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Serum E-selectin in Preeclampsia: A Case – Control Study

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ABSTRACT

Preeclampsia (PE) is an important disease in pregnancy, and is one of the causes of maternal morbidity, mortality and adverse neonatal outcomes. One of the basic pathophysiologies of preeclampsia is endothelial cell dysfunction as suggested by an elevated concentration of endothelin-selectin. The aim of this study was to compare the sera levels of endothelin-selectin (E-selectin) in normal and pre-eclamptic term pregnancy. This case-control study was followed on 80 patients admitted to the Departments of Obstetrics and Gynecology of the Ghaem and Emam Reza hospitals in Mashhad University of Medical Sciences. The Control group consisted of 40 normal term pregnant women (≥ 37 weeks) and the Case group was 40 term preeclamptic pregnant women. Participants were enrolled after approval by the ethics committee and received the informed consent. E-selectin concentration evaluated in two groups. The level of E-selectin was significantly in two groups. It was higher in sera of pre-eclamptic patients than the normal pregnancy ($p=0.0001$). Especially, it was significantly higher in severe pre-eclamptic patients ($p<0.05$). In conclusion, the found results showed that E-selectin was increased in term of PE that and may be useful for predicting the severity of pre-eclampsia.

Key words: Preeclampsia, Cell adhesion molecules, E-selectin.

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1. INTRODUCTION

Preeclampsia (PE) is an important disease in pregnancy and is one of the major causes of maternal morbidity, mortality and adverse neonatal outcomes (1). PE affects approximately 3–8% of all pregnancies in worldwide and principally appears during the late second trimester of pregnancy until term (1, 2). Despite intensive efforts to delineate pathophysiology of pre-eclampsia, neither a specific cause nor a pathogenesis has been identified (1). One of the basic pathophysiologies of PE is the endothelial cell dysfunction as suggested by elevated of some nonspecific parameters (3). The main mechanism of the endothelial dysfunction is unclear. A recent study showed that PE is characterized by leukocyte phenotypic, metabolic activity and intravascular inflammation (4). Therefore, an excessive maternal inflammatory response to pregnancy has been proposed to be responsible for the clinical syndrome of PE and endothelial cell dysfunction (5). Adhesion molecules due to endothelial cell dysfunction, play a central role in the endothelial cells- leukocytes adherence and the subsequent migration of white blood cells into perivascular tissue (4). Cellular forms of adhesion molecules mediate specific steps of leukocyte-endothelial cell interaction and have been implicated in the pathophysiology of PE (6). Adhesion molecules, such as E- selectin (produced by endothelial cells) is an inflammatory biomarker (4) and has been shown to correlate with the level of oxidative stress in preeclampsia (7, 8). Soluble forms of these molecules can be detected in plasma. Increase in soluble forms of E-selectin (SE-selectin) indicates the dysfunction of endothelial cell activation. Accordingly that the genetic differences have been identified to influence on some

biomarker levels (9). Therefore, the objective of this study was to assess and compare the concentration of Plasma E-selectin in peripheral blood of Iranian normal and pre-eclamptic pregnant women.

2. MATERIALS AND METHODS

2.1. Population

This case-control study was conducted on 80 patients admitted to Departments of Obstetrics and Gynecology of the Ghaem and Emam Reza hospitals in Mashhad University of Medical Sciences, by a research grant number 84381. Based on Cochran formula with à=0.05, β=0.2, p=0.3, q=0.7 and d=0.2, the sample size was acquired seventy patients, with the loss of samples, there calculated 40 patients in each group. The Control group consisted of 40 normal term pregnant women (≥ 37 weeks) and Case group was 40 term preeclamptic pregnant women. Participants were enrolled after approval by the ethics committee of Mashhad University of Medical Sciences (ethical number, 84381) and received the informed consent. All patients were basically examined by same gynecologist and were dedicated to case or control group.

