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Role of Uterine Artery Doppler in the First Trimester in the Prediction of Pre-eclampsia

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Abstract

Background: Abnormal uteroplacental vasculature early in pregnancy may result in pre-eclampsia, which has been linked to an increased risk for serious morbidity or mortality. Doppler study of the uterine artery (UtA) as a standalone biomarker, using pulsatility index (PI) or notching, may help to identify the at-risk women in the first trimester of pregnancy.

Objective: This research aimed to assess the potential of first trimester UtA Doppler ultrasound for the early diagnosis of pre-eclampsia, in at-risk pregnant cases.

Patients and methods: A prospective, observational cohort investigation was conducted on 120 singleton viable pregnant cases at hazard for pre-eclampsia. Doppler ultrasound at (110/7 to 136/7) weeks was performed on both uterine arteries and the potential of mean UtA-PI and notch was evaluated for its usefulness in the prediction of pre-eclampsia. One hundred twenty cases were categorized into two groups according to the pregnancy evolution as follows: group I (pre-eclampsia group) included 14 cases with pre-eclampsia and group II (control group) included 106 without pre-eclampsia.

Results: Both groups had demographic data that were comparable to one another. UtA-PI was significantly greater in the pre-eclampsia group as contrasted with the control group. Based on the results of receiver operating characteristic curve analysis, PI can significantly predict pre-eclampsia with AUC (area under the curve) of 0.709, P value of 0.022; at cut-off greater than 1.91, it gives 71.43 % sensitivity, 66.98 % specificity, 22.2 % PPV (positive predictive value), and 94.7 % NPV (negative predictive value).

Conclusion: This study concluded that UtA Doppler PI assessment in the first trimester (110/7 to 136/7) weeks is a screening method that is both effective and non-invasive for the development of pre-eclampsia in at-risk pregnant women.

Keywords: Doppler ultrasound, Pre-eclampsia, Uterine artery

1. Introduction

The term ‘pre-eclampsia’ was taken from a Greek term that meant lightning. The first known description of the disease was introduced by Hippocrates in the 5th century BC. Hypertension that develops during pregnancy, especially when accompanied by proteinuria and/or pathologic edema, is termed pre-eclampsia. Practically, multi-organ systems may be affected. Pre-eclampsia complicates 2–8% of all pregnancies worldwide, with associated fetomaternal morbidity and mortality. In the United States, the incidence of pre-eclampsia increased by 25% since the 1990s, owing to alterations in maternal predisposing factors (e.g. increased maternal age, chronic hypertension, diabetes, and increased pre-pregnancy weight). The exact etiology and pathogenesis of pre-eclampsia are not fully comprehended. Current researches demonstrate that incomplete trophoblastic invasion due to aberrant regulation and/or generation of cytokines, extracellular matrix metalloproteinases, adhesion molecules, and major histocompatibility complex molecules plays an essential role in the development of pre-eclampsia.
Suboptimal uteroplacental perfusion, accompanied by an increased inflammatory response and vascular endothelial injury, results from abnormal growth and remodeling of spiral arteries in the deep myometrial tissues. This results in organ failure and the different clinical aspects of the disease as a result of vascular hyperpermeability, thrombophilia, and hypertension.

Reduced uteroplacental blood flow and vascular insufficiency are known to contribute to the development of pre-eclampsia; other hazard factors involve hyperton, obstructive sleep apnea, renal illness, thrombophilia, diabetes mellitus, and autoimmune disease. Pre-eclampsia is more likely to develop in women who have a number of hazards for the condition, including a prior history of pre-eclampsia or HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, numerous pregnancies, a high BMI, a first pregnancy, a long time between births, age more than 40, and a family history of pre-eclampsia (in a mother or sister).

Several chemical biomarkers as a disintegrin and metalloprotease 12 (ADAM12), soluble fms-like tyrosine kinase 1 (sFlt-1), serum pregnancy-associated plasma protein-A (PAPP-A), placental growth factor (PIGF) and placenta protein 13 (PP13), and many others have been assessed for the ability to predict pre-eclampsia in the first trimester, prior to the onset of clinical signs. Nevertheless, the reliability of these biomarkers is not sufficient for clinical use. The pulsatility index (PI), the resistivity index (RI), and the existence of an early diastolic notch can be inferred from Doppler ultrasonography measurements of blood flow in the uterine artery (UtA). Incomplete growth and transformation of the uterine spiral arteries have been linked to the preservation of aberrant velocity features of the blood flow, such as the early diastolic notch.

