampsia. Abnormal uterine artery Doppler flow velocimetry is defined as a mean PI more than 1.45 or/and the presence of bilateral early diastolic notches. Although the uterine artery Doppler has a high negative predictive value for the prediction of adverse perinatal outcomes, the strength of the association between abnormal results and adverse events is not so considerable to justify its introduction as a screening test [6].

In this study, uterine artery Doppler velocimetry in the mid-trimester will be analyzed, and its role in the prediction of later pregnancy complications (preeclampsia and intrauterine growth restriction) will be discussed.

Study Objectives

General Objective

The aim of this study is to predict the risk for the development of adverse pregnancy outcomes on the basis of mid-trimester uterine artery Doppler velocimetry.

Specific Objectives

a. To screen the risk of preeclampsia and intrauterine growth restriction among low-risk pregnancies using mid-trimester uterine artery Doppler velocimetry
b. To determine the rate of adverse pregnancy outcomes (pre-eclampsia and intrauterine growth restriction) among low-risk pregnancies
c. To determine the specificity, sensitivity, positive and negative predictive values of uterine artery Doppler velocimetry in identifying adverse pregnancy outcomes (pre-eclampsia and intrauterine growth restriction) among low-risk pregnancies.

Research Methodology

a. Study Design

This is a prospective cross-sectional study for preeclampsia and intrauterine growth restriction using uterine artery doppler sonography in low-risk pregnancies carried out from February 2017- December 2017 at East Avenue Medical Center.

b. Sampling Design

All patients with singleton pregnancy between ages 20-34 years on their 16 to 22 weeks age of gestation seen at the obstetric outpatient department of East Avenue Medical Center Obstetrics from February 2017 to December 2017 were selected for the purpose of this study.

Inclusion Criteria

The following criteria were used in the selection of subjects included in this research study:

- Singleton pregnancies
- Aged 20-34 years old
- 16 to 22 weeks age of gestation
- Gravidity < 6

Exclusion Criteria

- Patients with adverse obstetric history (e.i., preeclampsia, abruption placenta, preterm labor, intrauterine fetal death).
- Patients with adverse medical history (e.i., chronic hypertension, renal disease, diabetes)
- Patients with family history of hypertension, renal disease and diabetes.

A minimum of randomly selected 160 patients who satisfied the inclusion/exclusion criteria were required at 95% confidence level and expected precision of 4%, to obtain an 80% chance of detecting the predictive value of uterine artery Doppler velocimetry in identifying adverse pregnancy outcomes based on observed 88.2% who developed pre-eclampsia among those with abnormal Doppler results. However, if these sample size could not be obtained, a minimum of 113 and 69 patients are required at 90% and 80% confidence level, respectively.

C. Study Procedure

One of the most widely studied Doppler indices is the pulsatility index. The pulsatility index (PI) for each uterine artery was obtained by averaging the value of three consecutive uterine artery blood velocity waveforms (peak systolic − end-diastolic velocity)/mean velocity). Next, the mean PI from the left and right uterine arteries was calculated. If the mean PI was more than 1.45, the flow velocity waveforms were considered abnormal.

The subjects were recruited from the out-patient department of the East Avenue Medical Center. Patients were issued identification cards as proof of enrollment into the study. The evaluation was done between 16^{th} to 22^{nd} gestational age. It included uterine doppler velocimetry and complete baseline laboratory tests (CBC, BUN, creatinine, AST, ALT, sodium, potassium, LDH, protime and prothrombin time). Subjects were followed-up with blood pressure measurements until 28 weeks then every two weeks until 36 weeks then weekly thereafter until they are admitted for delivery. After delivery, the subjects' were reevaluated for the detection of post-partum preeclampsia.

Preeclampsia was defined based on the Clinical Practice Guidelines on Hypertension in Pregnancy as blood pressure greater than or equal to 140 mmHg systolic or 90 mmHg diastolic on two occasions as least 4 hours apart after 20 weeks age of gestation in a woman with a previously normal blood pressure with proteinuria defined as dipstick reading of at least +1 [7].

Intrauterine growth restriction was defined as those whose estimated fetal weights were below the 10^{th} percentile for their gestational age [8].

