Correlation between Uterine Artery Diastolic Notch, Serum Human Chorionic Gonadotropin and Severity of Preeclampsia

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Abstract

Background: Early midtrimester measuring of plasma levels of Human Chorionic Gonadotropin (HCG) is recommended because of its predictive value of diagnosing preeclampsia and its severity. Uterine artery Doppler studies also are recommended to be performed between 22-26 weeks' gestation as it increases the predictive value for adverse pregnancy outcomes including preeclampsia and/or IUGR.

Aim of Study: Determine the correlation between uterine artery Doppler diastolic notch, serum human chorionic gonadotropin and severity of preeclampsia.

Patients and Methods: One hundred twenty pregnant women are classified in to three groups, Group one consists of 40 women with normal pregnancy, Group 2 consists of 40 patients with mild pre-eclampsia and Group 3 consists of 40 patients with sever pre-eclampsia and followed-up between 20-36 weeks' gestation regularly every 4 weeks until 28 weeks gestation then every two weeks until 36 weeks with measuring plasms HCG level during early midtrimester and uterine artery Doppler studies between 22-26 week' gestation.

Result: The level of maternal serum HCG of normal control group is found to be the lower followed by mild group then sever group and the difference is found to be statistically highly significant (p<0.001). In addition to, the uterine artery Doppler S/D ratio and RI in the control group is found to be lower in normal control group followed by mild then sever group.

Conclusion: There is strong positive correlation between the level of maternal serum HCG, uterine artery Doppler indices and severity of preeclampsia.

Recommendation: We recommend to measure HCG level in addition to performance uterine artery Doppler studies for prediction of severity of pre-eclampsia.

Key Words: Serum human chorionic gonadotropin – Uterine artery diastolic notch – Sever pre-eclampsia.

Introduction

PRE-ECLAMPSIA is a pregnancy-specific, multisystem disorder that is characterized by the development of hypertension and proteinuria after 20 weeks of gestation. The disorder complicates approximately 5 to 7 percent of pregnancies [1].

Although, the exact pathophysiologic mechanism is not clearly understood, but preeclampsia is primarily a disorder of endothelial function with associated vasospasm. Roberts et al., [2] proposed that maternal endothelial cell dysfunction is the key event resulting in the diverse clinical manifestation of preeclampsia. It can decrease uteroplacental blood flow about 30-50% compare to the normal pregnancy. The mechanisms involved in induction of endothelial cell dysfunction are poorly understood, but evidence points to the placenta as a key source of the factors that lead to pathophysiology of PE is based on the incapability of the trophoblast to invade properly the myometrium causing a limited remodeling of spiral arteries [3]. In fact, studies have shown that the degree of incomplete trophoblastic invasion of the spiral arteries is directly correlated with the severity of subsequent maternal hypertension. This is because the placental hypoperfusion resulting from the incomplete invasion leads by an unclear pathway to the release of systemic vasoactive compounds that cause an exaggerated inflammatory response, vasoconstriction, endothelial damage, capillary leak, hypercoagulability, and platelet dysfunction.

Abbreviations:

HCG : Human Chorionic Gonadotropin.
IUGR : Intra Uterine Growth Restriction.
S/D : Systolic Diastolic ratio.
PI : Pulsatility Index.
all of which contribute to organ dysfunction and the various clinical features of the disease [3].

Risk factors for pre-eclampsia include medical conditions with the potential to cause microvascular disease (e.g., diabetes mellitus, chronic hypertension, vascular and connective tissue disorders), antiphospholipid antibody syndrome, and nephropathy [4].

Preeclampsia is a disease unique to human pregnancy characterized by hypertension and proteinuria. The clinical manifestations of preeclampsia range from mild hypertension at term to severe hypertensive crisis, seizures (eclampsia), and development of HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). In developing countries, preeclampsia is consistently responsible for 10-15% of maternal mortality. Worldwide, there are approximately 76,000 deaths [5].

Because the clinical manifestations of preeclampsia can be heterogeneous, diagnosing preeclampsia may not be straightforward. Preeclampsia without severe features may be asymptomatic. Many cases are detected through routine prenatal screening.

Patients with preeclampsia with severe features display end-organ effects and may complain of the following:

• Headache.
• Visual disturbances: Blurred, scintillating scotoma.
• Altered mental status.
• Blindness: May be cortical or retinal.
• Dyspnea.
• Edema: Sudden increase in edema or facial edema.
• Epigastric or right upper quadrant abdominal pain.
• Weakness or malaise: May be evidence of hemolytic anemia.
• Clonus: May indicate an increased risk of convulsions.

