

## Correlation of maternal C-reactive protein and s.fibrinogen with the severity of pre-eclampsia

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**مقدمة:** ما قبل تسمم الحمل هو مرض يصيب المرأة الحامل ويحدث بعد الأسبوع العشرين من الحمل ويكون غالباً في السيدات الأقل من العشرين عاماً أو الأكثر من الثلاثين عاماً من العمر.

**الهدف من الدراسة:** لتحديد مستوى الفايبرينوجين و سي رياكتف بروتين في مصل الدم في تسمم ما قبل الحمل وعلاقتها مع تطور المرض .

**الطريقة:** أجريت الدراسة في مستشفى الزهراء التعليمي في النجف الأشرف وكانت تشمل ٢٦ امرأة ذو حمل طبيعي و ٢٦ امرأة تعاني من ارتفاع متوسط في ضغط الدم و ٢٦ امرأة أخرى تعاني من ارتفاع شديد في ضغط الدم وكانوا جميعهم في الأشهر الثلاثة الأخيرة من الحمل وتم إجراء التحاليل للمريضات ومن ضمنها سيروم فايبرينوجين و سي رياكتف بروتين .

**النتائج:** لوحظ أن مستوى سيروم فايبرينوجين و سي رياكتف بروتين قد ارتفع بشكل ملحوظ عند النساء التي تعاني من ارتفاع ضغط الدم المتوسط والشديد مقارنة بالنساء ذوات الضغط الطبيعي . وقد أظهرت الدراسة وجود ارتباط قوي بين هذه المستويات في مصل الدم وتقدم المرض.

### **Obstruct:**

**Objective:** The aim of this study was to determine the level of plasma fibrinogen and C-reactive protein in pre-eclampsia and their associations with severity of the disease.

**Study design:** C-reactive protein and plasma fibrinogen levels were investigated in 26 cases of normal pregnant women, 26 cases with mild pre-eclampsia ,26 cases with sever pre-eclampsia in the third trimester of pregnancy. Mean atrial pressure(MAP)was used as indicator of the severity of the disease .Analysis of variance with kruskal- wallis test used when the three groups were compared.

**Result:** C-reactive protein and plasma fibrinogen levels in mild and sever pre-eclampsia patients were markedly higher than that of normal third trimester pregnant women.

**Conclusion:** we found higher levels of plasma fibrinogen and C-reactive protein and presence of a good correlation between C-RP and MAP in pre-eclampsia.

### **Introduction:**

#### **Definition:**

Preeclampsia is a multisystem disorder that complicate about 7-10 % of human pregnancies. It is characterized by development of elevated blood pressure to the extent 140/90 mmhg or more ,with a proteinuria after 20 wk in a previously normotensive and non proteinuric patient.

Despite a progress in medical practice ,preeclampsia remain as a leading cause of maternal mortality throughout the world.(1)

Several aetiologies have been implicated in the development of preeclampsia, some of them include abnormal trophoblaste invasion of uterine blood vessels, and immunological intolerance between fetoplacental &maternal tissues.(2)

Pathophysiology of pre-eclampsia :

The underlying basic pathology is endothelial dysfunction and intensive vasospasm , affecting almost all vessels ,particularly those of the uterus,kidney and brain.

There is a failure of trophoblast invasion into the myometrium and the maternal spiral arteries do not undergo their physiological vasodilatation . Only the most superficial decidual portion of the spiral artery is invaded by trophoblast, this inadequate trophoblast invasion is also seen in pregnancies complicated by fetal growth restriction (without pre-eclampsia) , demonstrating that the maternal syndrome of pre-eclampsia must be related to additional factors.

The diminished dilatation of the spiral arteries, associated with increased resistance in uteroplacental circulation and an impaired intervillous blood flow probably result in an inadequately perfused placenta.

Endothelial dysfunction is accompanied by elevated levels of inflammatory markers indeed , such markers have been shown to be much higher in women with preeclampsia than those seen in normal pregnancy. (3)

As can be expected C-Reactive protein (CRP) is a marker of systemic inflammation.(4)

C-Reactive protein is an objective and sensitive index of overall inflammatory activity in the body. (5), Its level increase during inflammatory response to tissues injuries.(6)

Recently, there has been a growing interest in the role of inflammation as a key factor of endothelial dysfunction.(7)

Also there are a studies evaluating fibrinogen in preeclampsia(8,9).

