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

WasanW.Ibrahem* **FICOG**
Raya Kh. Al-Assaly** **FICOG**
Nada Saeed Al-Haddad** **FICOG**

Abstract:

Background: Preeclampsia is most common medical disordersduring pregnancy, and the rate of hypertension ranges from 5 – 8 % f or 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 ofserum 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.

Fac Med Baghdad 2017; Vol.59, No.1
Received: Oct..2016
Accepted: Jan..2017

Patients and method: A prospective case-control studywhich was carried out in the department of gynecology and obstetric at Baghdad teaching hospital from 1st ofJanuary 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- 125in 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 . theplasma fibrinogen levels in mild and sever 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 placentation 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 deciduas are proposed as the underlying mechanism for elevation in serum (CA-125) in preeclampsia

** Dept. of gynecology, College of Medicine, University of Baghdad. wasan Wajdi@gmial.com*
***Baghdad Teaching Hospital*

.(7,8)

C-reactive protein is produced by hepatocytes. It is apart of the acute phase immune response.(9,10)In pregnancy systemic maternal inflammatory response to pregnancy is responsible for the endothelial dysfunction which gives the clinical and pathological picture of preeclampsia.(11,12)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.(13)

Fibrinogen is a 340 kDa plasma glycoprotein that plays a key role in coagulation. During pregnancy there is ahypofibrinolytic, hypercoagulable state, both plasminogen and fibrinogen levels in plasma increase by 50 to 60 % in third trimester.(14) Fibrinogen levels are actually elevated in preeclampstic women as compared with normotensive patients, low fibrinogen level in preeclampsia or eclampsia are usually associated with abruption placenta or fetal demise (due to consumption).(15)

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 chorioaminionitis.The demographic characteristics of each patient were assessed including maternal age and parity. Gestational age calculatedfrom 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 bymercury sphygomomanometer in left lateral position, In mild preeclampsia blood pressure equal to or more than 140/90 in two consecutive readingsfour 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, urine analysis, coagulation screen. CA 125 was measured by Enzyme - linked immune 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 fined 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 groupregarding the mean arterial pressure (mmHg)as shown table 1.

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

Parameters	Control (n= 70) Mean ± SD	Mild PE (n=35) Mean± SD	Severe PE(n=35) Mean± SD
Age (yr)	26.69±7.49 (16-43)	26.14±7.26 (18-45)	26.09±7.18 (17- 42)
Gestational age (wk)	33.80±3.82 (29-38)	33.49±3.64 (28-39)	33.74±3.87 (30-39)
Parity	3.0±2.01 (1-5)	2.63±1.9 (0-6)	2.49±1.82 (0-5)
Mean arterial pressure (mmHg)	77.13±10.39 (65-93)	114.40±5.36 (106-120) α	144.06±11.63 (125-164) β

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) respectivelywhich 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.

Parameters	Control (n=70) mean±SD	Mild PET (n=35) mean±SD	P value
CA125 (IU/ml)	14.4±4.11	33.60±4.52	< 0.0001
Plasma fibrinogen (mg/dl)	342.97±56.6	470.37±51.1	< 0.0001
CRP (mg/l)	8.17±1.56	15.62±2.6	< 0.0001

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 PET group by unpaired t-test.

Parameters	Control (n=70) Mean±SD	Severe PET (n=35) Mean±SD	P value
CA125 (IU/ml)	14.4±4.11	37.35±4.85	< 0.0001
Plasma fibrinogen (mg/dl)	342.97±56.6	563.14±48.28	< 0.0001
CRP (mg/l)	8.17±1.56	29.3±7.02	< 0.0001

The plasma fibrinogen (mg/dl) in women with mild PE was (470.37±51.1), while in women with severe PET was (563.14±48.28) and, there was significant differences between the two groups with higher results in women with severe PE as p value < 0.0001.The CRP (mg/l) in women with mild PE was (15.62±2.6) while in women with severe PE was (29.3±7.02), there was significant difference between the two groups with higher result in women with severe PE as p value < 0.0001.(Table 4).

Table (4): Comparison of CA125, plasma fibrinogen and C-reactive protein between mild PE group and severe PE group by unpaired t-test.

Parameters	Mild PET (n=35) mean±SD (Range)	Severe PET (n=35) mean±SD (Range)	P value
CA125 (IU/ml)	33.60±4.52	37.35±4.85	0.0013
Plasma fibrinogen (mg/dl)	470.37±51.1	563.14±48.28	< 0.0001
CRP (mg/l)	15.62±2.6	29.3±7.02	< 0.0001

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.

