The Relationship between Preeclampsia and Quadruple Screening Test in Nuliparous

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**ABSTRACT**

**Introduction:** Early diagnosis and prediction of preeclampsia needs appropriate obstetric care. Preeclampsia predicting methods are important. This study was designed to determine the correlation between preeclampsia and quadruple screening test in the nuliparous.

**Materials and Methods:** This case - control study was conducted on 54 pregnant women with preeclampsia (case group) and 108 healthy pregnant women (control group) who referred to health centers in Sanandaj, Iran. Ultrasoundography was performed to determine the gestational age by a radiologist. Maternal serum levels of Alpha-fetoprotein (AFP), human Chorionic Gonadotropin (hCG), unconjugated estriol (uE3), and inhibin-A were measured in the second trimester of pregnancy. Data were analyzed using SPSS statistical software and Chi-square test, T-test, sensitivity, specificity, positive and negative predictive values.

**Results:** The results showed that the sensitivity and specificity for the diagnosis of preeclampsia in pregnant women for hCG were 35.2% and 79.6 respectively. These findings for estriol were 20.4% and 88.9%, for inhibin-A were 38.8% and 88% and for alpha-fetoprotein were 38.8% and 74.1%. The positive predictive value for hCG, estriol, inhibin-A and alpha-fetoprotein were 46.3%, 47.8%, 61.8% and 42.9% respectively. The negative predictive value for hCG, estriol, inhibin-A and alpha-fetoprotein were also 71%, 69.1%, 74.2% and 70.8% respectively.

**Conclusion:** There was a relationship between preeclampsia and high levels of inhibin-A and hCG. Further studies on these markers and evaluating their usefulness in the diagnosis and management of preeclampsia are recommended.

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**Introduction**

Hypertensive disorders occur in 5 to 10 percent of pregnancies that along with bleeding and infections constitute a deadly triad. Among hypertensive disorders, preeclampsia syndrome either alone or as added on chronic hypertension is the most dangerous mode. Hypertensive disorders are responsible for 16 percent of maternal deaths in developed countries (1).

Preeclampsia is a pregnancy-specific syndrome which can affect almost all organs of the body. This syndrome was described in two stages. The first stage is created due to improper penetration of placenta into the vessels. This process leads to the second stage which includes hypertension, proteinuria and damage to the end organs such as liver, kidneys, and brain (2).

Pathophysiology of preeclampsia is not precisely known, but one of the main factors is vasospasm which can lead to vascular damage, localized hypoxia, bleeding, necrosis and end-organ dysfunction (1).

In preeclampsia the synthesis of nitric oxide and prostacyclin 12 reduce significantly and Thromboxane A2 rises. These changes happen from week 22 of pregnancy in women who later suffer from preeclampsia (3).

Endothelial cell dysfunction is probably the main cause of preeclampsia. In pregnancies complicated by preeclampsia, 30 to 50 percent of uterine blood flow is reduced which leads to compensatory increases in the number of placental capillaries in order to increase blood flow to the uterus. The increase in placental villi...
can be placenta early maturation factor (4). Risk factors for preeclampsia include nulliparity, family history, age over 40 years, chronic hypertension, chronic kidney diseases, Diabetes and multiple pregnancies (2). Early diagnosis and prediction of preeclampsia require appropriate obstetric care. Preeclampsia predicting methods are important (4). In recent years more than 100 biochemical and clinical tests to predict preeclampsia have been developed, but so far the method with high sensitivity and specificity has not been determined (5).

Various types of biological, biochemical and biophysical markers have been introduced in order to predict the occurrence of preeclampsia. Researchers have tried to identify markers of dysfunction in placenta, reduction in placental perfusion and coagulation (6). Quadruple tests are the second trimester screening tests which predict congenital defects. Approximately 75 to 80 percent of the problems related to the crebrospinal development as well as genetic disorders would be determined by blood test. High levels of Alpha-fetoprotein (AFP) indicate cerebrospinal problems or twin fetus and its low levels than normal show the risk of having a baby with Down syndrome. The higher levels of hCG and Inhibin-A, which are hormones produced by the placenta also show the risk of this syndrome and lower than normal levels of estriol also determines risk of this genetic defect (7). Some studies have indicated the HCG serum levels measurement as a tool for diagnosis and clinical management of preeclampsia (8), but some studies have rejected (9, 10).