#### **PATIENT AND METHOD:**

This is a cross-sectional prospective study was conducted at al zaharaa hospital , department of obstetrics & gynecology from mars 2010 to may 2011.

This study was performed in 3 groups of women's all of them were non smokers .

Group A : consisted of 35 women in third trimester of pregnancy with mild pre-eclampsia at time of admission.

Mild pre-eclampsia include a sustained raise of blood pressure of more than 140/90 mmhg but less than 160 systolic or 110 diastolic.

Group B: consisted of 26 women in third trimester of pregnancy with sever pre-eclampsia .

Group C: consist of 50 healthy normotensive women in third trimester of pregnancy.

C-RP is affected by body mass index, so that statistics between groups were preformed in body mass index –match subgroups (n=26 for all groups ) that had been selected from the above population.

#### **1- CONTROL GROUP:**

All controls were singleton primigravid monitored at the department of Obstetrics and Gynecology of our hospital with gestational age 28-40 weeks , no chronic medical disorder and not in labor .

They were normotensive and had normal blood pressures throughout gestations.

#### **2- PRE-ECLAMPSIA:**

-primeravidas

-28-40 weeks gestational age

Pre-eclampsia was diagnosed when a blood pressure higher than 140/90 & protein urea higher than 300mg/24hr. Were observed at least two occasions more than 6 hr apart , in absence of urinary tract infection.

Women with pre-eclampsia was considered to have sever disease if they met one or more of the following criteria :

- ♣ a systolic blood pressure > 160 mmHg
- ♣ Diastolic blood pressure > 110 mmHg
- ♣ Headache ,visual disturbance , epigastric pain or right upper quadrant pain,
- ♣ Oligurea ( < 30 ml/hr )

Protein urea level > 2 gr /24h or 3+ to 4+ on dipsticks collected at least 4hr apart .Only two patient in sever pre-eclampsia group had more than three of these criteria .All other 24 women in sever pre-eclampsia group had a combination of hypertension and protein urea .

The group of sever pre-eclampsia did not include women with HELLP syndrome .Gestational age was calculated by ultrasound.

**EXLUSION CRITERA:**

- ♣ Patient with history of diabetes mellitus ,renal disease ,other cardiovascular illness, infectious disease which will be excluded during routine interviews , clinical & laboratory investigations.
- ♣ Premature rupture of membranes or clinical chorio-amnionitis .
- ♣ Patient taking corticosteroids less than 7 days.
- ♣ Patient in labor.

In the pre-eclmpsic group blood samples were collected when the patient presented for evaluation and before initiation of medical therapy.

In all patient , Erythrocyte sedimentation rate (ESR), C-RP , Plasma level of fibrinogen were determined , for C-RP was performed using a commercial kit .The assay has a detection limit of o.1 mg/l

- ♣ Fibrinogen was measured with use of clotting system.
- ♣ Mean arterial pressure (MAP) was used as an indicator of the severity of the disease.

MAP was calculated using the following formula :

$$\text{MAP} = ( 2 \times \text{diastolic blood pressure} + \text{systolic blood pressure} ) / 3$$

**Statistical Analysis:**

SPSS . ver.18 statistical software for window was used to analyzed data. Analysis of variance with Kruskal – Wallis test was used to compare the three groups of study. When differences were detected, comparison between each two groups was performed using the Mann-Whitney *U*-test. The strength of the association between the parameters was estimated by Sperman's rank correlation coefficient.  $P < 0.05$  ,  $p < 0.01$  were considered to be significant at 5% and 1% respectively.

**RESULTS :**

Table 1 shows the clinical data on the pre-eclamptic women and healthy controls .

