CA-125, plasma fibrinogen and C-reactive protein in correlation with severity of preeclampsia.

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Abstract:

Background: Preeclampsia is most common medical disorders during pregnancy, and the rate of hypertension ranges from 5 – 8 % for all types of pregnancy. There was a significant difference between cancer antigen -125, plasma fibrinogen and C-reactive protein to the severity of preeclampsia.

Objective: To determine the level of serum CA-125 level, C-reactive protein and plasma fibrinogen in preeclampsia and their association with the severity of disease and progression of mild preeclampsia to severe type.

Patients and method: A prospective case-control study which was carried out in the department of gynecology and obstetric at Baghdad teaching hospital from 1st of January 2015 to 1st of July 2015. One hundred forty pregnant women were included; they were selected and divided into three groups:

Group A: Thirty five (35) pregnant women with mild preeclampsia.
Group B: Thirty five (35) pregnant women with severe preeclampsia.
Both group A and B are selected according to the clinical signs, symptoms and investigations and admitted to obstetrics ward for evaluation.

Group C: Seventy (70) pregnant women with uncomplicated singleton pregnancies as control group. Blood samples were taken for measurement of serum cancer antigen -125, C-reactive protein and plasma fibrinogen for all groups.

Results: The mean level of Cancer antigen -125 in control, mild and severe preeclampsia groups was (14.4±4.11), (33.60± 4.52) and (37.35± 4.85) respectively which was a significant difference between control, mild groups (p value < 0.0001) and between control and severe preeclampsia groups (p value < 0.0001), the mean level of C-reactive protein in mild and severe preeclampsia was(15.62± 2.6) and (29.3± 7.02) which was significant higher in comparison to control group which was (8.17 ± 1.56) The P value was < 0.0001. The plasma fibrinogen levels in mild and severe preeclampsia was (470.37±51.1) and (563.14±48.28) which were markedly higher than that of control group (342.97±56.6) in third trimester pregnant women.

Conclusion: Serum Cancer antigen -125, Serum C-reactive protein and Serum plasma fibrinogen were significantly higher in preeclampsia groups in comparison to the control group and these increments was directly correlated with the severity of preeclampsia.

Key Words: preeclampsia, plasma fibrinogen, CA 125, C – reactive protein.

Introduction:

Preeclampsia (PE) is a multi-system disorder of human pregnancy, potentially dangerous for both mother and fetus. (1) It’s characterized by hypertension blood pressure ≥140/90 mm Hg on at least two consecutive occasions 4 hours apart or 160/110 on one occasion associated with proteinuria (300 mg protein per day) occurring after the 20th week of pregnancy in women who have had no previous symptoms. (1,2) PE is characterized by abnormal vascular response to placenta that is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system and endothelial cell dysfunction. (3) Pre-eclampsia complicates approximately 5 – 8 % of pregnancies but the incidence varies depending on the exact definition used & population studied. (4) The incidence of preeclampsia in nulliparous population ranges from 3 to 10 percent. The incidence in multiparous is also variable but is less than that for nulliparous. (5) Cancer antigen - 125 (CA-125) is a high molecular weight glycoprotein complex antigen expressed by epithelial ovarian tumor. (6) Elevated levels in maternal serum originate from decidual cells affected by chorionic invasion or placental separation. The extension of decidual destruction and separation of trophoblasts from decidua are proposed as the underlying mechanism for elevation in serum (CA-125) in preeclampsia.
C-reactive protein is produced by hepatocytes. It is a part of the acute phase immune response. In pregnancy, systemic maternal inflammatory response to pregnancy is responsible for the endothelial dysfunction which gives the clinical and pathological picture of preeclampsia. The association between first trimester C-reactive protein levels and subsequent preeclampsia supports the hypothesis that systemic inflammation is involved in the pathogenesis of preeclampsia.

Fibrinogen is a 340 kDa plasma glycoprotein that plays a key role in coagulation. During pregnancy there is hypofibrinolytic, hypercoagulable state, both plasminogen and fibrinogen levels in plasma increase by 50 to 60 % in third trimester. Fibrinogen levels are actually elevated in preeclamptic women as compared with normotensive patients, low fibrinogen level in preeclampsia or eclampsia are usually associated with abortion or fetal demise (due to consumption).

