Severe Early–Onset Preeclampsia: Prognostic Role of Uterine Artery Doppler Examination

Lilyan W. Sersam*, Shamam Y. Mohammed**, Eftekhar Shmkhee Abood***

ABSTRACT:
BACKGROUND:
Preeclampsia is essentially an endothelial disease. Early-onset preeclampsia appears to be linked mainly to a failed placental vascular remodeling. Uterine artery Doppler is a validated noninvasive surrogate of trophoblastic invasion and placental perfusion.

OBJECTIVE:
To evaluate the predictive capacity of uterine artery Doppler investigation for maternal and neonatal complications in women with severe early-onset preeclampsia.

METHODS:
This prospective comparative study was carried out on sixty-five Iraqi pregnant women with severe early-onset preeclampsia. Their gestational age ranged from 16–24 weeks of gestation. A uterine artery Doppler examination was performed on admission to the participants. According to the result of Doppler ultrasound, they were arranged into two main groups: group one comprising twenty-nine patients with normal uterine artery Doppler results, and group two comprising thirty-six patients with abnormal uterine artery Doppler results. The maternal and neonatal outcome of women with abnormal uterine Doppler results was compared to those with normal Doppler results, and the results were analyzed accordingly.

RESULTS:
Sixty-five patients were enrolled in this study. In 57% of them, uterine artery Doppler results were abnormal. This group showed statistically significant lower birth weight (p = .011), higher caesarean section rate (p = .011), abnormal umbilical artery Doppler examinations (p = .001) and higher neonatal complications rate (P = .011). Regarding the maternal complications (HELLP syndrome, neurological manifestations, acute renal failure and pulmonary oedema), occurred at higher rate in the group with abnormal uterine artery Doppler compared with those having normal Doppler results (57% versus 42%), but only acute renal failure reached the statistical level of significance (P = .011).

CONCLUSION:
Women with severe early-onset preeclampsia are at higher risk of maternal and neonatal complications if abnormal uterine blood flow is present.

KEY WORDS: uterine artery doppler, early-onset preeclampsia.

INTRODUCTION:
Preeclampsia (PE) affects about 5% of pregnancies and is a major cause of maternal and perinatal morbidity and mortality (1-5). Doppler studies were carried out in pregnancies presenting with preeclampsia or fetal growth restriction reported that the outcome was worse if there was increased, rather than normal, impedance to flow in the uterine arteries (1,5). In recent years, it has been established that early- and late-onset preeclampsia are associated with different biochemical and clinical features: whereas the early-onset form is almost invariably associated with placental insufficiency and growth restriction, the late-onset form is more prevalent and, in general, placental involvement is minimally present (6). Early-onset Preeclampsia and fetal growth restriction are placenta-mediated diseases that share important similarities as recently demonstrated by Crispi et al. (7,8). Umbilical artery (UA) and middle cerebral artery (MCA) Doppler examinations are standard parameters used in the management of pregnancies at risk of placental insufficiency (5). Uterine artery (UtA) Doppler has been widely studied for the prediction of preeclampsia and intrauterine growth

*Department of Obstetrics and Gynaecology, College of Medicine, Al-Mustansiriya University, Al-Yarmouk Teaching Hospital.
**Department of Radiology, Al-Yarmouk Teaching Hospital.
***Department of Obstetrics and Gynaecology, Al-Yarmouk Teaching Hospital.
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This prospective comparative study was conducted at the department of Obstetrics and Gynecology at AL-Yarmouk Teaching Hospital for period extending from the first of November to the end of January. The study comprised a total of 180 Iraqi pregnant women in their third trimester, their gestational age ranged from to weeks of gestation, with a diagnosis of severe preeclampsia. Severe preeclampsia was defined as preeclampsia with severe hypertension (diastolic blood pressure \( \geq 110 \) mmHg or greater, systolic blood pressure \( \geq 160 \) mmHg or greater) and/or with symptoms, and/or biochemical and/or haematological impairment \(^{1}\); A uterine artery Doppler examination was performed on admission to the emergency ward to all participants. Exclusion criteria were: \(^1\) undetermined gestational age; \(^5\) Women in labor and/or with uterine activity; \(^7\) twin pregnancies; \(^8\) clinical urgency with maternal hemodynamic instability or an indication for immediate termination of pregnancy; \(^9\) preexisting maternal chronic medical problems: chronic hypertension, diabetes mellitus, autoimmune disease, renal diseases, maternal heart disease, and thromboembolic disease ; \(^9\) pregnancy with congenital fetal abnormalities; and \(^4\) Dead fetus at admission to hospital. According to Doppler ultrasound results, our subjects were divided into main groups: Group \(^4\): Normal uterine artery Doppler results (control group). Group \(^7\): Abnormal uterine artery Doppler results (case group).