Statistical Analysis Plan

All valid data from evaluable subjects were included in the analysis. Summary statistics were presented in tables or graphs and reported as n (%) for qualitative measures. Chi-square test was used to compare proportions. Sensitivity, specificity, positive and negative predictive values and corresponding 95% CI were estimated. Screening accuracy was assessed by calculating receiver-operating characteristics (ROC) curves for these outcomes. Statistical significance was based on p-value ≤ 0.05. Data processing and statistical analyses will be done using STATA v13.

Results

Table 1: The number of abnormal Doppler results for each adverse outcome

Adverse Outcomes	Abnormal Doppler Result n = 7 (20.60%)	Normal Doppler Result n = 27 (79%)	Total Number of Cases n = 34	*p*-value
Pre-eclampsia	3 (42.9%)	2 (7.4%)	5	0.0500
Intrauterine growth restriction	0	0	0	0

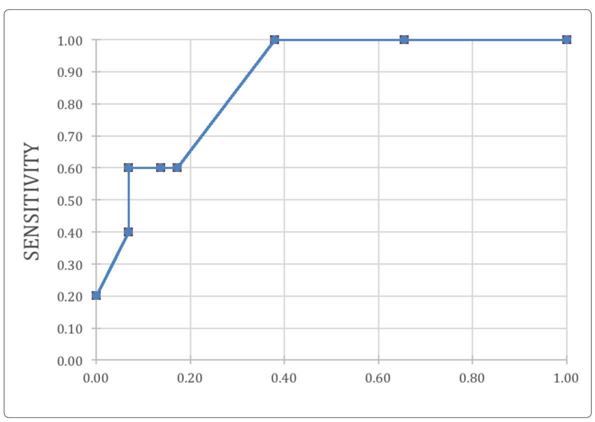
A total of 34 women were enrolled in this study. Table 1 shows the pregnancy outcomes that were analyzed by uterine artery Doppler findings at 16-22 weeks of gestation. Among the 34 evaluated cases, who were between 20-34 years old, 7 cases or 20.60 % had abnormal uterine artery Doppler findings, which were defined by a mean pulsatility index of >1.45 while 27 cases (79%) had normal uterine artery Doppler findings.

Preeclampsia occurred significantly more commonly in the group with an abnormal doppler result, compared to pregnancies with normal doppler findings. That is 42.9% (3 out of 7) for abnormal doppler result versus 7.2% (2 out of 27%) for those with normal doppler findings. However, none of the 34 evaluated cases developed intrauterine growth restriction as shown also in Table 2.

Table 2: Sensitivity, specificity, and predictive values of abnormal Doppler results for each outcome

Adverse Outcomes	Specificity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Pre-eclampsia	86%	60%	43%	93%
Intrauterine growth restriction	0	0	0	0

CI: confidence interval; **PPV:** positive predictive value; **NPV:** negative predictive value.



SPECIFICITY

Figure 1: Receiver-operating characteristics (ROC) curve

In this study, abnormal uterine artery Doppler findings at 16-22 weeks, which were defined as pulsatility index >1.45, had a specificity of 86%, a sensitivity of 60%, a negative predictive value (NPV) of 93%, and a positive predictive value (PPV) of 43%, for the prediction of preeclampsia. For intrauterine growth restriction, it had a specificity of 0, a sensitivity of 0, a NPV of 0, and a PPV of 0 since none of the evaluated cases developed IUGR. These results are shown in Table 2 and Figure 1. The findings showed that an abnormal uterine artery Doppler result had a high specificity and negative predictive value for predicting preeclampsia.

Discussion

Abnormal uterine artery Doppler result at 16-22 weeks is associated with adverse pregnancy outcomes. In this study, it was well correlated with the development of preeclampsia but not with intrauterine growth restriction. The finding that uterine artery Doppler sensitivity with pre-eclampsia was superior to that for IUGR is an intriguing one. Conventionally, it is assumed that IUGR and pre-eclampsia share inadequate trophoblastic invasion of the spiral arteries as a common etiology, suggesting that uterine artery Doppler should be equally effective in detecting both. There are three possible explanations for this finding. First, it is possible that although pre-eclampsia and IUGR share a common etiology, the effects of poor placental invasion may require a further response to manifest the disorder. For example, disorders that exhibit vascular endothelial dysfunction, such as diabetes, renal cardiac disease and chronic hypertension, are strongly associated with subsequent development of pre-eclampsia, but are not independent risk factors for IUGR after exclusion of IUGR secondary to pre-eclampsia [9].