HCG is a glycoprotein with lipid structure that expressed in trophoblast and various malignant tumors. Physiological concentration of HCG significantly increased in vitro capillary formation and migration of endothelial cells in a dose dependent manner and has a novel function in uterine adaptation to early pregnancy [6]. Because the possible role of hCG in pathophysiology of preeclampsia is not well understood and changes in it’s level can reflect the placental reaction to the preeclampsia, we are promoted to determine correlation of serum concentration of BHCG and preeclampsia placental implantation with abnormal trophoblastic invasion of uterine vessels is a major cause of hypertension associated with preeclampsia syndrome. Several studies have confirmed that elevated second trimester maternal serum free HCG is associated with subsequent development of preeclampsia [7].

Pathophysiology of PE is based on the incapability of the trophoblast to invade properly the myometrium causing a limited remodeling of spiral arteries. The impaired placental perfusion caused by vascular abnormalities precedes clinical manifestations of PE and it can be detected by Doppler Ultrasound (US). The latter has been considered a useful method for prediction of PE and adverse pregnancy outcome [8]. Uterine artery is the most studied vessel in the Doppler evaluation in PE, because it represents the maternal vascular condition, through the pulsatility and resistance index (PI and RI respectively) and the presence of early diastolic Notch (N) [9]. Doppler velocimetry is a useful tool for measuring blood flow, vascular resistance and central haemodynamics. It may be of value in monitoring and planning treatment for patients with preeclampsia. Doppler velocimetry is used to examine relationships among central hemodynamic, uteroplacental circulation and perinatal outcomes in pregnancies complicated by severe preeclampsia [8].

The aim of this study was to investigate the potential value of combining uterine artery Doppler ultrasonography with the measurement of maternal serum, free P-hCG in prediction of pregnancies that will develop pre-eclampsia.

Patients and Methods

The study was conducted at the Clinic of Obstetrics and Gynecology, Benha University during the period between December 2014 and December 2015.

Prospecting cross sectional observational (case control) study performed aiming to determine the correlation between uterine artery diastolic notch,
serum human chorionic gonadotropin assay and severity of pre-eclampsia.

One hundred twenty pregnant women attending the Obstetrics and Gynecology Clinic at Benha University classified to three groups, group one consists of 40 women with normal pregnancy, group two consists of 40 patients with mild pre-eclampsia and group three consists of 40 patients with severe pre-eclampsia for whom both Doppler ultrasound and serum HCG assay were done.

Pregnant women in the period between 20-36 weeks of gestation. All women went through regular follow-up every four weeks until 28 weeks’ gestation then every two weeks until 36 weeks’ gestation.

**Inclusion criteria:** Pregnant women in the period between 20-36 weeks of gestation.

**Exclusion criteria:**
1. Chronic hypertension.
2. Chronic renal disease.
3. Chronic hepatic diseases.
4. Fetal anomalies.
5. Multiple pregnancies

**Follow-up protocol:** During the initial visit, every pregnant woman will be subjected to the following:

Full history taking and complete examination including general and abdominal examination. All candidates will be subjected to the basic study investigations as follows: Rh typing, gestational oral glucose tolerance test, complete blood picture, complete urine analysis, kidney functions including serum uric acid and liver function tests all investigations will be done at the first antenatal visit and repeated when indicated. Ultrasonographic and Doppler examination were done for all pregnant women the routine trans-abdominal U/S was done to assess biometric measurement for gestational age and fetal growth, placental location and grading, fetal wellbeing, amount of liquor amnii and its turbidity and fetal biophysical profile according to the modified Manning scoring system after 28 weeks gestation. Doppler velocimetry of the uterine arteries: The presence or absence of diastolic notch will be noted and identified whether unilateral or bilateral. The criteria used to determine the presence or absence of a notch were those described by (Bower et al., 1993) a notch was considered to be present "no matter how small the notch was seem to be, from either uterine artery [10]. Serum HCG assay: For B-hCG estimation, the random venous 2cc blood samples were centrifuged at 2000g for 10 minutes at 4ºC. Sera were collected and stored at -20ºC until analysis. Serum level of (B-HCG) were measured by chemiluminescence.

**Outcome variables:** Outcome variables were the development of preeclampsia whether mild or severe cases also the development of gestational hypertension.

**Statistical analysis:** The data were tabulated and statistically analyzed and the three groups were compared with student t-test and chi-square. p less than 0.05 is considered significant.