The maternal and neonatal outcomes of women with abnormal uterine artery Doppler results (group\(^7\)) were compared with those with normal Doppler results (group\(^4\)). The women in both groups were matched for maternal age, body mass index (BMI) and gestational age. This study was approved by the Institutional Ethics Committee, and verbal informed consent was obtained from the patients. In this study, National Institute for Health and Clinical Excellence Clinical Guideline definitions were used to define preeclampsia \(^{10}\). A detailed history was taken from all participants and complete examination (general and obstetric examination) was done and investigations were performed, all women were followed up till delivery to verify maternal and neonatal outcomes. All study subjects were submitted to an obstetrical Doppler scan standardized for the study, carried out by one single operator (the principal investigator), who was contacted at the time of inclusion of each woman in the study. The examinations were carried out using a color Doppler ultrasound scanner (Siemens, Acuson, Germany) with a \(7.5 \text{ MHz} \) transducer and with the filter adjusted to \(1.0 \ldots 1.1 \text{ Hz} \). Umbilical artery Doppler ultrasound examination was performed to the women in the left lateral recumbent position. The umbilical artery was identified and flow velocity waveforms were obtained from a free-floating loop of the cord during fetal quiescence. Flow velocity waveforms were considered abnormal when the mean PI was above the \(\text{70th centile for gestational age using published reference values}^{15}\). Then the transducer was positioned on the lower right and left quadrant of the patient’s abdomen, visualizing the external iliac artery and medially identifying the uterine arteries. Scans of each uterine artery were obtained at the point close to the external iliac artery prior to the division of the uterine artery into branches, following this, pulsatility index (PI) was measured, and the presence or absence of an early diastolic notch was noted. The process was then repeated for the contralateral uterine artery, and the mean PI (mPI) of the two vessels was calculated. Flow velocity waveforms were considered abnormal when the mean PI was above the \(\text{70th centile for gestational age using published reference values}^{11}\) or the presence of notching was noted. To evaluate maternal outcome, the following complications were considered: oliguria (defined as hourly diuresis \( < 500 \text{ ml/h} \)), acute pulmonary edema (presence of maternal respiratory distress with fine basal crepitations detected at pulmonary auscultation requiring the use of diuretics), eclampsia and other neurological manifestations (visual disturbances or severe headache that persisted \( > 4 \text{ hours} \)); HELLP syndrome and acute renal failure Adverse neonatal outcome was defined by the presence of the following criteria: small-for-gestational age, fetal or neonatal death, etc.
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minute Apgar score < 7, or significant neonatal morbidity: (seizures, hypoxic ischemic encephalopathy, acute renal failure, or cardiac failure).

Statistical analysis:
Analysis of data was carried out using the available statistical package of SPSS-18 (Statistical Packages for Social Sciences- version 18 "PASW" Statistics). Data were presented in simple measures of percentage, mean, standard deviation and range (minimum-maximum values) The significance of difference of different means (quantitative data from different study groups and from comparison group) was tested using independent student t-test for difference between two means, while different percentages (qualitative data from different study groups and from comparison group) were tested using Pearson Chi-square test (χ² -test). Statistical significance was considered whenever the P value was less than .05.