Pregnant cases with hazard factors for pre-eclampsia might potentially benefit from screening for the condition utilizing a standalone biomarker, and a regular first trimester ultrasonography Doppler evaluation of the uterine arteries could give such an opportunity.

We thus hypothesized that Doppler ultrasonography of the UtA in the first trimester may be used to detect pre-eclampsia in elevated-risk pregnancies.

2. Patients and methods

A prospective observational cohort research was conducted in pregnant cases who attended Al-Azhar University Hospital at the outpatient clinics of the Obstetrics and Gynecology department between August 2021 and February 2022. It included 150 pregnant women with gestational age at (11\textsuperscript{67} – 13\textsuperscript{67}) weeks from the first day of the last normal menstrual period validated by early ultrasound examination.

Informed written consent was taken from all the participants. Before the commencement of the study, approval of the local ethical committee was obtained. The inclusion criteria are viable singleton pregnancies and gestational age between 11\textsuperscript{67} and 13\textsuperscript{67} weeks.

The exclusion criteria represented by vaginal bleeding or infections, chronic inflammatory diseases, multiple pregnancies, fetal anatomical abnormalities, or chromosomal abnormalities that necessitated medical termination of pregnancy and recent treatment with non-steroidal anti-inflammatory medicines and corticosteroids (14 days prior to inclusion).

2.1. Methodology in details

Ethical approval from the local Ethics Committee of the Faculty Council was obtained in August of the year 2020—2021.

Individual, menstrual, obstetric, past, present, and family histories were all collected from every case. Each patient was subjected to a thorough physical examination, including the chest, back, abdomen (obstetric), and pelvis. Every patient had standard pretreatment tests (such as a full blood count, a resumption of normal hormone levels, a measurement of fasting and postmeal glucose levels, an evaluation of hepatitis indicators, kidney functions, liver functions, plus a urine analysis). During the first trimester (weeks 110–136), every woman had routine ultrasound measures [such as measuring crown–rump length (CRL), nuchal translucency, detecting fetal heart activity, and doing a Doppler evaluation of the UtA].

Suitable ultrasound equipment was used, with a big convex abdominal probe operating at frequencies among 2.0 and 5.0 MHz for the ultrasonography. Less than a 30° angle was needed among the incident ultrasound beam and the vessel under investigation throughout the treatment. At least three waves with the same visual characteristics and spectrum outline were used in the calculations used to establish the indicators.

Color Doppler and power Doppler were used to locate blood arteries in the uterus and the developing fetus, while pulsed Doppler was used for quantitative and qualitative analysis. Maternal uteroplacental blood flow has its own unique hemodynamics, and this was represented in the velocimetric assessment of the UtA.

Sagittal sections of the cervix were collected during regular ultrasonography between weeks (110/7) and (136/7) of pregnancy. The transducer was angled to
locate the paracervical plexus while the probe was held steady in the midline. The UtA was located at the level of the internal cervical os with an application of color Doppler. Doppler ultrasound using a pulsed wave and a sampling gate of 2 mm allowed for full vessel coverage. Take caution that the insonation angle is not higher than $30^\circ$. If the peak systolic velocity is more than 60 cm/s, the UtA will be checked instead of the arcuate artery. Measurements were taken at the cervico-corporeal junction prior to the UtA splitting into the arcuate arteries.12

There is no need for proteinuria to diagnose pre-eclampsia if you have new-onset hypertension, thrombocytopenia (platelets less than $100,000 \times 10^9/\text{l}$), renal insufficiency (doubling of baseline serum creatine or serum creatinine $>1.1 \text{mg/dl}$), pulmonary edema, impaired liver function $[\text{AST (aspartate aminotransferase)/ALT (alanine aminotransferase)}$ higher than the twice upper limit of normal], or headache that does not respond to treatment and has no known etiology.13

3. Results

Between August 2020 and February 2021, 150 consecutive singleton at-risk pregnant women with a live fetus at $[11^{07/7} - 13^{6/7}]$ week's gestation were invited for inclusion in this study. Out of 150 patients seen, 30 were excluded from the study: 5 declined to participate, 12 did not meet the study criteria, 3 ended in fetal loss or miscarriage before 24 weeks, and 10 missed outcome data, leaving 120 patients eligible for final analysis.