Second, it is possible that IUGR and pre-eclampsia do not share similar placental characteristics. Studies of primary villous trophoblast in pregnancies complicated by pre-eclampsia alone, IUGR alone and pre-eclampsia with IUGR showed different phenotypes of villous trophoblast development and differentiation for these conditions. Differences in placental pathology between IUGR and pre-eclampsia would explain variations in the sensitivity of uterine artery Doppler for these pregnancy complications [10].

This study showed that uterine artery Doppler can be used as a useful method for identifying pregnancies at risk for developing preeclampsia. Uterine artery PI >1.45 can provide further information for the prediction of preeclampsia in order to conduct appropriate clinical interventions to avoid perinatal morbidity.

In 2004, a systematic review by Dr. Cristiane Barbieri revealed that Doppler studies of uterine artery blood flow in the second trimester may be useful in predicting pre-eclampsia and/or intrauterine growth restriction (IUGR). In normal pregnancy, pulsatility values decrease significantly with advancing gestational age until 24-26 weeks. In the absence of this physiologic decrease, a higher incidence of hypertensive disorders and adverse perinatal outcomes could be expected. The advantage of PI and RI, among the different indices, is that they consist of the ratio of Doppler shift frequencies and thus are independent of the transmit frequency and Doppler angle [11].

In another study by Torres C and Raynor B et al. in 2005, they studied the uterine artery score and adverse pregnancy outcomes in a low-risk population during the second trimester. The uterine artery score assigned one point to each abnormal parameter (RI >0.57, PI >1.0, S/D ratio >2.6 and notching) for each uterine artery, ranging from 0 (normal findings in both uterine arteries) to 8 (all abnormal in both arteries). Adverse outcomes included preeclampsia, IUGR, and preterm delivery before 37 weeks. A score of 5 or more was associated with significant differences in the outcomes. In predicting preeclampsia, the score of 5 or more had a specificity of 89.5%, a sensitivity of 25%, an NPV of 77%, and a PPV of 46%. For IUGR, the score had a specificity of 86.3%, a sensitivity of 16.7%, an NPV of 81%, and a PPV of 23% [12]. In our study, the mean PI of uterine artery Doppler measurement of more than 1.45 was considered abnormal at 16-22 weeks, which was found in 20.6% of the patients. Abnormal Doppler findings in predicting pre-eclampsia had a specificity of 86%, a sensitivity of 60%, a negative predictive value (NPV) of 93%, and a positive predictive value (PPV) of 43%.

Another research done in 2005 by Becker R and Vonk R correlated uterine artery Doppler results at 20-23 weeks of gestation and adverse obstetric outcomes [13]. They assessed the diagnostic value of Doppler sonography of the uterine arteries at 20-23 weeks as a screening procedure in a low-risk population. In this study, uterine artery impedance in 7508 patients were evaluated using the mean PI of the left and right arteries or diastolic notching. The outcome variables were preeclampsia, IUGR, intrauterine/neonatal death, and preterm delivery, before 32 weeks. They showed a clear relationship between the elevation of impedance and the frequency of adverse pregnancy outcomes, with the frequency of complications varying from 3.2 to 38.4%. The mean PI in this study was considered to be 2 and they concluded that Doppler sonography of the uterine arteries at 20-23 weeks had the capacity to predict at least a part of the adverse pregnancy outcomes [13]. In our study, Doppler screening was done at 16-22 weeks and it had predicted pre-eclampsia with acceptable specificity and sensitivity.

Toal M and Keating S et al., evaluated the adverse perinatal outcomes in high-risk women with abnormal uterine artery Doppler images and studied the prognostic role of abnormal uterine artery Doppler at 19-23 weeks of gestation, in 2007 [14]. They also evaluated the placental shape and texture abnormalities in this gestation period. They showed that the combined abnormal uterine artery Doppler findings and placental dysmorphology identified a subset of women who were at risk for adverse outcomes, such as intrauterine fetal death, delivery before 32 weeks of gestation, and IUGR. In our study, Doppler screening was done at 16-22 weeks and we evaluated all the women with singleton pregnancies and without abnormal obstetric or medical history. We did not include the placental shape. The abnormal Doppler result had identified women at risk for pre-eclampsia.