RESULTS:
The study represents a case-control study on 180 pregnant Iraqi women, in their third trimester, with a diagnosis of severe preeclampsia; In 80%, 7% of the cases (180/180), the uterine artery Doppler examination was abnormal, while it was normal in 20%, 3% (41/180). Both groups were demographically comparable on bases of their maternal age (P=0.84), BMI (P=0.59), gestational age at admission (P=0.16), and gestational age at delivery (P=0.99). There was no statistically significant difference between both groups as the P value was more than .05. Table 1 shows the demographic characteristics for patients with normal and abnormal uterine artery Doppler findings. The mean maternal age (years) was 21±2 for the abnormal uterine artery Doppler group (case group), with a range of (18-28). For the normal uterine artery Doppler group (control group) the mean was (21±2), with a range of (20-28). Regarding the gestational age at admission, the mean gestational age (weeks) was (31±1) for the case group with a range of (28-34) while the mean was (31±1) for the control group, with a range from (28-34). The mean maternal BMI (kg/m²) was 29±2 for the case group with a range from (21-31) while the mean was 28±2 for the control group, with a range from (21-31). Among patients with abnormal uterine Doppler results, birth weights were significantly lower (P = 0.01) compared with the control group, with a mean of (2.4±0.7 kg) in study group versus (2.7±0.8 kg) in control group, as shown in Table 1. Table 2 illustrates caesarean section distribution among both groups. In abnormal uterine artery Doppler group, caesarean section rate was significantly higher compared with controls, 8.7% (8/8) versus 4% (4/100), (p=0.01), while only two patients (2, 2%) delivered by vaginal route in the study group versus eight patients (8, 8%) delivered by vaginal route in control group. In abnormal uterine artery Doppler group, abnormal umbilical artery Doppler examination rate was significantly higher compared with the control group, 80% (8/10) versus 41% (41/100), (p=0.01), as shown in table 2. Table 2 summarized the maternal complications. Patients in the study group had a higher rate of maternal complications than those in the control group (88% versus 78%, P=.01) respectively although the difference between the two groups didn’t reach the statistical level of significance. Further categorization of the results of maternal complications for the patients in the study and control groups, HELLP syndrome was seen in (11%, 1%) versus (11%, 1%) respectively whereas neurological manifestations occurred in (2% versus 0%), acute renal failure developed in (8% versus 4%) and pulmonary oedema complicated (8% versus 4%) respectively, all these complications were seen at higher rate in study group compared with the control group, but only acute renal failure reached the statistical level of significance (P=0.01). Table 3 reveals the neonatal complications for both groups which were higher in patients with abnormal uterine artery Doppler (40%, 40%) in comparison to that of controls (30%, 30%). This difference in the neonatal complications was statistically highly significant (P=.001). Regarding small-for-gestational age, study group developed higher rate of small-for-gestational age than control group (40% versus 14%), Apgar score at 5 minute was seen in (3, 3%) versus (3, 3%) respectively, significant neonatal morbidity developed in (14%, 6%) versus (14%, 6%) respectively, and perinatal death complicated (20% versus 5%) respectively which was statistically highly significant (P=.001).
Table 1: Demographic characteristics, for patients with normal and abnormal uterine artery Doppler.

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>Cases (n=66)</th>
<th>Control (n=29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Range</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>27.0±6.4</td>
<td>18.2-41</td>
<td>24.0±6.6</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.2±1.8</td>
<td>37.1-39.3</td>
<td>38.1±1.8</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>38.0±1.5</td>
<td>37.1-39.0</td>
<td>38.1±1.5</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>28.0±4.8</td>
<td>16.3-44</td>
<td>24.0±4.0</td>
</tr>
</tbody>
</table>

*Significant using Students-t-test for difference between two independent means at *P* level of significance

Table 2: Birth weight distribution among both groups.

<table>
<thead>
<tr>
<th>Birth weight (Kg)</th>
<th>Cases (n=66)</th>
<th>Control (n=29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>&lt;1250</td>
<td>*6</td>
<td>9</td>
<td>*2</td>
</tr>
<tr>
<td>1250-1800</td>
<td>26</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td>1800-2500</td>
<td>14</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>≥2500</td>
<td>5</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

*Significant using Pearson Chi-square test for difference between proportions and Students-t-test for difference between two independent means at *P* level of significance

Table 3: Cesarean section distribution among both groups.

<table>
<thead>
<tr>
<th>Cesarean section</th>
<th>Cases (n=66)</th>
<th>Control (n=29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>39</td>
<td>59</td>
<td>11</td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
<td>41</td>
<td>18</td>
</tr>
</tbody>
</table>

*Significant using Pearson Chi-square test for difference between proportions at *P* level of significance

Table 4: Rate of abnormal umbilical artery Doppler distribution among both groups

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Cases (n=66)</th>
<th>Control (n=29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>39</td>
<td>59</td>
<td>11</td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
<td>41</td>
<td>18</td>
</tr>
</tbody>
</table>

*Significant using Pearson Chi-square test for difference between proportions at *P* level of significance

Table 5: Maternal complications, for patients with normal and abnormal uterine artery Doppler

<table>
<thead>
<tr>
<th>Maternal complication</th>
<th>Cases (n=66)</th>
<th>Control (n=29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HELLP</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Neurological manifestations</td>
<td>3</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>5</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

*Significant using Pearson Chi-square test for difference between proportions at *P* level of significance
DISCUSSION:

