A comparative study of vascular cell adhesion molecule-1 and high-sensitive C-reactive protein in normal and preeclamptic pregnancies

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Abstract: *Background:* Preeclampsia is characterized by hypertension, dyslipidemia, and systemic inflammatory response. The aim of this study was to determine the level of serum level of soluble vascular cell adhesion molecule-1 (sVCAM-1) and high-sensitive C-reactive protein (hsCRP) in preeclampsia and to compare normal pregnant, mild preeclamptic, and severe preeclamptic women. *Methods:* A cross-sectional study was conducted to determine the plasma concentrations of sVCAM-1 and hsCRP in peripheral blood obtained from normal pregnant ($n = 40$), mild preeclamptic ($n = 37$), and severe preeclamptic women ($n = 38$). A concentration of soluble adhesion molecule was determined with enzyme-linked immunosorbent assay. hsCRP was measured with immunoturbidometric. *Results:* There was significant difference in the means serum hsCRP between normal pregnant women and mild preeclamptic women ($P < 0.05$). Serum concentration of hsCRP and sVCAM-1 (ng/mL) were significantly higher in severe preeclampsia ($P < 0.05$) than normal pregnancy. There were also significant differences in hsCRP and sVCAM-1 levels between mild and severe ($P < 0.05$). There was no difference in the mean sVCAM-1 between normal pregnant and mild preeclamptic women. *Conclusion:* We have determined the serum concentration of VCAM-1 and hsCRP in normal pregnancy and preeclampsia. sVCAM-1 is elevated in severe preeclampsia compared with normal pregnancy, and hsCRP is elevated in severe preeclampsia compared with mild preeclampsia and normal pregnancy.

Keywords: preeclampsia, soluble vascular cell adhesion molecule-1 (sVCAM-1), high-sensitive C-reactive protein (hsCRP), normal pregnancies, systemic inflammatory response

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 preeclampsia [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].

Preeclampsia (PE) develops in 4–5% of human pregnancies. It is characterized by an elevated blood pressure and proteinuria and develops after 20 weeks of gestational age. PE can result in eclampsia when convulsions develop or manifest as the hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Several etiologies have been implicated in the development of preeclampsia. Some of them include abnormal trophoblast invasion of uterine blood vessels, immunological intolerance between fetoplacental and maternal tissues, maladaptation to the cardiovascular changes or dietary deficiencies, and genetic abnormalities [5].

Adhesion molecules such as soluble vascular cell adhesion molecule-1 (sVCAM-1) 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 inplasma, and their concentrations are thought to reveal the degree of activation of a particular cell type. Increase in soluble forms of sVCAM-1 and soluble forms of intercellular adhesion molecule-1 (sICAM-1) indicate endothelial cell activation/dysfunction.

C-reactive protein (CRP) is a marker of systemic inflammation [6]. It has been shown that CRP is elevated in women with PE [7].

High-sensitive (hs) CRP is a protein measured by either antibodies that are labeled with an enzyme (ELISA) or a fluorescent compound or antibody-coated polystyrene beads. Determination of hsCRP has been suggested to be more sensitive than conventional measurement of CRP and provides better sensitivity in confirmation of inflammation [8, 9].

Therefore, the objective of this study was to determine whether normal pregnancy and preeclampsia were associated with changes in the concentrations of sVCAM-1 and hsCRP.

Materials and Methods

A cross-sectional study was designed to compare the plasma concentration of vascular cell adhesion molecule-1 and high-sensitive CRP in peripheral blood obtained from normal pregnantwomen and pregnant patients with preeclampsia at the Departments of Obstetrics and Gynecology of the Ghaem academic 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-h urine collection or one dipstick measurement ≥1+) according to the Committee of Terminology of ACOG definition [10].

Severe preeclampsia was diagnosed on the basis of diastolic blood pressure ≥110 mmHg or significant proteinuria (dipstick measurement of G2+) 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 preeclampsia, 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).

All patients had delivery under supervision of same gynecologist in Ghaem Academic Hospital and all of them had vaginal delivery. Venipuncture was performed, and the blood was collected into tubes containing ethylenediamine-tetraacetic acid (EDTA).

The patient's serum samples stored at –20 °C until assay (collected blood samples were centrifuged at 1500 *g* for 10 min and stored at –20 °C). The concentrations of soluble adhesion molecules were measured using enzyme-linked immunoassays (Bender Med system, Human sVCAM-1, BM232, Austria). In all patients and normal pregnant women, serum hsCRP level was measured with immunoturbidometric assay (Diagnostica Kit, Germany).

The sensitivity of the assay for sVCAM-1 was 0.63 ng/mL. The inter- and intra-assay coefficients of variation were 7.66% and 4.1%, respectively, for sVCAM-1.