**Results**

The three groups of control normal pregnancy, mild and severe pre-eclampsia were compared and the results show the following:

Table (1) shows non significant difference between the control, mild and severe preeclampsia groups regarding the gestational age, gravidity and parity.

Table (2) shows that there is significant difference between the three groups regarding the mean systolic blood pressure, the mean diastolic blood pressure and HCG level.

Table (3) shows the mean level of Doppler of control was the lower (SD 2.29, RI 0.56), followed by Mild preeclampsia (SD 2.66, RI 0.62). Then severe preeclampsia (SD 3.32, RI 0.71) and the difference were statistically significant (p<0.001). Post hoc analysis revealed that Doppler of mild preeclampsia, control were significantly differ from severe preeclampsia and severe preeclampsia.

Table (4) shows correlation coefficient between HCG and variables:

For control: HCG was significantly correlated with DBP only (r=0.44 & p=0.04).

Mild preeclampsia: There is significant correlation between HCG and any of variables.

Severe preeclampsia: HCG was significantly correlated with proteinuria, SBP, DBP.
Table (1): Demographic characteristics of the studied groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=40)</th>
<th>Mild preeclampsia (n=40)</th>
<th>Severe preeclampsia (n=40)</th>
<th>Test of significance</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/years</td>
<td>24.85±6.22</td>
<td>23.4±5.19</td>
<td>23.95±5.22</td>
<td>F=0.36</td>
<td>0.77 (N.S.)</td>
</tr>
<tr>
<td>Gestational age mean ± standard deviation</td>
<td>38.65±1.18</td>
<td>38.55±0.99</td>
<td>37.95±1.63</td>
<td>F=1.81</td>
<td>0.15 (N.S.)</td>
</tr>
<tr>
<td>Gravity no. %:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>21±5.5</td>
<td>26±8.0</td>
<td>15±75.0</td>
<td>(χ²) 3.43</td>
<td>0.32</td>
</tr>
<tr>
<td>3-4</td>
<td>16±30.0</td>
<td>12±10.0</td>
<td>3±15.0</td>
<td>(χ²) 3.13</td>
<td>0.37</td>
</tr>
<tr>
<td>&gt;4</td>
<td>3±15.0</td>
<td>2±10.0</td>
<td>2±10.0</td>
<td>(χ²) 0.38</td>
<td>0.94 (N.S.)</td>
</tr>
<tr>
<td>Parity no. %:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primipara</td>
<td>18±40.0</td>
<td>24±70.0</td>
<td>12±60.0</td>
<td>(χ²) 3.81</td>
<td>0.28</td>
</tr>
<tr>
<td>1-3</td>
<td>19±45.0</td>
<td>14±20.0</td>
<td>6±30.0</td>
<td>(χ²) 2.96</td>
<td>0.39</td>
</tr>
<tr>
<td>&gt;3</td>
<td>3±15.0</td>
<td>2±10.0</td>
<td>2±10.0</td>
<td>(χ²) 0.38</td>
<td>0.94 (N.S.)</td>
</tr>
</tbody>
</table>

Table (2): Mean of systolic, diastolic blood pressure, serum human chorionic gonadotropin, among control and study patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study groups</th>
<th>Control</th>
<th>Mild preeclampsia</th>
<th>Severe preeclampsia</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP: Mean ± SD</td>
<td></td>
<td>113.0±5.7@</td>
<td>145.2±4.9@</td>
<td>173.5±12.5#</td>
<td>198.1</td>
<td>0.000</td>
</tr>
<tr>
<td>DBP: Mean ± SD</td>
<td></td>
<td>72.0±7.67@</td>
<td>92.9±4.07@</td>
<td>114.5±6.86#</td>
<td>115.9</td>
<td>0.000</td>
</tr>
<tr>
<td>Human chorionic gonadotropin (miu/ml): Mean ± SD</td>
<td></td>
<td>18343.83±1765.17@</td>
<td>22989.88±2421.48@</td>
<td>54511.39±3213.87@</td>
<td>878.7</td>
<td>0.000</td>
</tr>
</tbody>
</table>

@: This group significantly differ from other groups. Anova Test.
# : This group significantly differ from other groups except with this symbol.

Table (3): Doppler indices in control and study groups.