Preeclampsia remains an important cause of maternal and neonatal complications and death (12, 13). Doppler ultrasonography of the uterine arteries is becoming a routine part of pregnancy surveillance in high-risk pregnancies and is a promising technique for predicting these complications (14). This study demonstrates that in severe early-onset preeclampsia there is higher rate of abnormal uterine artery Doppler examinations (9, 10%) compared to normal uterine artery Doppler (4, 7%) , this finding was in agreement with that reported by Meler et al. (15) who studied the predictive capacity of umbilical, cerebral and uterine artery Doppler in women with preeclampsia (PE) , and the associated complications and adverse perinatal outcome. In both early- and late-onset forms, uterine artery Doppler examinations showed a greater capacity than umbilical and middle cerebral artery Doppler examinations for predicting adverse perinatal outcome. Pulsatility index (PI) is a good predictor of adverse outcome of pregnancies. Ghosh et al. (16) demonstrated that RI and PI as measures of third trimester utero-placental vascular impedance were the best predictors of adverse outcome in high risk pregnancy. In this study we depend on PI and/or notching as a predictor of adverse maternal and neonatal outcome. In their study, Cnossen, et al. (17) reported that pulsatility index alone or combined with notching, was the most predictive Doppler index in high risk pregnancy eg. preeclampsia. In the present study, abnormal uterine artery Doppler in the third trimester of pregnancy in women with severe early-onset preeclampsia was found to be predictive of a higher rate of maternal and neonatal complications. These findings were in agreement to those reported by Meler et al. in 18, 19. While Ghi et al. in 20, 21 studied the usefulness of uterine artery Doppler in the prediction of outcome in patients with late-onset preeclampsia, They found that women with late-onset preeclampsia showed a higher risk of perinatal complications if uterine resistance was increased although maternal outcome does not seem to be related to Doppler findings.

With respect to the evaluation of the biological characteristics of the patients enrolled in the present study, there was no statistically significant difference between two groups with respect to maternal age, BMI, gestational age at admission, gestational age at delivery, with a tendency towards overweight found in the present study, this was similar to the profile observed in patients with a greater risk for preeclampsia in pregnancy and was in agreement with the results reported by de Melo et al. (22). With respect to gestational age at delivery, mean gestational age was lower in the group with a resistant uterine artery Doppler compared to the group with normal uterine artery Doppler, but the difference was not significant, this finding disagree with Meler et al. (23), Ghi et al. (24), de Melo et al. (25) who found statistically significant difference in gestational age at delivery. This might be due to small sample size enrolled in this study. Among patients with abnormal uterine Doppler results, mean birth weight was significantly lower in study group compared with controls. A higher rate of small-for-gestational age was also found in study group compared to controls. These findings were in agreement to those reported by Vergani et al. (26) and Yu et al. (27).

In the current study, a significantly higher rate of cesarean delivery was found in group with increased uterine artery resistance in the third trimester. Our findings were in agreement to those reported by Vergani et al. (26). It might seem
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reasonable to expect that in cases with high-resistance placental circulation there would be reduced fetal tolerance to the intermittent oxygen deprivation produced by labor contractions leading to higher rate of fetal distress.

In abnormal uterine artery Doppler group, abnormal umbilical artery Doppler examination was significantly higher compared to controls 

(p=...). This finding was consistent with that reported by Chosh and Gudmundsson (1), they also reported that these two vessels were comparable in predicting adverse outcome.

This study shows that patients with severe preeclampsia with increased uterine artery resistance in their third trimester were at higher risk of obstetric and perinatal complications. As shown in table 8, maternal complications rate was higher in study group compared with controls, although it didn't reach statistical level of significance. Nevertheless, the absolute frequency of all the complications was evaluated. These higher rates reported in our study did not reach statistical significant difference, except for acute renal failure in which the difference was statistically significant (p=...). This partially agree with the results found by Meler et al. (5), who reported a significantly higher rate of maternal complications in patients with severe early-onset preeclampsia with increased uterine artery resistance in their third trimester. Regarding the rate of neonatal complications, for both groups it was significantly higher in abnormal uterine artery Doppler group as compared with controls, (P=...). In the present study there was a statistically highly significant difference in perinatal death rate between cases and controls (P=...), this may be contributed to high number of small-for-gestational age and lower birth weight in study group compared with controls. These findings agree with majority of researchers who investigated uterine artery Doppler as predictive tool of adverse neonatal complications (11,16).

It is possible that future studies with larger sample size will show statistically significant differences with respect to the frequency of these outcomes.

CONCLUSION:

Women with severe early-onset preeclampsia are at higher risk of maternal and neonatal complications if abnormal uterine blood flow is present. Uterine artery Doppler examination is a good predictor for maternal and perinatal outcome in pregnancies complicated with preeclampsia and can be included as a primary surveillance test for high risk group.

REFERENCES:

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