Original Article

The correlation between serum levels of soluble platelet -selectin in preeclampsia with & without intrauterine growth retardation versus normal pregnancy

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***Abstract*:**

Background: preeclampsia is characterized by endothelial dysfunction with vasoconstriction due to cell adhesion molecules or mediators released by defective placentation. Soluble platelet selectin, one of the cell adhesion molecules, is elevated in many inflammatory conditions including preeclampsia.

Objective: To investigate if soluble platelet-selectin levels can be used as a marker for adverse outcomes in pregnancy complicated with sever preeclampsia

Patients and methods:This study involved 115 pregnant women in their third trimester of pregnancy; divided into **Group A:** involves 25 pregnant women with preeclampsia complicated by intrauterine growth restriction. **Group B:** involves 35 pregnant women with preeclampsia without intrauterine growth restriction.Control group: involve 55 pregnant women with normal blood pressure and normal fetal growth .The data were conducted from patients by special questionnaire, this involve name, age, parity, examination included vital signs, abdominal, obstetrical examination and investigations including :Liver function test, Renal function test, Complete blood picture and maternal serum levels of soluble platelet selectin was measured by enzyme-linked immunosorbent assay ,albumin in urine and serial obstetrical ultrasound scan to confirm the diagnosis of intrauterine growth retardation and Doppler study to determine fetuses at risk .

Results: this study revealed a significantly higher concentration of soluble platelet selectin levels in serumofpreeclamptic women with and without intrauterine growth retardation versus normotensive and normal fetal growth. The maternal serum levels of sP-selectin in preeclampsia without intrauterine growth restriction were significantly higher than preeclampsia complicated by intrauterine growth restriction .Sensitivity was 91.7% and specificity 100% at cut off value 6.975 ng/ml of maternal soluble platelet _selectin for prediction of adverse pregnancy outcome .

Conclusion: soluble platelet -selectin levels have a positive significant correlation with the severity of preeclampsia, so it can beconsidered as a marker for its severity and can be used as a predictor for adverse outcomes as itsnegatively correlated with these complications

Keywords:soluble platelet-selectin ,preeclampsia with & without intrauterine growth retardation versus normotensive pregnancy .

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Introduction:

Pre-eclampsia(PE); is a multisystemicdisorder occurs during pregnancy (1, 2).

It is defined as an increase in BP after 20weeks gestation with protein ureaand resolution before the end of the 6th puerperium(1) ,it complicates 3%–8% of pregnancy.

The pathophysiology of pre-eclampsia still unclear,current theory:it occurs due to an impairment of trophoblast invasion (3) and failure of physiologic transformation of the spiral arteries(4). .Although the primary trigger for these abnormalities remain elusive (5), leukocyte –endothelial cell interaction affected by cellular adhesion molecules have been implicated in the pathophysiology of preeclampsia (6).

Soluble adhesionmolecules can be measured in plasma, and their levels may be related to the degree of activation of a specific cell type. Increase in soluble forms of vascular cell adhesion molecule 1(sVCAM-1) indicates endothelial cell activation/dysfunction.Recently soluble platelet-selectin a soluble cell adhesion molecule may play a role in the pathophysiology of preeclampsia (7).

Soluble P-selectin ; cell adhesion molecule,belong the selectin family localized in the membranes of granules of platelets which is considered as a major source (8) and endothelial cells granules (9),after cell activation these adhesion molecules are expressed on the surface of these cells ,and as a soluble can be found in the plasma as a circulating protein (10).

Because of haemodilutionthat occur in pregnancy there is decrease in platelet mass, although there is increases in

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platelet activation, There was a significant positive correlation between sP-selectin and platelet mass, and count ,but sP-selectin levels maintain the same level during normal pregnancy (11). Currently, there is significant increase in soluble vascular cell adhesion molecule-1, in women at risk of developing pre-eclampsia (12),sothese can use for early detection of preeclampsia.

Preeclampsiaincrease perinatal mortality rates, intrauterine growth retardation(IUGR), and preterm delivery (13).

IUGR describes a fetusthat has not reached its growth potential as a result of genetic or environmental factors or combination of both (14) .When an infant birth weight was below the 10th percentile a given gestational age, the term small for gestational age(SGA) is accurate(14) .

A combination of tests rather single fetal monitoring test use in order to predict fetal compromise in women with preeclampsiaand umbilical artery Doppler at the top of list when there is IUGR (15)

This study was conducted to evaluate the activation profile of the endothelium by measuring the plasma levels of soluble platelet selectinin pre-eclamptic pregnancy whether complicated by IUGR or not, versus normotensive pregnancy with normal fetal growth pattern.

