Serum Level of Vascular Cell Adhesion Molecule-1 (sVCAM-1) in Sera of Normal and Preeclamptic Pregnancies

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Abstract- Endothelial dysfunction is thought to be a central pathogenic feature in pre-eclampsia on the basis of elevated adhesion molecules. Soluble forms of these molecules can be detected in plasma, and their concentrations are thought to reflect the degree of activation of a particular cell type. The aim of the present study was to compare the levels of soluble vascular cell adhesion molecule-1 (sVCAM-1) in sera of normal and pre-eclamptic pregnancies. A cross-sectional study was conducted to determine the plasma concentrations of sVCAM-1 in peripheral blood obtained from normal pregnant women (n=40), mild pre-eclampsia (n=37) and severe pre-eclampsia (n=38). Concentrations of soluble adhesion molecule was determined with enzyme-linked immunosorbant assay (ELISA). Serum concentration of sVCAM-1 was significantly higher in severe preeclampsia (P<0.05) than normal pregnancy. There was also significant differences in sVCAM- 1 levels between mild and severe pre-eclampsia (P<0.05). There was no difference in the mean plasma log sVCAM-1between normal pregnant women and mild pre-eclamptic women. These results suggest soluble vascular cell adhesion molecule-1 are increased in severe pre-eclampsia, and sVCAM-1may be useful in predicting the severity of pre-eclampsia.

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Key words : Pre-Eclampsia; cell adhesion molecules; vascular cell adhesion molecule-1,VCAM-1

Introduction

Several studies have suggested that concentrations of different soluble adhesion molecules may be useful markers of inflammation, and their concentrations have been found to be altered in conditions such as sepsis, acute coronary artery disease, renal allograft rejection, acute pancreatitis and rheumatoid arthritis (1).

Endothelial cell dysfunction is considered central to the pathophysiology of pre-eclampsia (2,3), yet the mechanisms responsible for the development of endothelial dysfunction in this syndrome remain to be determined. Recent studies suggest that 'normal pregnancy is associated with changes in peripheral blood leukocytes similar to those observed in sepsis (4), and that pre-eclampsia is characterized by leukocyte phenotypic and metabolic changes consistent with intravascular inflammation (4,5). Therefore, an excessive maternal inflammatory response to pregnancy has been proposed to be responsible for the clinical syndrome of pre-eclampsia and endothelial cell dysfunction (6).

Adhesion molecules play a central role in the endothelial cells- leukocytes adherence and the subsequent migration of white blood cells into perivascular tissue. Cellular forms of adhesion molecules mediate specific steps of leukocyte –endothelial cell interaction, and have been implicated in the pathophysiology of preeclampsia.

Soluble forms of these molecules can be detected in plasma, and their concentrations are thought to reveal the degree of activation of a particular cell type. increase in soluble forms of vascular cell adhesion molecule 1 (sVCAM-1) indicate endothelial cell activation/dysfunction.

The objective of this study was to determine whether normal pregnancy and pre-eclampsia were associated with changes in the concentrations of sVCAM-1 one of soluble members of the immunoglobulin superfamily of adhesion molecules.

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Patients and Methods

A cross-sectional study was designed to compare the plasma concentration of vascular cell adhesion molecule 1 in peripheral blood obtained from normal pregnant women and pregnant patients with pre-eclampsia at the Departments of Obstetrics and Gynecology of the Ghaem hospitals in Mashhad University of Medical Sciences, Mashhad, Iran.

Preeclampsia was defined as hypertension (systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg after 20 weeks' gestation) and proteinuria (≥300 mg in a 24 hr urine collection or one dipstick measurement of ≥1+) according to the Committee of Terminology of ACOG definition [7].

Severe preeclampsia was diagnosed on the basis of diastolic blood pressure ≥110 mmHg or significant proteinuria (dipstick measurement of ≥2+) or the presence of severity evidences such as headache, visual disturbances, upper abdominal pain, oliguria, convulsion, elevated serum creatinine, thrombocytopenia, marked liver enzyme elevation, and pulmonary edema. Normal pregnant women had no hypertension,proteinuria, and edema.

The population consisted of 40 women with normal pregnancy, 37 women with mild pre-eclampsia, and 38 women with severe preeclampsia. three groups were similar in age and body weight (mild preeclampsia group mean age 27.4±6.4 years,severe preeclampsia 26.1±5.8 and pregnant control group 24.6± 4.2 years).

Venipuncture was performed, and the blood was collected into tubes containing ethylenediamine-tetraacetic acid (EDTA). The samples were centrifuged and stored at -20C until assay. The concentrations of soluble adhesion molecules were measured using enzyme-linked immunoassays (Bender Med system,Human sVCAM-1-BM232, Austria).