Since the gestational hypertension and preeclampsia in pregnant women are relatively common complications which leads to maternal and perinatal mortality and morbidity (11) this study was designed to determine the correlation between preeclampsia and quadruple screening test in the nulliparous.

Materials and Methods

This case - control study was conducted on 54 pregnant women with preeclampsia (case group) and 108 healthy pregnant women (control group) who referred to health centers in Sanandaj, Iran in 2015. The two groups were matched for age, gestational age and body mass index. Inclusion criteria included primigravidity and living in Sanandaj.

Exclusion criteria included; multiple pregnancies, history of chronic hypertension, diabetes, polycystic ovary syndrome, thyroid dysfunction, fetus genetic diseases and consuming medications (steroids, thyroid, gonadotropin and ACTH). Ultrasonography was performed to determine the gestational age by a radiologist.

Maternal serum levels of Alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), unconjugated estriol (uE3), and inhibin-A were measured in the second trimester of pregnancy.

For all study participants a questionnaire was completed that included demographic information and lab test results. Data were analyzed using SPSS statistical software and Chi-square test, T-test, sensitivity, specificity, positive and negative predictive values.

Results

The mean ages of pregnant women in case and control groups were 29.53±4.37 and 29.42±5.10 years respectively. Gestational age in case and control groups were 33.05±2.08 and 33.05±2.07 which was the same.

Body mass index was similar in both case and control groups and there was no significant difference statistically (p=.05).

The results showed that the sensitivity and specificity for the diagnosis of preeclampsia in pregnant women for hCG were 35.2% and 79.6 respectively. These findings for estriol were 20.4% and 88.9%, for inhibin-A were 38.8% and 88% and for alpha-fetoprotein were 38.8% and 74.1%. (Table 1)

The positive predictive value for hCG, estriol, inhibin-A and alpha-fetoprotein were 46.3%, 47.8%, 61.8% and 42.9% respectively. The negative predictive value for hCG, estriol, inhibin-A and alpha-fetoprotein were also 71%, 69.1%, 74.2% and 70.8% respectively.

Table: Comparison of the results of Lab tests in case and control groups

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Groups</th>
<th>Case No (%)</th>
<th>Control No (%)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive values</th>
<th>Negative predictive values</th>
<th>OR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCG</td>
<td>Abnormal</td>
<td>19(46.3)</td>
<td>22(53.7)</td>
<td>35.2</td>
<td>79.6</td>
<td>46.3</td>
<td>71</td>
<td>2.1(1.02-4.4)</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>35(28.9)</td>
<td>86(71.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estriol</td>
<td>Abnormal</td>
<td>11(47.8)</td>
<td>12(52.2)</td>
<td>20.4</td>
<td>88.9</td>
<td>47.8</td>
<td>69.1</td>
<td>2.05(84-5)</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>43(30.9)</td>
<td>96(69.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibin A</td>
<td>Abnormal</td>
<td>21(68.1)</td>
<td>13(38.2)</td>
<td>38.8</td>
<td>88</td>
<td>61.8</td>
<td>74.2</td>
<td>4.65(2.96-10.3)</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>33(25.8)</td>
<td>95(74.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha fetoprotein</td>
<td>Abnormal</td>
<td>21(42.9)</td>
<td>28(87.1)</td>
<td>38.8</td>
<td>74.1</td>
<td>42.9</td>
<td>70.8</td>
<td>1.83(91-3.65)</td>
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<tr>
<td></td>
<td>Normal</td>
<td>33(29.2)</td>
<td>80(70.8)</td>
<td></td>
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</tr>
</tbody>
</table>
Discussion & Conclusion

The findings of this study showed that quadruple tests for the diagnosis of preeclampsia in pregnant women in the second trimester had low sensitivity.