Patients and methods:

A case control study carried out at AL-Yarmouk Teaching Hospital from 1st of March 2015 till 1st of January 2016, the study was approved by ethical committee of Iraqi Board for Medical Specialization. This study involved 115 pregnant women; and divided in to three groups:Group A: involve 25 pregnant women with preeclampsia complicated by IUGR. Group B: involve 35 pregnant women with preeclampsia without IUGR.Control group: involve 55 normotensive pregnant women without IUGR, with normal blood pressure (The arterial blood pressure measurements did not exceed 135/85 mmHg), with singleton uncomplicated pregnancies, without renal, heart, and vascular disease.With normal laboratory tests included negative proteinuria.The pregnant women enrolled in our study were selected while visiting the antenatal care (ANC) or from labor room as inpatients. All pregnant women were primigravida between (32-42) completed weeks of gestation (calculated from reliable last menstrual periods and first, early 2nd ultrasound), with single viable fetus Their age was range from 16-40 years, BMI ranged between 29-32 f kg/m2. Exclusion criteria include:women with medical disease (cardiovascular, diabetes and renal diseases), mutiple pregnancy, pregnant with fetal congenital malformation, smokers and unconscious women .Verbal consent anddetailed history was taken from all women who's agreed to participate in the study, calculation of (BMI in Kg/m2) with the measurement of vital sign including blood pressure measurement(16)and assessment of severity of preeclampsia after complete examination (17)

All patients were assessed by the following investigations: urine for albumin, complete blood picture, coagulation profile,,Renal function test, Liver function test, and the serum sP-selectin level was determined using ELISA assay according to the manufacturer'sinstruction(humansP-selectin ELISA kit,SHANGHAI YEHUA Biological Technology Co., Ltd.Cat. No : YHB2778Hu) , ultrasound scans for assessment of fetal growth and Doppler study.IUGR suspected when the weight of the fetus was lower than expected for a given gestational ageby obstetrical examination and US scanas estimated birth weight (EBW) below the 10th percentile for gestational age usingfetal abdominal circumference) in addition to at least one of the following abnormal Doppler ultra-sonographic examination (elevated pulsatility index [PI] in the uterine arteries and/or early diastolic notches, elevated PI in umbilical arteries) with elevated head/ abdomen ratio and reduced AFI. The diagnosis was confirmed after birth by clinical features of IUGR and the infant's weight at birth (corrected for gestational age, use the percentile calculator).Pregnant women with PE and IUGR were included in the group A and those with PE and normal fetal growth were included in groupB.Statistical Package for Social Sciences (SPSS) version 20 was used for analysis .Frequency and percentage used for categorical variable .The Chi-square test was used for analysis of categorical data.The continuous variables were presented as averages and standard deviations.Analysis of variances (ANOVA) test was used to assess the significance of mean differences between continuous variables.Pearson's correlation test was used to assess the correlation between the continuous variables, the correlation considered was Weak when the coefficient of correlation (r) (0 - 0.3), moderate if (r= 0.3 – 0.7) and strong when (r>0.7). Receiver operator curves were used to assess reliability values (Sensitivity, specificity) as well as calculating cutoff values.P–Value less than 0.05 was used as the alpha level of significant

Results:

The gestational age of the patients in this study ranged from 32-40 weeks ,BMI ranged from 31.22- 26.71Kg/m2,there was no significant difference regarding maternal age, BMI ,but the gestational age was lower in the studied groups than control group and the difference was statistically significant.

Table1:Demographical analysis of the three groups

Variables	Control N=55 Mean±SD	Group A N=25 Mean±SD	Group B N=35 Mean±SD	p value
Age (years)	28±3.7	29.6±6.7	28.8±7.4	0.507
Body mass index(BMI kg/m2)	31.2±1.3	31.1±1.2	31.4±1.3	0.357
Gestational age (weeks)	37.8±0.9	34.4±1.6	34.7±1.9	<0.001*
ANOVA test, SD=Standard deviation,* Significant at 0.05 levels				

Table 2: shows Significantly higher systolic, diastolic blood pressure and maternal sp-selectin level s in both preeclamptic with and without IUGR groups in comparison with the control group .