2.2. Study design and treatments

PE was defined as hypertension (systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥90 mmHg after 20 weeks' gestational age) and proteinuria (≥300 mg in a 24 hr urine collection or one dipstick measurement of ≥1+) according to the American Congress of Obstetricians and Gynecologists (ACOG) definition (7).

2.3. Inclusion criteria

Non-severe preeclampcia was defined as hypertension (systolic blood pressure; 140-160mmHg and diastolic blood pressure; 90-110 mmHg after 20 weeks' gestational age) and proteinuria (300-2000 mg in a 24 hr urine collection or one dipstick measurement of up to 2^{+}. Severe PE was diagnosed based on diastolic blood pressure ≥110 mmHg or significant proteinuria (dipstick measurement of ≥2+) or the presence of severe preeclampsia criteria such as a headache, visual disturbances, epigastric pain, oliguria, convulsion, elevated serum creatinine, thrombocytopenia, elevated of liver enzymes and pulmonary edema. Normal pregnant women had no hypertension, proteinuria, and edema.

2.4. Exclusion criteria

Exclusive criteria for this study were the preterm gestation (<37 weeks), nephropathy, connective tissue disease, history of PE in the family and previous pregnancy, anti-phospholipids antibody disease, chronic hypertension, liver and cardiac disease.

2.5. Methods of study

Preeclamptic women were divided into two groups: proteinuria more than or equal to 2 gr in 24 hours and diastolic blood pressure ≥110 mmHg (severe) and proteinuria less than 2gr and diastolic blood pressure 90-110 mmHg (non-severe). 5cc brachial vein blood samples were taken from all subjects via clinicians personnel. No drugs were taken by these patients for 24 hours before sampling. On the case group, the BUN, bilirubin, creatinine, blood glucose, uric acid, Hb, hematocrit, platelet, aspartate transaminase (AST) and alanine transaminase (ALT) were assessed. The samples were centrifuged and stored at -20 ^{o}C until the assay. The concentrations of soluble adhesion molecules were measured using enzyme-linked immunosorbent assays (ELISA) (Bender Med System, Human sE-selectin-1-BM232, Austria, Europe). The sensitivity of the assay for sE-selectin was 0.4 ng ml^{-1}. The inter and intra-assay coefficients of variation were 7.3 % and 5.6% respectively. Neonatal weight assessed by neonatal analog scale (PORSA, YRBB-20, China) after birth. In addition, mother blood pressure was measured by an analog pressure indicator (ERKA switch comfort, Germany) in the sitting position half hour after the rest during 2 times for each patient at least 6 hours apart. The concentrations of soluble adhesion molecules were measured using enzyme-linked immunosorbent assays (ELISA) (Bender Med System, Human sE-selectin-1-BM232, Austria, Europe).

2.6. Statistical Analysis:

After collecting the required information (gestational age, maternal age, gravidity and parity, neonatal weight), all data analyses were performed using the Statistical Package for the Social Science (SPSS version 17). The Student's t-test was used for comparison of proportions. A level of $P < 0.05$ was regarded as statistically significant.

2.7. Ethical Considerations

The ethics committee of Mashhad University of Medical Sciences approved the study. All participants were notified about the study objective and its procedure. In addition, subjects were informed that their participation was voluntary and written consent was obtained from all participants.

3. RESULTS AND DISCUSSION

This study included 40 normal pregnant women and pre-eclamptic patients (15 severe PE and 25 non- severe PE). Table 1 shows the clinical characteristics of the two studied groups. There was no significant difference in gestational age, maternal age, parity and gravidity between normal and pre-eclamptic groups. Table 2 shows the laboratory characteristics of patients with pre-eclampsia. There was no statistically difference in BUN, bilirubin, creatinine, blood glucose, uric acid, Hb, hematocrit, platelet, AST and ALT between mild and severe preeclampsia. Neonatal birth weight was 2825.38±376.77 gr in control group and it was 2293.24±759.68 gr in case group. It was found that this amount was significantly

lower in case group (P=0.001). Serum concentration of E-selectin was significantly higher in PE compared to normal pregnant women (78.17±32.1 ng ml^{-1} vs. 53.32±16.65 respectively, P=0.0001) (Table 3).