- ♣ Gestational age was not significantly different between the groups.
- ♣ Maternal age in sever pre-eclampsia was slightly higher than that of mild and normal women's , but not significant.
- ♣ BMI in mild and sever pre-eclampsia patients was slightly higher than that of normal women but not significant.
- ♣ Systolic and Diastolic blood pressure, MAP, Fibrinogen &C-RP in mild and sever pre-eclampsia patients were markedly higher than that of normal women, also there was a significant difference (table 1).
- ♣ The values of CRP in mild & sever pre-eclampsia was markedly higher than that of normal third trimester pregnant women (table1), Also there was a significant differences between mild and sever pre-clampsia .
- ♣ ESR &S. Fibrinogen levels were significantly higher in mild and sever pre-eclampsia group than in control group. But there was no difference between mild and sever pre-eclampsia in ESR. But there is a significant difference in mild and sever pre-eclamptic group in S.Fibrinogen.
- ♣ When control group was taken into account there was no significant correlation between MAP and C-RP parameters, However a statistically significant correlation was observed between MAP and C-RP concentrations in pregnancy complicated with pre-eclampsia (P=0.000), also we found a significant correlation between MAP and Fibrinogen parameters in pre-eclampsia patient. (P= 0.000)

**Table (1) shows the clinical data on the pre-eclamptic women and healthy control womens.**

Parameters	Mild preeclampsia (n=26)	Sever preeclampsia (n=26)	Control (n=26)	p-Value
Maternal age(years)	24.5(18-33) <sup>NS</sup>	26.5(20-42) <sup>NS</sup>	25(18-33)	0.550
BMI(Kg/m <sup>2</sup> )	28(22-35) <sup>NS</sup>	27.2(23-36.2) <sup>NS</sup>	26.9(21-37)	0.092
Gestational age (w)	34(28-38) <sup>NS</sup>	35(28-39) <sup>NS</sup>	31(28-40)	0.205
S. blood pressure (mmHg)	140(140-160) <sup>a</sup>	167(150-150) <sup>ab</sup>	110(100-120)	0.000
D. blood pressure (mmHg)	95(90-105) <sup>a</sup>	110(100-125) <sup>ab</sup>	70(60-80)	0.000
MAP(mmHg)	110(106-123.3) <sup>a</sup>	133.3(123.3-166.6) <sup>ab</sup>	83.6(60-97)	0.000

Data of cases are presented as median(minimum – maximum), 95% confidence intervals.

<sup>a</sup><0.01 compared with control group.

<sup>ab</sup><0.01 compared with mild group.

<sup>c</sup><0.05 compared with control group

<sup>NS</sup>= no significant differences in comparison between groups.

**Table(2)**

<b>Fibrinogen (mg/dl)</b>	<b>500(380-650)<sup>a</sup></b>	<b>450(250-600)<sup>ab</sup></b>	<b>355(280-500)</b>	<b>0.000</b>
<b>CRP (mg/L)</b>	<b>51(10-120)<sup>a</sup></b>	<b>80(40-210)<sup>ab</sup></b>	<b>16(9-35)</b>	<b>0.000</b>
<b>ESR (mm/h)</b>	<b>33(10-70)<sup>a</sup></b>	<b>30(10-55)<sup>a</sup></b>	<b>18(9-32)</b>	<b>0.000</b>

- ♣ Gestational age was not significantly different between three groups.
- ♣ Maternal age in sever pre-eclampsia was slightly higher than that of mild and normal women's , but not significant.
- ♣ BMI in mild and sever pre-eclampsia patients was slightly higher than that of normal women but not significant .
- ♣ Systolic and Diastolic blood pressure ,MAP in mild and sever pre-eclampsia patients were markedly higher than that of normal women , which was a significant difference (table 1&2).
- ♣ The values of CRP in mild & sever pre-eclampsia was markedly higher than that of normal third trimester pregnant women (table 2), Also there was a significant differences between mild and sever pre- eclampsia.
- ♣ about the level of C-RP and fibrinogen as it was higher in sever as compared to mild pre-eclampsia. (tabe.2)
- ♣ ESR,C-RP&S. Fibrinogen levels were significantly higher in mild and sever pre-eclampsia group than in control group. But there was no difference between mild and sever pre-eclampsia in ESR levle. But there were a significant differences in mild and sever pre-eclampsic group in S.Fibrinogen and C-RP levels.
- ♣ So there was a correlation observed between MAP and C-RP concentrations in pregnancy complicated with pre-eclampsia (P=0.000), also we found a significant correlation between MAP and Fibrinogen parameters in pre-eclampsia patient. (P= 0.000).