The lowest limit of detection was 0.1 mg/L. The maximum inter- and intra-assay coefficients of variation for the range of concentrations evaluated were 3.5% for hsCRP.

Statistics

The one-way ANOVA and for post-hoc comparisons (Tukey) were used for comparison of proportions. Normal distribution was tested by Kolmogorov–Smirnov. A level of $P<0.05$ was regarded as statistically significant.

Results

This study included 40 normal pregnant women and 75 pregnant women with preeclampsia (37 mild preeclampsia and 38 severe preeclampsia). *Table I* and *II* list the clinical and laboratory characteristics of the three study groups.

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

In addition, hsCRP was detected in all specimens. There was a significant difference in the mean hsCRP between normal pregnant women and mild preeclamptic women (6.7±2 mg/L vs. 9.2±7.1 mg/L, $P<0.05$). Patients with severe preeclampsia had a significantly higher means plasma levels (12.8±7.3 mg/L) than normal pregnant and mild preeclamptic women ($P<0.05$).

Discussion

Preeclampsia is characterized by hypertension, dyslipidemia, and increased systemic inflammatory response and has been associated with an increased maternal risk of cardiovascular disease later in life [11].

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

Variable \ Groups	Normal pregnant (n=40)	Mild preeclampsia (n=37)	Severe preeclampsia (n=38)	P	P_a	P_b
Age (year)	24.6±4.2	27.4±6.4	26.1±5.8	NS	NS	NS
Gestational age at blood sampling and delivery time	37.1±2	35.7±4	32.7±5.6	NS	0.02*	<0.0001*
Maternal body weight	71.4±10.4	77±12.5	71.1±11.4	NS	NS	NS
Body mass index (kg/m^2)	22.1±1.9	23.05±2.0	22.95±1.86	NS	NS	NS
Birth weight (kg)	2.6±0.7	2.3±0.68	2.1±0.97	NS	NS	<0.05*
Blood pressure						
Systolic (mmHg)	111±14	149.1±15	154.7±19.7	<0.001*	NS	<0.001*
Diastolic (mmHg)	63±12	92±12	107.6±14.8	<0.001*	<0.001*	<0.001*
sVCAM-1 (ng/mL)	971.3±253	1019±288	1240±553	NS	<0.05*	<0.05*
hsCRP (mg/L)	6.7±2.0	9.2±7.1	12.8±7.3	<0.05*	<0.05*	<0.05*

P=comparison between normal pregnant and mild preeclampsia;
P_a=comparison between women with mild and severe preeclampsia;
P_b=comparison between normal pregnant and severe preeclampsia;
*=statistically significant, P<0.05; NS=non-significant

In recent years, endothelial dysfunction has emerged as the leading phenomenon responsible for the clinical signs of the disorder [12, 13].

Pathogenesis of preeclampsia is thought to be resulted from generalized endothelial dysfunction [14]. Recently, increased levels of cell adhesion molecules are believed to be indicators of endothelial dysfunction in preeclampsia [2].

Observational and experimental studies have demonstrated an association between inflammation and endothelial dysfunction [15, 16].

Previous studies of soluble adhesion molecules in the plasma of preeclamptic patients yielded conflicting results [17]. Some studies reported an increase of sP-selectin, sE-selectin, and sICAM-1 [18–20]. While others reported no changes [21, 22]. In contrast, all studies have reported an increase in sVCAM-1 [21–24].

Two studies reported an increased plasma concentration of sPECAM-1 in preeclampsia [18, 25]. Lyall et al. [21] reported that serum levels of VCAM-1 and E-selectin were not significantly different between normal and preeclamptic pregnancies. Chaiworapongsa et al. [26] suggested that serum levels of ICAM-1 have no differences between normal and preeclamptic pregnancies.

Our findings indicate that severe preeclampsia, but not mild preeclampsia and normal pregnancy, was associated with an increase in sVCAM-1. Similar findings have been reported by other investigators [18, 21, 23, 27].

This observation is of considerable importance because sVCAM-1 has a distinctive pattern of regulation and israpidly induced by pro-atherosclerotic conditions [28]. We interpret the elevation in sVCAM-1 in preeclampsia as evidence of endothelial cell activation/dysfunction and may be useful in predicting the severity of preeclampsia.

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 sICAM-1 and sVCAM-1 in uncomplicated pregnancies were normally distributed and varied over a small range. In contrast, out of 177 pregnancies with complications (with a prevalence of 11.5%), 97 (55%) had sICAM-1 or sVCAM-1 concentrations above the same cutoffs weeks before the onset of disease. Therefore, mid-gestation 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 [29].