Table 1. Demographic characteristics of the study population

Variable	*Control group Mean ± SD*	*Case group Mean ± SD*	*P.Value*
Mother age (year)	26.46±4.58	28.40±6.27	0.161
Parity(n)	1.53±1.02	1.81±1.24	0.34
Gravidity(n)	2.42±1.20	2.32±1.51	0.774
Gestational age (week)	38.5±1.1	38.2±1.20	0.25

Table 2. Laboratory findings of Non severe and severe pre-eclamptic patients

Group	Non severe Pre-eclampsia*	Severe Pre-eclampsia*	P-value
BUN (mg/dl)	20.75±6.13	23±8.03	0.393
BIL (mg/dl)			
Total	0.86±0.49	0.8±0.44	0.709
Direct	0.21±0.09	0.23±0.11	0.734
Creatinine (mg/dl)	0.72±0.20	0.77±0.17	0.469
Blood glucose (mg/dl)	93.6±22.94	91.21±25.54	0.793
Uric acid (mg/dl)	5.19±1.27	5.32±1.54	0.802
Hb (g/dl)	12.33±0.91	12.17±2.29	0.806
Hematocrit (%)	36.59±3.23	36.48±5.93	0.949
Platelet	159.86±53.91	196.52±81.25	0.149
AST(U/L)	40.93±55.37	54±101.23	0.656
ALT(U/L)	38.31±51.19	36.8±59.22	0.940
Urine Protein/L (gr/l)	1.10±0.96	2.26±1.60	0.04

***: Mean ± SD**

Table 3. Comparison Neonatal birth weight and E.Selection in control and Case group

Variable	*Control group Mean ± SD*	*Case group Mean ± SD*	*P.Value*
Neonatal birth weight(gr)	2825.38±376.77	2293.24±759.68	0.001
E.Selection (ng ml^{-1})	53.32±16.65	78.17±32.1	0.0001

Serum concentration of E-selectin was significantly higher in severe PE compared to non- severe PE (96.5±31.3 vs. 66.6±31.4 respectively, $p<0.05$) (Data not shown).

Studies during the last decade have provided a good understanding of the potential mechanisms for the pathogenesis of preeclampsia. The first event in preeclampsia has been perhaps to be reduced utero placental function .Placental ischemia/hypoxia may be to lead to widely activation/dysfunction of the maternal vascular endothelium that results in enhanced formation of endothelin, thromboxane, and increased vascular sensitivity to angiotensin II, and diminished formation of vasodilators such as (NO) nitric oxide and prostacyclin. These endothelial dysfunction, in turn, cause hypertension by damage renal function and increasing total peripheral vascular resistance. Although last studies protect a role for cytokines and other factors such as reactive oxygen intermediates and lipid peroxides as mediators of endothelial dysfunction (10). Biomarkers of endothelial activation, damage, and dysfunction were increased in patients with Preeclampsia (3). Adhesion molecules (E-selectin, S-selectin) and inflammatory markers such as Endocan play an important role in endothelial dysfunction, and PE (11). This family comprises selectins, integrins and molecules that belong to the immunoglobulin gene superfamily. During an inflammatory process, the selectins mediate the initial attachment and rolling of leukocytes on the vascular endothelial cells (4). In this study, E-selectin levels were elevated in PE (severe and non-severe) compared to normal pregnancy. In a study, Xing et al. indicated that E-selectin was a major pathological change of PE (12). In addition, in a recent study in Greece, E-selectin was found to increase significantly in pre-eclamptic women. In line with the findings of this study (13). Kim et al, indicated that serum levels of E-selectin were significantly higher in both mild and severe PE than a normal pregnancy. However, there were no statistical differences in the levels of E-selectin between mild and severe PE (14). In France, Bretelle et al and Bersinger et al in Switzerland reported similar results in increasing E-selectin in PE (15, 16). In Carty DM et al study, E-selectin concentrations were higher in women who develop PE in preterm labor lower than 28 weeks (8). Against to these results, Phocas et al (17) and Chaiworapongsa et al (6) could not detect an increased E-selectin serum level in PE.