The sensitivity of the assay was 0.63ng/ml .The inter- and intra-assay coefficients of variation were 5.6 % and 3.5 %, respectively. The t student-test was used for comparison of proportions. A level of $P < 0.05$ was regarded as statistically significant.

Results

This study included 40 normal pregnant women and 75 pregnant women with pre-eclampsia (37 Mild Pre-eclampsia and 38 Severe Pre-eclampsia). Table 1 lists the clinical characteristics of the three study groups.

There was no difference in the mean gestational age at venipuncture and the birth weight between normal pregnant and mild pre-eclamptic women.

Table 1. Clinical characteristics of the study population. Data are presented as mean ± standard deviation (SD)

	Normal pregnant (n = 40)	Mild Pre-eclampsia (n = 37)	p	Severe Pre-eclampsia (n = 38)	Pa	pb
Age (years)						
mean ± SD	24.6± 4.2	27.4±6.4	NS	26.1±5.8	NS	NS
range						
Gestational age at blood sampling (weeks)	37.1 ± 2	35.7 ± 4	NS	32.7 ± 5.6	0.02	0.0001
mean ± SD						
range						
Body weight	71.4±10.4	77±12.5	NS	71.1±11.4	NS	NS
Birth weight (kg)						
mean ± SD	2.6±0.7	2.3±o.68	NS	2.1±o.97	NS	0.05
range						
Blood pressure (mmHg)						
Systolic	111±14	149.1±15	<0.001	154.7± 19.7	NS	<0.001
diastolic	63±12	92±12	<0.001	107.6±14.8	<0.001	<0.001
sVCAM-1	971.3±253	1019±288	NS	1240±553	<0.05	<0.05

p, comparison between normal pregnant and Mild Pre-eclampsia ;
pa, comparison between women with mild &severe pre-eclampsia ;
pb normal pregnant and severe pre-eclampsia women;
*, statistically significant, p < 0.05; NS, non-significant

Table 2. Laboratory finding of the study population. Data are presented as mean ± standard deviation (SD)

Group	Mild Pre-eclampsia (n = 37)	Severe Pre-eclampsia (n = 38)	P
BUN	25.0 ± 14	25.7±12	NS
BIL			
Total	0.7± 0.20	0.87 ± 0.45	NS
Direct	0.26 ± 0.11	0.31±0.17	NS
Creatinine	0.62 ± 0.18	0.72±0.24	NS
Blood glucose	83.2±15.5	88.0± 20.3	NS
Uric acid	5.81 ± 1.37	6.29 ± 1.54	NS
Hb	11.92±1.39	12.47± 1.61	NS
Hematocrite	37.00± 3.93	38.16 ± 5.31	NS
Platlete	208217± 95180	191120±142383	NS
SGOT	22.26±10.63	36.92±28.57	<0.05
SGPT	18.39± 7.09	31.24±25.28	<0.05
Protein/L	1.10±1.96	2.26±2.60	<0.05

P, comparison between normal pregnant Mild Pre-eclampsia and severe pre-eclampsia
*statistically significant, p < 0.05; NS, non-significant

However, the mean gestational age at delivery (*P*=0.0001) and the birth weight (*P*=0.05) were significantly lower in the group with severe pre-eclampsia than in normal pregnant women.Table 2 shows the laboratory characteristics of patients with pre-eclampsia.

There was no difference in Bun ,Bilirubin, creatinine,blood glucose ,uric acid, Hb, hematocrite and platlete between mild and severe preeclampsia. While SGOT,SGPT and protein were significantly different between two groups(P<0.05).

soluble vascular cell adhesion molecule-1 were detected in all specimens. There was no difference in the mean sVCAM-1 between normal pregnant women (971.3±253) and mild pre-eclamptic women (1019±288). Patients with severe preeclampsia had a significantly higher mean plasma level (1240±553) than normal pregnant and mild pre-eclamptic women (*P*<0.05)

Discussion

Preeclampsia is a pregnancy dependent disorder that is clinically characterized by hypertension, proteinuria and edema which absolve after delivery. Despite the still unexplained

pathogenesis, preeclampsia is thought to be resulted from generalized endothelial dysfunction (8). Recently, increased levels of cell adhesion molecules are believed to be indicators of endothelial dysfunction in preeclampsia (9).

Adhesion molecules play an important role in endothelial cell–leukocyte interaction. 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.

Regarding the adhesion molecules in the immunoglobulin gene superfamily, soluble intercellular adhesion molecule-1(s ICAM-1), VCAM-1 and PECAM-1 are constitutively expressed mainly on vascular endothelial cells. The ligands for adhesion molecules of the immunoglobulin gene superfamily are the integrins, which are expressed on the surface of white blood cells. During leukocyte–endothelial interaction, lymphocytes attach mainly to ICAM-1 and VCAM-1, whereas neutrophils attach to ICAM-1. While ICAM-1 and VCAM-1 are necessary for firm attachment of leukocytes to endothelium, PECAM-1 is involved in transmigration of leukocytes through the intercellular junction of endothelial cells (10). VCAM-1 is important for recruiting leukocytes to sites of inflammation because it mediates the adhesion of lymphocytes, monocytes, and eosinophils to endothelium (11).