Patient and method:
A prospective case – control study conducted at Baghdad Teaching Hospital from the 1st of January 2015 to 1st of July 2015 in which One hundred forty women were included in this study and divided into three groups:

**Group A:** Thirty five (35) pregnant women with mild preeclampsia.

**Group B:** Thirty five (35) pregnant women with severe preeclampsia.

Both group A and B were selected according to the clinical signs, symptoms and investigations and admitted to obstetrics ward for evaluation.

**Group C:** Seventy (70) pregnant women were included with uncomplicated singleton pregnancies as control group.

**Inclusion criteria:** Singleton viable pregnancy, Gestational age 28 – 40 weeks.

**Exclusion criteria:** Multiple pregnancies, Cigarette smoking, Medical diseases (DM, HT, Renal disease, Cardiovascular disease, SLE, RA), Any ovarian disease (benign or malignant ovarian tumors), premature rupture of membrane or Clinical chorioamnionitis. The demographic characteristics of each patient were assessed including maternal age and parity. Gestational age calculated from the first day of last menstrual cycle or early ultrasonography, past medical history, and past obstetrical history.

Complete examination (general and obstetrical) was done for all participants, blood pressure was measured by mercury sphygmomanometer in left lateral position, In mild preeclampsia blood pressure equal to or more than 140/90 in two consecutive readings four hours apart, In severe preeclampsia, blood pressure 160/110. MAP (mean arterial pressure) was calculated using the following formula: MAP = (systolic blood pressure + 2 × diastolic blood pressure) / 3. Normal value (65–110 mmHg). Investigations were done for all patients in form of: complete blood count, renal function, liver function, urinalysis, coagulation screen. CA 125 was measured by Enzyme - linked immuno sorbent assay (ELIZA) method using bio check CA 125 enzyme immunoassay kit, CRP level measurement was done by direct latex test, qualitative method used to determine positive or negative CRP brings reagent and serum samples to room temperature. Plasma fibrinogen was measured by using clotting system (crochet Hook method).

**Statistical analysis:** Analysis of the data was carried out using variable SPSS-17 (statistical package for the social sciences version 17) + Microsoft excels 2013. Data were presented as mean ± standard deviation.

A comparison of means was done using unpaired standard t – test. P value < 0.05 was considered significant. Pearson correlation was done to find correlation coefficient value (r) either positive (direct correlation) or negative (in verse correlation) with value < 0.3 represent no correlation. 0.3 - <0.5 represent weak correlation. 0.5 - <0.7 represent moderate correlation. > 0.7 strong correlation.

**Results**
Patients and controls were matching for the maternal age and gestational age (weeks), There were no significant differences between them. There were significant differences between the control group and mild PE group regarding the mean arterial pressure (mmHg) as shown table 1.

**Table (1) : Demographic characteristic of women in control, mild PE and severe PE.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n=70) Mean ± SD</th>
<th>Mild PE (n=35) Mean ± SD</th>
<th>Severe PE (n=35) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk)</td>
<td>33.80±3.82 (29-38)</td>
<td>33.49±3.64 (28-39)</td>
<td>33.74±3.87 (30-39)</td>
</tr>
<tr>
<td>Parity</td>
<td>3.0±2.01 (1-5)</td>
<td>2.63±1.9 (0-6)</td>
<td>2.49±1.82 (0-5)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>77.13±10.39 (65-93)</td>
<td>114.40±5.36 (106-120) α</td>
<td>144.06±11.63 (125-164) β</td>
</tr>
</tbody>
</table>

α: significant difference with control ( p value < 0.0001)
β: significant difference with mild PE (p value <0.0001)

The mean level of CA 125 (IU/ml) in the control and mild PE group was (14.4±4.11) and (33.60±4.52) respectively which was significantly higher in mild PE, the p value < 0.0001.
The plasma fibrinogen (mg/dl) in the control group was (342.97±56.6) while in women with mild PE (470.37±51.1), the women with mild PE had higher values than the control group; There was significant difference between the two group as p value < 0.0001. The CRP (mg/l) in the control group and mild PE group was (8.17±1.56) and (15.62±2.6) which was significantly higher in mild PE as p value 0.0001. (Table 2).