Our findings indicated that e-selectin was higher in severe and non-severe PE despite normal pregnancy at term. Abnormally circulating levels of SE-selectin may have a predictive value for PE and IUGR, as they may be linked with dysfunction or damage of endothelial activation (18). Levels of SE-selectin were negatively associated with newborn weight. High circulating levels of maternal endothelial dysfunction markers such as E-selectin present in PE are associated with decreased nitric oxide (NO) synthesis in fetal endothelium and high risk for preterm delivery and very preterm delivery or fetal extremely low birth weight compared with women with low levels (19). Although, Chen study didn't show association between high serum sE-selectin and risk of preterm delivery. However, in cases of preterm delivery with and without preeclampsia, the highest quartile of sE-selectin during the 3rd trimester was associated with preterm delivery complicated by preeclampsia (20). In addition, in our study, neonatal birth weight in term pre-eclamptic patients was lower than a normal pregnancy. In our study, the serum concentrations of soluble adhesion molecules (E-selectin) in term pre-eclamptic women were higher compared to normal term pregnant women. In addition, E-selectin concentrations were markedly higher in severe pre-eclamptic women. It seems that E-selectin may be useful for predicting the severity of PE. The clinical screening of these molecules for predicting PE needs to perform further studies. The limitations of this study were the small sample size and do not evaluate the other soluble adhesion molecules, further studies with larger sample sizes, as well as clinical trial studies to decrease inflammatory factors such as E-selectin to prevent the rate of PE are recommended.

4. CONCLUSION

These results showed that sE-selectin was increased in PE. In addition, E-selectin concentrations were markedly higher in severe pre-eclamptic women. It seems that E-selectin may be useful for predicting the severity of PE.

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AUTHORS CONTRIBUTION

Study concept and design: Malihe Afiat; Analysis and interpretation of data: Homa Kianifar and Nayereh Khadem; Drafting of the manuscript: Malihe Afiat, Seyedeh Houra Mousavi Vahed and Fedyeh Haghollahi; Data collection: Homa Kianifar and Hossein Ayatollahi; Statistical analysis: Fedyeh Haghollahi.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this paper.