Although Inhibin A and Alpha-fetoprotein (AFP) compared to the estriol, and HCG had better situation.

Specificity of all 4 tests to reject preeclampsia in pregnant women was also relatively in better situation.

Inhibin A test had positive and negative predictive values of higher value than other three tests.

In a study by Florio, Inhibin A achieved a sensitivity of 39% and a specificity of 92% as a marker for prediction of preeclampsia (12). Muttukrishna reported Inhibin-A 67% sensitivity for preeclampsia in 19-15 weeks and 89% in 21-25 weeks of gestation (13). Walt reported in the pregnancies that went on to develop preeclampsia, early second trimester inhibin-A and hCG values were significantly raised and uE(3) values were significantly lowered, while AFP values were not significantly altered. They concluded that preeclampsia screening performance using the Quadruple test markers was materially better than that using the Triple test markers (14). In Yazdani study a correlation between preeclampsia and higher levels of Inhibin A was found, but no association between preeclampsia and Alpha-fetoprotein (AFP) was observed (15). There was no relationship between preeclampsia and Alpha-fetoprotein (AFP) in Wald study (16). Kang reported statistically significant relationship between preeclampsia with Inhibin A, but the relationship between preeclampsia with Alpha-fetoprotein (AFP) and estriol was not reported (17). In a study in second-trimester inhibin A and hCG levels were significantly but modestly elevated in women who later developed preeclampsia. A combination test of maternal age plus inhibin A and hCG predicted 23% of cases of preeclampsia with 95% specificity (18). In a review study inhibin A was introduced as the best predictor for preeclampsia (19). Although there are differences in the determined sensitivity and specificity for Inhibin A, the findings of this study are largely consistent with our findings.

In present study, the sensitivity and specificity of HCG was close to Inhibin A. Yaron reported as with increased second-trimester maternal serum alpha-fetoprotein levels, increased serum beta-human chorionic gonadotropin and low unconjugated estriol levels were significantly associated with adverse pregnancy-induced hypertension (20). Wald showed a reversed correlation between the increase of hCG and decrease of estriol (16), but there was no correlation in Yazdani’s study (15). Gagnon in a review study showed that elevation of hCG In the second trimester is associated with Gestational hypertension and proteinuria (21). Ong demonstrated that reducing maternal serum protein levels and increased levels of beta hCG at 10-14 weeks of pregnancy is associated with increased complications of pregnancy (22). Lee also showed that women with mild pre-eclampsia had a 2.61-times greater chance, while women with severe pre-eclampsia had a 6.13-times greater chance of having MShCG exceeding 2.0 multiples of the median than did women with a normal pregnancy (23). In a study by Hui Alpha-fetoprotein (AFP) and HCG level was increased in preeclampsia (11). In other studies high levels of Alpha-fetoprotein (AFP) was associated with preeclampsia (24, 25). These studies also confirmed findings of our study, because in our study the frequency of abnormal estriol were less than Alpha-fetoprotein (AFP) and hCG.

Wald et al showed that adding PIGF to the Quadruple test improves preeclampsia screening performance in the second trimester of pregnancy (26). Michael and Dugoff introduced combined markers and its relationship with disorders during pregnancy.

Simultaneous increase of these markers may increase the risk of pregnancy adverse outcomes. Because of low sensitivity and low positive predictive value of screening tests, detection of adverse pregnancy outcomes is not possible definitely (24-27).

There was a relationship between preeclampsia and high level of inhibin-A and hCG. Further studies on these markers and evaluating their usefulness in the diagnosis and management of preeclampsia are recommended. Currently there is no serum marker for preeclampsia as a screening test before 24 weeks of gestation. Large cohort studies with standard screening test parameters are required.

References