Increased concentrations of VCAM-1 may reflect increased expression of this molecule on the endothelial surface. The expression of VCAM-1 on cells is regulated, at least in part, by multiple microenvironmental influences, such as changes in cytokine concentrations (12). For example, VCAM-1 expression on endothelial

cells is induced by interleukin-1, interleukin-4, tumor necrosis factor- , and interferon gamma (11).

Inflammation results in altered expression of cell adhesion molecules. Changes in the plasma concentration of soluble adhesion molecules usually reflect altered cell surface turnover and proteolytic cleavage. Therefore, their plasma concentrations have been used as markers of activation of each cellular component of the inflammatory process.

Elevated soluble vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 measurements during pregnancy can be considered as major risk factors. Elevated levels of these substances in the plasma of pregnant women with preeclampsia support the concept of a primary endothelial cell involvement in the pathogenesis of preeclampsia. Although currently based on a limited database, significantly elevated levels of soluble vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in the plasma of otherwise healthy pregnant women suggest a very high predictive value of these molecules for the earliest identification of women at risk of developing pre-eclampsia (13).

Previous studies of soluble adhesion molecules in the plasma of pre-eclamptic patients yielded conflicting results. Some studies reported an increase of sP-selectin, sE-selectin and sICAM-1 (14-16). While others reported no changes [17,18]. In contrast, all studies have reported an increase in sVCAM-1 (17,18,20,21). Two studies reported an increased plasma concentration of sPECAM-1 in pre-eclampsia (15,22).

Lyall et al. [23] reported that serum levels of VCAM-1 and E-selectin were not significantly different between normal and preeclamptic pregnancies. Chaiworapongsa et al. (24) suggested

that serum levels of ICAM-1 were no differences between normal and pre-eclamptic pregnancies.

Our findings indicate that severe preeclampsia, but not mild pre-eclampsia and normal pregnancy, was associated with a increase in sVCAM-1. Similar findings have been reported by other investigators (15,17,19,21). This observation is of considerable importance, because sVCAM-1 has a distinctive pattern of regulation and is rapidly induced by pro-atherosclerotic conditions (25). We interpret the elevation in sVCAM-1 in pre-eclampsia as evidence of endothelial cell activation/dysfunction and may be useful in predicting the severity of pre-eclampsia.

In one study Plasma sICAM-1 and sVCAM-1 were analyzed between weeks 22 and 29 of gestation in 1543 pregnant women and related to the outcome of pregnancy in a prospective longitudinal study. Plasma sVCAM-1 and sICAM-1 in uncomplicated pregnancies were normally distributed and varied over a small range. In contrast, of 177 pregnancies with complications (prevalence, 11.5%), 97 (55%) had sVCAM-1 or sICAM-1 concentrations above the same cutoffs weeks before the onset of disease. Therefore midgestation measurements of circulating sICAM-1 and sVCAM-1 have a high predictive value and may recognize up to 55% of pregnant women who will later develop a severe pregnancy-related complication (26).

Matsubara ,et al serially measured serum concentrations of sVCAM-1,TNFalpha, sICAM-1, soluble E-selectin (sE-selectin) and soluble P-selectin (sP-selectin) using enzyme immunoassay kits in 10 normal pregnant women and 10 pregnant women who developed PIH late in gestation. Serum TNFalpha, sICAM-1 and sE-selectin levels in PIH affected women were significantly higher from the first trimester compared with those in normal pregnancy. sVCAM-1 and sP-selectin levels were not significantly changed. He concludes that Serum TNFalpha, sE-selectin and sICAM-1 levels might be effective indicators of the onset of PIH (27).

Phocas and et al show a selective significant elevation of maternal serum sVCAM-1 in preeclampsia, with the highest values in cases complicated with fetal growth restriction, perhaps reflecting its angiogenic function. Hence, sVCAM-1 could be helpful in the diagnosis of this fetal complication in pre-eclampsia (28).

Kim et al studied the serum levels of sVCAM-1, sICAM-1 and sE-selectin in normal pregnant women ,mild and severe pre-eclampsia . Serum concentrations of sVCAM-1 were significantly higher in both mild (P=0.004) and severe pre-eclampsia (P=0.000) than normal pregnancy. There were also significant differences in sVCAM- 1 levels between mild and severe pre-eclampsia (P=0.002). sICAM-1 levels of severe pre-eclampsia were statistically different from those of normal pregnancy (P=0.038). These results recommend that all three soluble adhesion molecules are increased in severe preeclampsia, and sVCAM-1 among them may be useful in predicting the severity of preeclampsia (29).

Acknowledgments

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