REFERENCES

1. Cetin I, Huppertz B, Burton G, Cuckle H, Gonen R, Lapaire O, et al. Pregenesys pre-eclampsia markers consensus meeting: what do we require from markers, risk assessment and model systems to tailor preventive strategies? Placenta. 2011;32:S4-S16.
2. Staff AC, Benton SJ, von Dadelszen P, Roberts JM, Taylor RN, Powers RW, et al. Redefining preeclampsia using placenta-derived biomarkers. Hypertension. 2013;61(5):932-42.
3. Tuzcu ZB, Asicioglu E, Sunbul M, Ozben B, Arikan H, Koc M. Circulating endothelial cell number and markers of endothelial dysfunction in previously preeclamptic women. American journal of obstetrics and gynecology. 2015;213(4):533. e1-. e7.
4. Oggé G, Romero R, Chaiworapongsa T, Gervasi MT, Pacora P, Erez O, et al. Leukocytes of pregnant women with small-for-gestational age neonates have a different phenotypic and metabolic activity from those of women with preeclampsia. The Journal of Maternal-Fetal & Neonatal Medicine. 2010;23(6):476-87.
5. Redman C, Sargent I. Pre-eclampsia, the placenta and the maternal systemic inflammatory response—a review. Placenta. 2003;24:S21-S7.
6. Chaiworapongsa T, Romero R, Yoshimatsu J, Espinoza J, Kim Y, Park K, et al. Soluble adhesion molecule profile in normal pregnancy and pre-eclampsia. The journal of maternal-fetal & neonatal medicine. 2002;12(1):19-27.
7. Shaw J, Tang Z, Schneider H, Saljé K, Hansson SR, Guller S. Inflammatory processes are specifically enhanced in endothelial cells by placental-derived TNF-α: Implications in preeclampsia (PE). Placenta. 2016;43:1-8.
8. Carty DM, Anderson LA, Freeman DJ, Welsh PI, Brennand JE, Dominiczak AF, et al. Early pregnancy soluble E-selectin concentrations and risk of preeclampsia. Journal of hypertension. 2012;30(5):954-9.
9. Lutsey P, Cushman M, Steffen L, Green D, Barr R, Herrington D, et al. Plasma hemostatic factors and endothelial markers in four racial/ethnic groups: the MESA study. Journal of Thrombosis and Haemostasis. 2006;4(12):2629-35.
10. Granger JP, Alexander BT, Llinas MT, Bennett WA, Khalil RA. Pathophysiology of preeclampsia: linking placental ischemia/hypoxia with microvascular dysfunction. Microcirculation. 2002;9(3):147-60.
11. Gülşen S, Çekmez Y, Ulu İ, Garip Ş, Aksoy FT, Türkmen SB, et al. Investigation of the relation of maternal serum endocan levels to preeclampsia presence and severity. LaboratoriumsMedizin-Journal of Laboratory Medicine. 2017;41(3):117-21.
12. Xing A, Liu S, You Y, Yang K. VCAM-1 and E-selectin expression in extravillous cytotrophoblasts of severe preeclampsia. Sichuan da xue xue bao Yi xue ban= Journal of Sichuan University Medical science edition. 2006;37(3):408-11.
13. Papakonstantinou K, Economou E, Hasiakos D, Vitoratos N. Antepartum and postpartum maternal plasma levels of E-selectin in pre-eclampsia, gestational proteinuria and gestational hypertension. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2010;153(1):112-3.
14. Kim S-Y, Ryu H-M, Yang JH, Kim M-Y, Ahn H-K, Lim H-J, et al. Maternal serum levels of VCAM-1, ICAM-1 and E-selectin in preeclampsia. Journal of Korean medical science. 2004;19(5):688-92.
15. Bretelle F, Sabatier F, Blann A, D'Ercole C, Boutière B, Mutin M, et al. Maternal endothelial soluble cell adhesion molecules with isolated small for gestational age fetuses: comparison with pre-eclampsia. BJOG: An International Journal of Obstetrics & Gynaecology. 2001;108(12):1277-82.
16. Bersinger NA, Smárason AK, Muttukrishna S, Groome NP, Redman CW. Women with Preeclampsia Have Increased Serum Levels of Pregnancy-Associated Plasma Protein A (PAPP-A), Inhibin A, Activin A and Soluble E-selectin. Hypertension in Pregnancy. 2003;22(1):45-55.
17. Phocas I, Rizos D, Papoulias J, Xyni K, Sarandakou A, Salamalekis E. A comparative study of serum soluble vascular cell adhesion molecule-1 and soluble intercellular adhesion molecule-1 in preeclampsia. Journal of Perinatology. 2000;20(2):114.
18. Coata G, Pennacchi L, Bini V, Liotta L, Di Renzo G. Soluble adhesion molecules: marker of pre-eclampsia and intrauterine growth restriction. The Journal of Maternal-Fetal & Neonatal Medicine. 2002;12(1):28-34.
19. Veas CJ, Aguilera VC, Muñoz IJ, Gallardo VI, Miguel PL, González MA, et al. Fetal endothelium dysfunction is associated with circulating maternal levels of sE-selectin, sVCAM1, and sFlt-1 during pre-eclampsia. The journal of maternal-fetal & neonatal medicine. 2011;24(11):1371-7.
20. Chen X, Scholl TO. Maternal biomarkers of endothelial dysfunction and preterm delivery. PloS one. 2014;9(1):e85716.