Among the remaining 120 cases, 14 women (9.33 %) developed pre-eclampsia (group 1) and 106 women (70.67 %) did not develop pre-eclampsia (control group) following a physiological evolution of the pregnancy (Fig. 1).

Baseline characteristics of the studied groups as age, BMI, gestational age at enrollment, parity, maternal ethnicity, and smoking status during pregnancy were comparable between both groups. As regards the last inter-pregnancy intervals, cases with pre-eclampsia had significantly shorter intervals as contrasted with the control group $(P < 0.001)$. Cases with pre-eclampsia had significantly higher incidence rate of hypertension contrasted with the control group $(P = 0.001)$ (Table 1).

There was a statistically significant difference regarding the incidence rate of previous preterm birth, pre-eclampsia (either in family history or in previous pregnancies), pre-existing diabetes mellitus, and hypertension, being higher in cases with pre-eclampsia as contrasted with the control group $(P = 0.022, 0.002, <0.001, 0.002, \text{and} \ 0.003, \text{respectively})$. There was no statistically significant difference as regards the history of previous intrauterine fetal death, pre-existing chronic kidney disease, and antiphospholipid syndrome between both groups (Table 2).

Pregnancy consequence of the studied groups as cases with pre-eclampsia had significantly smaller newborns for gestational age, hence lower birth weight and a higher rate of neonatal intensive care unit (NICU) admission when contrasted with the control group $(P < 0.001)$. In terms of gestational age at birth, it was significantly shorter in the pre-eclampsia group as contrasted with the control group $(P < 0.001)$. Cases with pre-eclampsia had a significantly greater incidence rate of placental abruption contrasted with the control group $(P = 0.013)$ (Table 3).

In terms of Mean UtA-PI, it was significantly greater in the pre-eclampsia group with a median of 2.56 and IQR between 1.68 and 2.69 as contrasted with the control group, which had a median PI of 1.59 and IQR between 1.26 and 1.96 $(P = 0.011)$. CRL and Doppler waveforms were comparable between both groups (Table 4).

Based on the results of receiver operating characteristic curve analysis, PI can significantly predict pre-eclampsia with AUC (area under the curve) of 0.709, $P$ value of 0.022; at cut-off greater than 1.91, it gives 71.43 % sensitivity, 66.98 % specificity, 22.2 % PPV (positive predictive value) and 94.7 % NPV (negative predictive value) (Fig. 2 and Table 5).

4. Discussion

In the current study, it was found that demographic data including age, gender, BMI, gestational age at enrollment, parity, and maternal ethnicity were comparable between both groups. In line with our results,14 we conducted a case—control study for the purpose of determining whether or not a history of spontaneous abortion and pre-
About 180 women were engaged in each study group. There was no statistically significant difference among pre-eclampsia cases and controls with respect to age, parity, BMI, or gestational age at enrollment \((P = 0.884)\). Also, conducted a case–control study to evaluate vitamin D status in pre-eclamptic and non-pre-eclamptic pregnant cases. About 40 women were involved in each study group. The results showed that there was no significant difference in age, parity, BMI, and gestational age at enrollment amongst...
the pre-eclampsia patient and control group ($P = 0.999$).  

In the present study, regarding last inter-pregnancy intervals, patients with pre-eclampsia had significantly shorter intervals as contrasted with the control group ($P < 0.001$).

In accordance with our results, we investigated whether the long time interval effect pre-eclampsia or a paternity change may have had a role. Female

Table 5. Diagnostic performance of PI to predict early onset of pre-eclampsia in the studied patients.

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI &gt;1.91</td>
<td>71.43</td>
<td>66.98</td>
<td>22.2</td>
<td>94.7</td>
<td>0.709</td>
<td>0.022*</td>
</tr>
</tbody>
</table>

AUC, area under the curve; NPV, negative predictive value; PI, pulsatility index; PPV, positive predictive value.