Parameters	Sensitivity	Specificity	Accuracy rate
CA 125	96.7%	98.7%	97.7%
Plasma fibrinogen	87.14%	97.14%	92.14%
C-reactive protein	97.18%	98.57%	97.87%

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 Y.ustun 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

PE than normotensive women. (16) Also its concordant to that revealed by Cebesoyet 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 Schijetlineet 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). Which is agree to that mentioned by Ozatet al, 2010 study (in Turkey), they found that the CA125 is biochemical marker which reflects the severity of the underlying inflammation processes in PE in third trimester(21). Cebosyetal, 2009 (17) study reported the same result stated that the CA125 increase with the severity of PE.While Bon G. et al, 2001 study (22); they assessed CA 125 and CA15-3 and compared their level in 350 women with normal pregnancy outcome and pathological pregnancies including PE, found that the maternal serum level of CA 125 and CA 15-3 were significantly different in the first and third trimester of pregnancy, but no significant difference found in normal pregnancy from that obtained in pathological one including PE patients.This finding probably due to different timing of measurement during pregnancy and in their study (first and third trimesters), while our study done in the third trimester only.According to the results of specificity and sensitivity of CRP and CA 125, plasma fibrinogen level obtained in current study, these three indices can be used as a marker of severity of preeclampsia.

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:

Wasaswajdi : supervision

Raya : writing statistics and discussion

Nada : Data collection , statistics and discussion .

References:

1. *Pinheiro M. B, Gomesa KB, Dusse LM. Fibrinolytic system in preeclampsia. ClinicaChimicaActa. 2013 Feb 1;416:67-71.*

2. *ACDG Practice bulletin. Diagnosis and management of preeclampsia and eclampsia. American College of Obstetricians and Gynecologists. 2002 Apr;77,67-75.*

3. *Program NH. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. AJOG. 2000 Jul 31;183(1):s1-22.*

4. *Baker NP: Disorders of placentation. In: Obstetrics by ten teachers, Edward Arnold publishing. 2006; 18(13): 156-68.*

5. *Cunningham FG, leveno JK, Bloom SL. Pregnancy Hypertension. In: Williams Obstetrics, McGraw-Hill company's publisher. 2010; 23 (34): 706-56.*

6. *Roberts JM, Cunningham FG, Lindheimer MD, editors. Chesley's hypertensive disorders in pregnancy. Academic Press; 2009 Apr 16.*

7. *Duran-Reyes G, Gomes-Melendez MR, Morali De, La Brena G, Mrecado-Pichardo E, Medina-Navarro R, Hicks-Gomez JJ. Nitric oxide synthesis inhibition suppresses implantation and decreases CGMP concentration and protein peroxidation. Life Sci. 2001;65:2259–2268.*

8. *Roberts JM. Endothelial dysfunction in preeclampsia. SeminReprodEndocrinol. 1998;16:5–15.*

9. *Wander K, Brindle E , Kathleen AO: C-Reactive Protein Across the Menstrual Cycle. In: American Journal Of Physical Anthropology. 2012;136:138–46.*

10. *Yaps H, Moshage HJ and Hazenberg BP: Tumor necrosis factor inhibits interleukin(IL) and or IL-6 stimulate synthesis of C-Reactive protein and serum amyloid A in primary culture of human hepatocytes In: Bio chem. Bio phys. 2001;1091:405-8.*

11. *Mark B. Pepys and Gideon M: C-reactive protein: a critical update. In :Journal of Clincal Invest. 2013; 111(12):1805–12.*

12. *Verma S, Wang CH and Li SH,: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. In:Circulation.2002;106:913- 19.*

13. *Granger JP, Alexander BT and LlinasMT : Pathophysiology of Hypertension During Preeclmpsia Linking placental Ischaemia With Endothelial Dysfunction. In: Hypertension. 2001; 38:718-22.*

14. *Hajjar KA: Molecular mechanism of fibrinolysis, William hematology, 6th edition, 2001, pp. 1479-93.*

15. *Reynolds C, MD, William C, Mabie WC, MD, and Baha M. Sibai MD: Hypertensive state of pregnancy, current Obtetrics and gynecologic diagnosis and treatment 9th edition, 2003, PP. 338-68.*

16. *Ustün Y, Engin-Ustün Y, Kamaci M:Association offibrinogen*

and C- reactive protein with severity of preeclampsia. In: Eur J ObstetGynecolReprodBiol , 2005; 121:154–8.

17. *Cebesoy FB, Balat O andDikensoyE,Kalayci H and Ibar Y: CA-125 and CRP are Elevated in Preeclampsia. In: Hypertension inPregnancy.2009; 28:201–11*

18. *Tefanović M, VukomanovićP,Milosavljević M, utlešić R, TubićPavlović A. Insulin Resistance And C-Reactive Protein In Preeclampsia. In: Bosnian journal of basic medical sciences 2009; 9 (3): 235-8 .*

19. *PeppleNd, Handeman MR, Mullin AM, Reid HL, Erythrocyte deformability and erythrocyte aggregation in pre – eclampsia. ClinHemorteolMicrocirc 2001; 24: 43-8.*

20. *Schjetlein R, Abdelnoor M, Haugen G, Husby H, Sandset PM, Wisloff F. Hemostation variables as independent predictors for fetal growth retardation in preeclampsia. ActaobstetgynecolScand 2009; 78: 191-7.*

21. *Ozat M, Pektas MK and Yenicesu O: Serum concentrations of CA-125 in normal and preeclamptic pregnancies. In: Archives Of Gynecology And Obstetrics,2010:1-9.*

22. *Bon GG, Kenemans P and Verstraeten AA. Maternal serum Ca125 and Ca15-3 antigen levels in normal and pathological pregnancy. In: Fetal DiagnTherpy. 2001;16(3):166-72.*