**DISCUSSION :**

Pre-eclampsia is a disease of pregnancy associated with endothelial cell damage or activation and hypercoagulation (11-12).

It is suggested that the cause of pre-eclampsia is the release of placental factors that damage maternal vascular endothelium.

However, because most studies have been conducted during pregnancy, it has not been possible to separate maternal from placental mechanisms underlying endothelial dysfunctions in pre-eclampsia .(13)

There is increasing evidence that pre-eclampsia is asystemic inflammatory disease.(14). Recently there has been a growing interest in the role of inflammation as key factor of endothelial dysfunction.

C-RP a sensitive marker of tissue damage and inflammation was proposed to play a role in eliciting the inflammatory response characteristic of pre-eclampsia.

C-RP is an acute phase reactant produced by liver in response to the proinflammatory cytokines , because it has a relatively short half-life , the serum C-RP levels dependent almost entirely on the rate of hepatic synthesis therefore , it is a sensitive index of systemic inflammation.(10) The relationship between the levels of C-RP and pre-eclampsia has already been studied higher concentration of C-RP has reported during

pregnancy.(7,9 ).

The relationship between the levels of C-RP has been reported during pre-eclampsia (5,12) Belo et al found significantly higher levels of C-RP in pre-eclampsia but statistical significance was lost after adjustment of maternal weight.

Maternal C-RP levels have been shown to be elevated in a healthy pregnant women compared with levels in those who were not pregnant , Teran et al(7).found higher values of C-RP in pre-eclampsia. compared with normal pregnant women and non pregnant controls.

Belo et al found a significant higher levels of C-RP in pre-eclampsia but statistical significance was lost after adjustment for a maternal weight (8). In this study the level of C-RP were found to be significantly higher in women with mild and sever pre-eclampsia than in normotensive woman.

Deveci et al .(15). Found that the mean serum C-RP levels were increased significantly in the pre-eclamptic group compared with control group , also found a statistical significant correlation between MAP & C-RP concentrations in pregnancies complicated with pre-eclampsia.(15).

Mirazic et al. (6) found a significant correlation between serum C-RP levels and systolic blood pressure and diastolic blood pressure and urinary protein excretion in pre-eclampsia.(6).

Kumru et al, (16) showed a positive correction between serum C-RP levels and diastolic blood pressure and urinary excretions.

Ustum et al (17) found that C-RP levels were positively related to the degree of blood pressure elevation .

In our study levels of C-RP were found to be significantly higher in womens with a simillarchronological age , gestational age ,and parity.

In our study ,we found that C-RP levels were higher in pre-eclamptic women than control group and positively related to the degree of blood pressure elevation.

Our data are simillare to results in studies by Teran et al (7),Belo et al(8), Mirazaie et al (16), kumru et al (16),Ustun et al (17).

Determination of plasma C-RP levels in third trimester pregnant women was of great significance in predicting the prognosis of pre-eclampsia (17).

In several studies ,comparison of fibrinogen in the third trimester of normal and pre-eclamptic pregnancies showed similar values (8,9).

In some studies, plasma levels of fibrinogen were decreased in the presence of pre-eclampsia (12,18).In our study,we evaluated the role of fibrinogen in normal pregnancy and pre-eclamptic pregnancies. we found significantly higher levels of fibrinogen in primigravid women with pre-eclampsia than in control women, despite similar maternal age ,gestational age and body mass index which Consistent with Marten s report (20).

We also found a significant correlation between fibrinogen and MAP. Fibrinogen was significantly increased with MAP .This indicates a correlation between the severity of disease and inflammation.

### **CONCLUSION:**

We found evidence of inflammation in pre-eclampsia.

High C-RP and fibrinogen levels were associated with sever pre-eclampsia. C-RP and fibrinogen correlate positively and significantly with the severity of disease in pre-eclampsia.Consistant with other studies, our findings suggest that increased C-RP may reflect endothelial cell dysfunction in pre-eclampsia and may be a potential marker of

risk.

We also conclude that fibrinogen is a clinically useful marker in patients with pre-eclampsia like C-RP.

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