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**Table 3. Pregnancy outcome of the studied groups.**

<table>
<thead>
<tr>
<th></th>
<th>Pre-eclampsia group $(n = 14)$</th>
<th>Control group $(n = 106)$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine fetal death</td>
<td>0 (0 %)</td>
<td>1 (7.14 %)</td>
<td>0.117</td>
</tr>
<tr>
<td>Gestational hypertension (%)</td>
<td>0 (0 %)</td>
<td>6 (5.66 %)</td>
<td>1.00</td>
</tr>
<tr>
<td>Antepartum hemorrhage (%)</td>
<td>2 (14.29 %)</td>
<td>0 (0 %)</td>
<td>0.013*</td>
</tr>
<tr>
<td>GA at birth (week) Mean ± SD</td>
<td>35.5 ± 1.99</td>
<td>38.7 ± 1.54</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Birth weight (g) Median (IQR)</td>
<td>2500 (2258–2918)</td>
<td>3190 (2440–3450)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Min–Max</td>
<td>1320–3450</td>
<td>1400–4500</td>
<td></td>
</tr>
<tr>
<td>SGA newborns</td>
<td>≤5th percentile 3 (21.43 %)</td>
<td>2 (1.89 %)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>≤10th percentile 6 (42.86 %)</td>
<td>4 (3.77 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of birth</td>
<td>VD 6 (42.86 %)</td>
<td>46 (43.4 %)</td>
<td>1.00</td>
</tr>
<tr>
<td>CS 8 (57.14 %)</td>
<td></td>
<td>60 (56.6 %)</td>
<td></td>
</tr>
<tr>
<td>Indication of CS</td>
<td>Maternal 2 (14.29 %)</td>
<td>13 (12.26 %)</td>
<td>0.475</td>
</tr>
<tr>
<td>Fetal 4 (28.57 %)</td>
<td></td>
<td>19 (17.92 %)</td>
<td></td>
</tr>
<tr>
<td>Labor dystocia 2 (14.29 %)</td>
<td></td>
<td>28 (26.42 %)</td>
<td></td>
</tr>
<tr>
<td>NICU admission 4 (28.57 %)</td>
<td></td>
<td>7 (6.6 %)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

CS, cesarean section; GA, gestational age; IQR, interquartile range; NICU, neonatal intensive care unit; SGA, small for gestational age; VD, vaginal delivery.

**Table 4. First trimester uterine artery Doppler ultrasound measurement.**

<table>
<thead>
<tr>
<th></th>
<th>Pre-eclampsia group $(n = 14)$</th>
<th>Control group $(n = 106)$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRL (mm) Median (IQR)</td>
<td>50 (44.75–54)</td>
<td>53 (44.25–59.75)</td>
<td>0.282</td>
</tr>
<tr>
<td>Min–Max</td>
<td>42–68</td>
<td>42–80</td>
<td></td>
</tr>
<tr>
<td>Mean uterine artery PI</td>
<td>2.56 (1.68–2.69)</td>
<td>1.59 (1.26–1.96)</td>
<td>0.011*</td>
</tr>
<tr>
<td>Min–Max</td>
<td>0.95–3.35</td>
<td>0.9–3.3</td>
<td></td>
</tr>
<tr>
<td>Doppler waveforms (%)</td>
<td>No notch 2 (14.29 %)</td>
<td>53 (50 %)</td>
<td>0.067</td>
</tr>
<tr>
<td>Right side 1 (7.14 %)</td>
<td></td>
<td>9 (8.49 %)</td>
<td></td>
</tr>
<tr>
<td>Left side 3 (21.43 %)</td>
<td></td>
<td>12 (11.32 %)</td>
<td></td>
</tr>
<tr>
<td>Bilateral notch 8 (57.14 %)</td>
<td></td>
<td>32 (30.19 %)</td>
<td></td>
</tr>
</tbody>
</table>

CRL, crown–rump length; IQR, interquartile range; PI, pulsatility index.

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**Fig. 2. Receiver operating characteristic curve of pulsatility index to predict pre-eclampsia in the studied patients. AUC, area under the curve.**
patients with and without a history of pre-eclampsia were included in the 547 238 pregnancies analyzed. When comparing cases with pre-eclampsia to a control group, the findings indicated that the pre-eclampsia group had significantly shorter intervals amongst pregnancies ($P < 0.001$). A greater incidence of hypertension and placental abruption was seen in the pre-eclamptic group in contrast to the control group in the current research. Both of these findings were statistically significant ($P = 0.013$ and $0.001$, respectively).