Table (2): Comparison of CA125, plasma fibrinogen and C-reactive protein between control group and mild PE group by unpaired t-test.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n=70)</th>
<th>Mild PET (n=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA125 (IU/ml)</td>
<td>14.4±4.11</td>
<td>33.60±4.52</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Plasma fibrinogen (mg/dl)</td>
<td>342.97±56.6</td>
<td>470.37±51.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>8.17±1.56</td>
<td>15.62±2.6</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

The CA 125 was significantly higher in the women with severe PE compared to control group as p value < 0.0001. The plasma fibrinogen (mg/dl) in the control group was (342.97±56.6) while in the women with severe PE was (563.14±48.28), the plasma fibrinogen was significantly higher in women with severe PE compared to control as p value was 0.0001. The CRP (mg/l) in the control group was (8.17±1.56), while in the women with severe PE was (29.3±7.02), The CRP was significantly higher in women with severe PE compared to control group as p value < 0.0001. (Table 3)

Table (3): Comparison of CA125, plasma fibrinogen and C-reactive protein between control group and severe PE group by unpaired t-test.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n=70) Mean±SD</th>
<th>Severe PET (n=35) Mean±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA125 (IU/ml)</td>
<td>14.4±4.11</td>
<td>37.35±4.85</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Plasma fibrinogen (mg/dl)</td>
<td>342.97±56.6</td>
<td>563.14±48.28</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>8.17±1.56</td>
<td>29.3±7.02</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

The sensitivity of CA125 was (96.7%), the specificity was (98.7%), and the Accuracy was (97.7%); while the sensitivity of plasma fibrinogen was (87.14%), the specificity was (97.14%), and the accuracy was (92.14%). While in C – reactive protein the sensitivity was (97.18%), the specificity was (98.57%), and the accuracy was (97.87%). As shown in Table (5).

Table (5): Sensitivity, specificity and accuracy rate of CA125, plasma fibrinogen and C – reactive protein in control and all PE.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 125</td>
<td>96.7%</td>
<td>98.7%</td>
<td>97.7%</td>
</tr>
<tr>
<td>Plasma fibrinogen</td>
<td>87.14%</td>
<td>97.14%</td>
<td>92.14%</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>97.18%</td>
<td>98.57%</td>
<td>97.87%</td>
</tr>
</tbody>
</table>

Discussion:
Preeclampsia is a hypertensive disorder of pregnancy which may cause morbidity and even mortality for both mother and fetus. Its exact pathogenesis remains uncertain. A generalized systemic inflammatory process has recently been implicated in its pathogenesis. A systemic inflammatory response involves the immune system, clotting system and fibrinolytic systems. In the current study preeclampsia is associated with increase CRP level, and CRP was positively correlated with the severity of the disease, and there is statistically significant differences between control and mild preeclamptic group (p value < 0.0001) and between mild and severe preeclamptic group (p value < 0.0001). This is concordant with that revealed by Yustun et al, 2005 study (in Turkey), when they measuring the level of plasma fibrinogen and CRP in 58 women with PE compared with 54 normotensive women found that the level of CRP was significantly higher in women with mild and severe...
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PE than normotensive women. (16) Also its concordant to that revealed by Cebesoy et al, 2009 study (in France), who found that the CRP level was statistically significant higher in the study group compared to control group.(17) But it is not concordant with Milanstefanoviet al, study, who found no differences between preeclampsia and normotensive women with regard to CRP concentration. This may be attributed to the small samples size in this study.(18) Regarding the plasma fibrinogen, the current study show that there is statistically significant differences between mild, severe preeclampsia and control normotensive group as ( p value < 0.0001) , Which is similar to that found in a cross – sectional study done by Pepple etal, 2001 (in India), when they found a significant increase in plasma fibrinogen level in preeclamptic women than in normal women. (19) while it is inconsistent with Schijetlinneet al,(20) study (in Spine), show plasma levels of fibrinogen was decrease in the presence of preeclampsia. Regarding CA125, the current study shows that serum CA125 level was significantly higher in preeclampsia than control group( p value < 0.0001).

References:

Conclusion:
The concentration of serum Cancer antigen -125, SerumC -reactive protein and Serum plasma fibrinogen is increase in preeclampsia and these increments was directly correlated with the severity of preeclampsia.

Authors’ Contributions:
Wasasawajdi : supervision
Raya : writing statistics and discussion
Nada : Data collection , statistics and discussion.

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