Table 2:The difference between the level of maternal Blood pressure and maternal SP-selectin in the three groups

Variables	Control N=55 Mean±SD	Group A N=25 Mean±SD	Group B N=35 Mean±SD	p value
Systolic blood pressure (mm Hg)	121.8±7.5	171.2±8.8	169.7±7.8	<0.001*
Diastolic blood pressure (mm Hg)	73.5±5.5	114±7.1	113.1±4.7	<0.001*
Maternal sP-selectin (con./OD)	6.53±0.21	7.04 ±0.36	7.2±0.85	<0.001*
ANOVA test, SD=Standard deviation, * Significant at 0.05 levels				

As table 3 shows the percentage of vaginal delivery was significantly lower in both preeclamticgroups ,while the percentage of caesarean section and under weight was significantly higher in both preeclamptic group

Table 3 percentage of mode of delivery and percentile birth weight category

Variables	Control N=55 No. (%)	Group A N=25 No. (%)	Group B N=35 No. (%)	p value
Mode of delivery				
Vaginal delivery	41 (74.5%)	6 (24%)	10 (28.6%)	<0.001*
Caesarean section	14 (25.5%)	19 (76%)	25 (71.4%)	
Birth-weight categories				
Under-weight	2 (3.6%)	25 (100%)	22 (62.9%)	<0.001*
Appropriate-weight	53 (96.4%)	0 (0%)	13 (37.1%)	
Chi-square test, * Significant at 0.05 levels				

Table 4: shows 14.3% women in Group B (PE without IUGR) and 4% in GroupA(PE with IUGR) had adverse pregnancy outcome(1case developed eclampsiain group A and 3 cases in group B /2 IUD cases in group B) as figure 4 shown.

Table 4 Relationship of maternal and fetal outcomes between the three groups

Outcomes	Control No. (%)	Group A No. (%)	Group B No. (%)	Total No. (%)
Negative	55 (100%)	24 (96%)	30 (85.7%)	109 (94.8%)
Positive (eclampsia/IUD)	0 (0%)	1 (4%) (eclampsia)	5 (14.3%) (3eclampsia/2IUD)	6 (5.2%)
Total	55 (100%)	25 (100%)	35 (100%)	115 (100%)
Chi-square test, p-value = 0.012 (Significant at 0.05 levels)				

Table 5 shows inverse non significant correlation between maternal sP_selectin levels and maternal age and presence of adverse outcomes (IUD/eclampsia). And on the other hand there was positive significant correlation between maternal sP_selectin levels with systolic , diastolic blood pressure ,albumin in urine gestational age and birth weight at time of delivery ,caesarean section mode of delivery in three groups ,also a positive correlation with growth restriction in utero and BMI but it was statistically not significant

Table 5Correlation of Maternal sP-selectin levels with different parameters and outcomes in the three groups

Variables	Maternal sP-selectin (con./OD)	p value
	Correlation coefficient (r)	
Age (years)	-0.082	0.381
Gestational age (weeks)	-0.346	<0.001*
Body mass index (kg/m2)	0.107	0.109
Diastolic blood pressure (mm Hg)	0.488	<0.001*
Systolic blood pressure (mm Hg)	0.486	<0.001*
Significant albumin in urine	0.504	<0.001*
IUGR	0.172	0.066
Outcomes(IUD, eclampsia)	-0.009	0.92
Mode of delivery(C/S)	0.424	<0.001*
birth weight /g percentile	-0.308	<0.001*
Pearson's correlation, * Significant at 0.05 levels		

the sensitivity of maternal sP_selectin levels as a predictor for the adverse pregnancy outcomes is 91.7% and specificity was 100% at cut off value of maternal sP-selectin 6.975 ng/ml,area under curve and confidence interval was 0.917(0.847-0.987)as shown in figure 1.

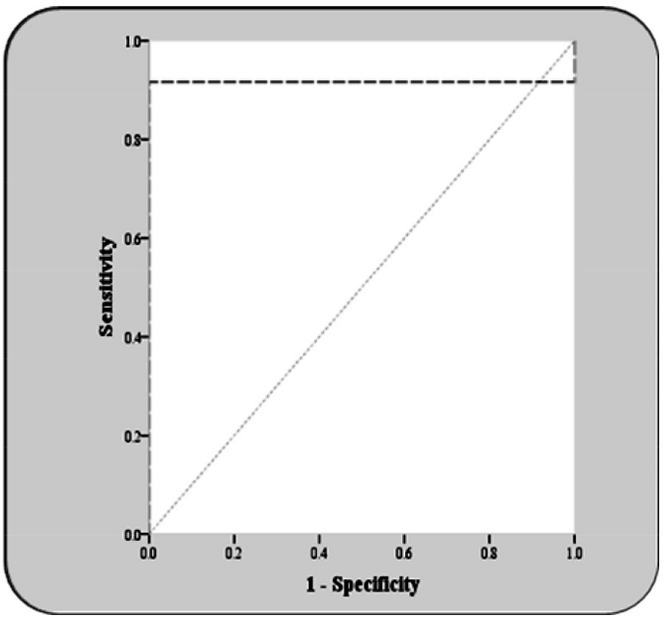

Figure 1 Receiver operator curve (ROC), maternal sP-selectin sensitivity and specificity prediction for adverse pregnancy outcome

The levels of Sp –selectinsignificantly increase in both groups of preeclamptic women as compared with control in this study, this results in agreement with ;

Marzena et al(18), as he observed significantly higher levels of sP-selectin in both preeclamptic groups versus normotensive and normal fetal growth pregnant women , he suggested such high sP-selectin levels may reflect a systemic inflammatory process and platelets activation inpreeclamptic rather than in normotensive pregnancy.