<table>
<thead>
<tr>
<th>Doppler indices</th>
<th>Study groups</th>
<th>Control</th>
<th>Mild preeclampsia</th>
<th>Severe preeclampsia</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD: Mean ± SD</td>
<td></td>
<td>2.29±0.29@</td>
<td>2.66±0.18@</td>
<td>3.32±0.11 @</td>
<td>184.1</td>
<td>0.000 (H.S.)</td>
</tr>
<tr>
<td>RI: Mean ± SD</td>
<td></td>
<td>0.56±0.06@</td>
<td>0.62±0.03</td>
<td>0.71±0.01</td>
<td>157.2</td>
<td>0.000 (H.S.)</td>
</tr>
</tbody>
</table>

Table (4): Correlation coefficient between HCG and laboratory results, blood pressure and Doppler indices.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>Mild preeclampsia</th>
<th>Severe preeclampsia</th>
<th>r</th>
<th>p</th>
<th>r</th>
<th>p</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.09</td>
<td>0.71</td>
<td>0.003</td>
<td>0.98</td>
<td>-0.27</td>
<td>0.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational Age (GA)</td>
<td>-0.18</td>
<td>0.43</td>
<td>0.25</td>
<td>0.27</td>
<td>0.35</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gravity</td>
<td>-0.03</td>
<td>0.87</td>
<td>0.07</td>
<td>0.76</td>
<td>-0.09</td>
<td>0.69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>-0.03</td>
<td>0.87</td>
<td>0.03</td>
<td>0.89</td>
<td>-0.09</td>
<td>0.69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>-0.02</td>
<td>0.91</td>
<td>0.26</td>
<td>0.25</td>
<td>0.70**</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>0.44*</td>
<td>0.04</td>
<td>-0.11</td>
<td>0.64</td>
<td>0.62*</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>0.44*</td>
<td>0.04</td>
<td>-0.11</td>
<td>0.64</td>
<td>0.62*</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doppler SD</td>
<td>0.18</td>
<td>0.43</td>
<td>-0.09</td>
<td>0.68</td>
<td>-0.25</td>
<td>0.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doppler RI</td>
<td>0.09</td>
<td>0.67</td>
<td>-0.24</td>
<td>0.30</td>
<td>-0.28</td>
<td>0.22</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: p<0.05 (significant). **: p<0.001 (Highly Significant).
Discussion

Since pre-eclampsia is a major contributor to maternal mortality and morbidity, reliable screening tests to predict women at risk of developing pre-eclampsia and to identify preventable causes of pre-eclampsia have been investigated of pre-eclampsia due to the complex and heterogeneous nature of the disease [1].

Current data suggest that there is an association between elevated maternal serum free $\beta$-hCG in the second trimester, uterine artery diastolic notch and subsequent development of adverse obstetrical outcomes, including pre-eclampsia [11].

The findings of this study, that Doppler proved to be more efficient at predicting a complicated pregnancy in those patients who were at high risk: A positive medical history alone was associated three-fold greater risk of developing preeclampsia and or IUGR. In the high risk group a single pathological Doppler sign accounted for an additional three to four fold increased risk, and the combination off all three pathological signs, a seven fold additional risk for latter disease [12]. And so, studies of uterine artery early diastolic notch have demonstrated its usefulness as a marker for fetal well-being. The early diastolic notch represents the reflected blood flow of uteroplacental circulation [8]. Also, Zimmermann et al., [12] stated that persistent bilateral notching in the main uterine artery at 21-24 weeks of gestation was one of the criteria defining abnormal Doppler finding in their study.

Data from the study indicated that maternal serum HCG level concentration in preeclamptic patients are higher than controls and this difference was more obvious in mild and severe disease. In the study there was not statistically significant difference between BhCG level in mild preeclampsia and controls qnd showed that BhCG level in severe preeclampsia differed from normal pregnancy and this difference is statistically significant ($p$ is less than 0.001) while in mild preeclampsia, although, HCG values were higher than controls, but this difference was not statistically significant ($p$=0.18). The study showed that HCG level is significantly higher in preeclamptic patients [13].

Two previous studies have also reported that the detection rate of pre-eclampsia was higher by combining uterine artery Doppler sonography and maternal serum biochemistry than with either method alone. Thus, in a study that included 35 patients who subsequently developed pre-eclampsia, reported that for a false positive rate of about 7% the detection rate with uterine artery Doppler at 18-22 weeks' gestation was 60% and this increased to 71% by combining Doppler scan with maternal serum HC [14].

References

Correlation between Uterine Artery Diastolic Notch, Serum HCG

13. LIM K.H., FRIEDMAN, S.A., ECKERT, JANUARY. LET.

14. AQUILINA J., BARNETT A., THOMPSON OCTOBER