Valensise et al., examined the uterine arteries in 272 primigravidas at 22 weeks of gestation [15]. Abnormal results, including a mean RI of >0.58, were found in 9.6% of the patients. The sensitivity of the test to predict pre-eclampsia was 89% and for IUGR it was 67%. The specificity was 93% and 95%, respectively.

Cnossen and colleagues found that uterine artery Doppler ultrasonography more accurately predicted pre-eclampsia than intrauterine growth restriction and that the most powerful Doppler index for predicting pre-eclampsia was an increased pulsatility index with notching in the second trimester. For severe pre-eclampsia, they found that an increased pulsatility index or bilateral notching best predicted the condition [16].

There is a growing evidence that multiparametric models in the first trimester have the potential to improve detection rates for preeclampsia and other adverse pregnancy outcomes. Algorithms that combine maternal characteristics, uterine artery Doppler velocimetry, and biochemical markers in the first trimester have the potential to improve the detection rate of early-onset preeclampsia to over 90% at a false positive rate of 10%. Further research is required to evaluate the generalizability of multiparametric models in different resource settings, in addition to assessing the impact of screening on clinical outcomes.

In addition to uterine artery Doppler ultrasonography, a variety of proteins and hormones have been studied as potential early biomarkers of pre-eclampsia and intrauterine growth restriction. Second-trimester maternal serum screening markers for aneuploidy (the presence of an abnormal number of chromosomes), β human chorionic gonadotropin (β-hCG) and α-fetoprotein have been associated with increased risk [17, 18]. Alterations in first-trimester serum levels of the biomarkers placental protein-13 (PP-13) and pregnancy-associated plasma protein-A (PAPP-A) have also been reported to be predictors of adverse outcomes [19].The purpose of the review by Cnossen and colleagues was not to address the potential additional benefit of measuring maternal biomarkers. However, consideration of a combination of screening tests in a select patient population may be beneficial to patients and health care resources.

Conclusion

Uterine artery Doppler analysis has the potential to predict pregnancy complications associated with uteroplacental insufficiency before the onset of clinical features. In this study, it has been found that uterine artery doppler during the second trimester can predict pre-eclampsia but not intrauterine growth restriction. 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) [20]. Just as aneuploidy screening in the first trimester has become the accepted standard of care, Uterine artery Doppler analysis can also be done 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.

The early prediction of later pregnancy adverse outcomes permits the initiation of management strategies that may prevent or mitigate these complications.

Although pre-eclampsia and intrauterine growth restriction are not uncommon and may pose serious health risks to both mother and fetus, we are still searching for preventive strategies for these at-risk pregnancies. The first step is to identify patients at risk, followed by increased surveillance and therapy. Uterine artery Doppler ultrasonography in isolation, and perhaps in combination with other modalities, may by the key to improved perinatal outcomes in these clinical conditions.

Recommendations

This study only used abnormal uterine artery doppler studies for the prediction of adverse pregnancy outcomes. Abnormal uterine artery doppler studies at 16-22 weeks may be associated with subsequent adverse outcomes as was seen in this study. As an isolated marker of future disease, its sensitivity in predicting preeclampsia in low risk pregnant women is moderate, at 40–70%. Nevertheless, to be more accurate and to do interventions in order to prevent adverse outcomes based on abnormal Doppler results, more studies are needed.

Multiple biochemical markers have been studied individually and in combination as potential markers for adverse pregnancy outcomes. These biochemical markers include PAPP-A and free βhCG. Other disease markers proposed for the prediction of preeclampsia and other adverse pregnancy outcomes include soluble endoglin (sEng), soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), inhibin-A, activin-A, a disintegrin and metalloprotease 12 (ADAM12), and placental protein 13 (PP13), as outlined in Table 1 [37]. As a recommendation for future studies, doppler studies may be used in combination with biochemical markers. Multiparametric predictive models, combining first-trimester uterine artery pulsatility index with maternal characteristics and biochemical markers, can achieve a detection rate for early-onset preeclampsia of over 90%. The ideal combination would allow health care providers to screen the appropriate women and target antenatal surveillance and therapeutic interventions at those who were at risk for pregnancy complications in hopes of improving outcomes. These tests and their validation in various patient populations will be the focus of future research [21].

Since this study did not predict intrauterine growth restriction, it is also recommended that a serial ultrasound be done and documented to determine if indeed there was no occurrence of intrauterine growth restriction. A longer study period as well as a higher number of samples is also recommended in future studies so as to yield a more acceptable and significant result.

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