In addition to cases of pre-eclampsia ($n = 6487$), the research also included frequency-matched controls ($n = 25 948$). There was a statistically significant increase in the risk of abruption and hypertension among individuals with pre-eclampsia contrasted with the control group ($P < 0.001$). Additionally, 18 contrasted the perinatal mortality rate of cases who developed abruptio placentae to cases who did not develop this complication in a case–control study in order to assess which cases admitted for expectant management of early onset severe pre-eclampsia develop abruptio placentae. There were around 69 women in each research group. Cases diagnosed with pre-eclampsia were found to have a greater rate of abruption and hypertension than the control group ($P < 0.001$).

In the present study, it was discovered that there was a statistically significant increase in the pre-eclampsia group contrasted with the control group regarding the incidence rate of previous preterm birth, pre-eclampsia (either in family history or in previous pregnancies), pre-existing diabetes mellitus, and hypertension ($P < 0.05$).

In agreement with our results, we assessed about 125 consecutive women with pre-eclampsia. Study characteristics were contrasted with a control group and consisted of things like parity, mode of delivery, most prevalent reasons for cesarean section, birth weight, gestational age and neonatal problems, and mortality. The findings revealed that cases with pre-eclampsia had significantly smaller newborns for gestational age, hence lower birth weight and a higher rate of NICU admission when contrasted with the control group. Also, gestational age at birth was significantly shorter in the pre-eclampsia group in comparison to the control group ($P < 0.001$).

Furthermore, collected blood samples were from the cord blood of 36 newborns who had been subjected to pre-eclampsia throughout pregnancy, and 35 babies and their moms who did not experience any pregnancy complications. Birth weights were lower ($P < 0.03$) in babies whose mothers experienced pre-eclampsia during pregnancy compared to healthy women.

On the contrary, we conducted a retrospective analysis of a case–control study. Cases were separated into two groups: group A involved about 28 cases with pre-eclampsia and group B included about 61 healthy women. The results showed that there was no statistically significant difference amongst the pre-eclampsia and healthy group in terms of birth weight ($P = 0.11$) and gestational age ($P = 0.06$). This contradiction between both studies can be justified by the fact that there are differences between sample sizes in both groups.

In the present study, it was found that APGAR scores 1 and 5 min after birth in each group were significantly increased after 5 min as compared to 1 min measurement in both groups. Meanwhile, APGAR score after 1 and 5 min was significantly lower in the pre-eclampsia group contrasted with the control group ($P < 0.001$).

In agreement with our results, we conducted a retrospective cohort study on 447 pre-eclamptic singleton pregnant women to determine APGAR scores among those patients. The results showed that APGAR score after 1 and 5 min was significantly lower in pre-eclampsia group ($P < 0.001$). They also stated that early onset of pre-eclampsia (adjusted OR = 4.577; 95 % CI = 2.147–9.757) was an independent hazard factor for having an infant with a low APGAR score at 1 min.

In agreement with our results, we conducted a prospective case–control study that involved 50 pregnant cases with pre-eclampsia with or without intrauterine growth restriction. Thirty women with uneventful pregnancies, matched for age, parity, and gestational age, functioned as controls.

In agreement with our results, we conducted an observational cross-sectional study to show that UA spectral Doppler screening is effective for predicting pre-eclampsia. Pre-eclampsia developed in almost 70 pregnant cases and was not seen in the control group of 6. Pre-eclampsia patients had considerably greater PI levels contrasted with controls ($P < 0.001$).

5. Conclusion

Birth interval and gestational age at birth were shorter in patients with pre-eclampsia when contrasted with the control group. Meanwhile, placental abruption and hypertension were higher in cases with pre-eclampsia when contrasted with the control group. UtA Doppler PI was significantly greater in the pre-eclampsia group as contrasted with the control group with a valuable predictive value. UtA Doppler examination in the first trimester ($1^{10/7} \sim 1^{3/7}$) weeks is a reliable non-invasive screening tool for identifying high-risk
pregnant cases with a potential for developing pre-eclampsia.

Conflicts of interest

There are no conflicts of interest.

References