Laskowska et al(19) study shows significantly higher levels of spselectin in cord blood of preeclamptic women with either pattern of fetal growth versus control group. This increase in Sp_selectin levels may reflect platelet activation in women with PE compared to normal pregnancy.Same result was suggested by Holthe et al (20),as their observation support the process of increased platelet activation with increased basal expression of sP-selectin in PE.Bosio et al (21) observed the sP_selectin levels elevated in pregnancy with preeclampsia in comparison with control group,andthis elevation in P-selectinlevel reflect endothelium activation in cases with severe preeclampsia as suggested by Salazar et al(22). Other investigators reported negative correlation between serum P-selectin and the activity of the platelet antioxidant enzyme superoxide dismutase (SOD) in pregnancy complicated by hypertension (21). this study demonstrate significantly increase SP-selectin levels in preeclamptic women with normal intrauterine fetal growth versus preeclampsia patients complicated by IUGR and control group, this result can be explained as sp-selectin

considered as trigger of procoagulantstate and as a marker for platelet activation.AsLaskowskaet al(19) foundsignificantly higher cord sP-selectin levels in thepreeclamptic patients with appropriate fetal growth in comparison with preeclampsia complicated by intrauterine growth restriction and with control group, they explained their result by increase platelets activation and endothelial dysfunction in PE versus normotensive patients .The same suggestion by Sheppard et al(23) as he notice that the physiological changes of the spiral arteries present in IUGR pregnancy whether complicated by PE or not ,he concluded that no arteriopathy was found which was specific for PE.

Another explanation of low sP_selectin levels in PE with IUGR in comparison with PE and normal fetal growth restriction is the disturbances in sP_selectin activity associated with destructive changes in PE without IUGR. in contrast Phocas et al(24) study which carried out on 25pregnant women with and without IUGR versus normotensive control group studied the level of vascular cell adhesion molecules-1 (sVCAM-1) in sera of normal and PE women, the conclusion was that sVCAM-1 was significantly elevatedinwomen with preeclampsia, further increase if complicated with fetal growth restriction this result might reflect the angiogenic function of sVCAM -1, so sVCAM-1 could be of value in the diagnosis of IUGR in preeclampsia .This study show the average gestational age was earlier at delivery in preeclamptic pregnant women in comparison with control , and there is significant inverse correlation between sP_selectin levels with the gestational age in the three groups, ,while Holmes et al(25)showed no significant correlation between sP_selectin levels and GA and the sP_selectin levels remain stable throughout normal pregnancy This study revealed significant positive correlation between sP_selectin levels and systolic, diastolic blood pressure, same result was concluded byHalim et al (26), as he found significant elevatationof sP-selectin in preecalampsia and eclampsia cases in comparison with normal pregnancy. Kim et al(27) shown the levels of sVCAM-1 and sp-selectin pregnant women can be used as an indicator for the severity in preeclampsia when the study selected 30 pregnant women with mild PE, 45 with sever PE in comparison with 60 control. There was significant difference in sVCAM-1 and sP_selectin levels between mild and severe PE, and statistically significant higher levels in severe preeclampsiaThis study observed that spselectinlevels was negatively correlated with adverse fetal and maternal outcomes (eclamptic fit and intrauterine fetal death),as the level of sp-selectin tend to decrease as the complications developed whether fetal or maternal and further the incidence of caesarean section as shown in the study there is significant positive correlation with sP_selectin levels. In this study all three groups there were no significant correlations between BMI and the levels of sP-selectin, and inverse correlation between Sp-selectin levels and fetal weight percentile which is in agreement withMarzena et al (18) ,he found an negative correlation between Sp-selectin levels and fetal weight percentile observed in normotensive women with IUGR.According to the area under curve AUC, the cut off value of Sp_selectin levels is 6.975ng/ml; specificity is 100% and sensitivity 91% as a predictor of fetal and maternal complications.

Conclusions:

SP-selectin levels may play a role in the pathogenesis of preeclampsia, and can be used as apredictor for adverse outcomes in pregnant women with sever preeclampsia.

Auther's contribution:

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