Early enhanced activation of endothelial cells, platelets, and leukocytes seems to be present in preeclamptic patients, especially in those that develop severe preeclampsia [30]. There is increasing evidence that preeclampsia is a systemic inflammatory disease [31]. CRP is responsible for the clearance of membranes and nuclear [4, 7, 31] antigens and acts as a scavenger [32].

Some reports have shown that elevated CRP levels during first trimester of pregnancy are indicative of preeclampsia [33], but another study reported that serum levels of CRP at 23–25 weeks of gestation were similar in pregnant women who subsequently developed preeclampsia and in women without complications of pregnancy [34].

Although normal pregnancy is associated with increased pro-inflammatory markers, it has been suggested that the cause of serum hsCRP elevation in the preeclamptic women may be as a result of reduced plasma volume in these patients [31, 32].

The relationship of CRP levels and preeclampsia has already been studied and higher concentration of CRP has been reported during preeclampsia [7, 35]. It has al-

Table II ‖ The laboratory characteristics of patients with preeclampsia

Test \ Group	Normal pregnancy ($n=40$)	Mild preeclampsia ($n=37$)	Severe preeclampsia ($n=38$)	P	P_a	P_b
BUN (mg/dL)	23.5±11.5	25.0±14	25.7±12	NS	NS	NS
Bilirubin						
Total (mg/dL)	0.59±0.30	0.7±0.20	0.87±0.45	NS	NS	NS
Direct (mg/dL)	0.19±0.12	0.26±0.11	0.31±0.17	NS	NS	NS
Creatinine (mg/dL)	0.6±0.17	0.62±0.18	0.72±0.24	NS	NS	NS
Blood glucose (mg/dL)	84.2±16.1	83.2±15.5	88.0±20.3	NS	NS	NS
Uric acid (mg/dL)	4.2±1.21	5.81±1.37	6.29±1.54	NS	NS	NS
Hb (g/dL)	12.1±1.42	11.92±1.39	12.47±1.61	NS	NS	NS
Hematocrit (%)	38.1±3.89	37.00±3.93	38.16±5.31	NS	NS	NS
Platelets (cell/μL (mm^3))	210150±85135	208217±95180	191120±142383	NS	NS	NS
AST(U/L)	12.35±8.37	22.26±10.63	36.92±28.57	<0.05*	<0.05*	<0.05*
ALT(U/L)	10.48±6.01	18.39±7.09	31.24±25.28	<0.05*	<0.05*	<0.05*
Urine protein(g/L)	0.81±0.86	1.10±1.96	2.26±2.60	<0.05*	<0.05*	<0.05*

There was no statistically significant difference in BUN, bilirubin, creatinine, blood glucose, uric acid, Hb, hematocrit, and platelet between mild and severe preeclampsia, while AST, ALT, and urine protein were significantly different between two groups ($P<0.05$).
P=comparison between normal pregnant and mild preeclampsia;
P_a=comparison between women with mild and severe preeclampsia;
P_b=comparison between normal pregnant and severe preeclampsia;
*=statistically significant, $P<0.05$; NS=non-significant

so been shown that women with a history of preeclampsia had increased CRP levels [36].

In our study, levels of hsCRP were found to be significantly higher in women with mild and severe preeclampsia than in normotensive women with similar chronological age.

Belo et al. found significantly higher levels of CRP in preeclampsia but statistical significance was lost after adjustment for maternal weight [37]. Üstün et al. showed that level of CRP to be significantly higher in women with mild and severe preeclampsia than in normal pregnant women with similar chronological age, gestational age, and body mass index [38].

Although inflammation may not be the exact cause of preeclampsia, it may enhance the pathology of the disorder in the presence of the anti-angiogenic factors [12].

Hwang et al. showed that hsCRP levels were positively correlated to pregnancy duration in healthy women and could be used as a severity marker in women with severe PE [9]. In 2011, Can et al. found that in severe preeclampsia group, hsCRP levels were significantly higher than mild preeclamptic and normotensive groups [39].

There are also some studies concerning CRP levels due to severity of preeclampsia [40]. In these studies, it has been shown that CRP levels were positively related to the degree of blood pressure elevation. In our study, we found significantly higher levels of hsCRP in severe preeclampsia than mild preeclampsia.

Conclusion

We have determined the serum concentration of soluble adhesion molecule VCAM-1 and hsCRP in normal pregnancy and preeclampsia. sVCAM-1 is elevated in severe preeclampsia compared with normal pregnancy, and hsCRP is elevated in severe preeclampsia compared with mild preeclampsia and normal pregnancy and may be useful in predicting the severity of preeclampsia. The clinical validity of the monitoring of hsCRP needs to be established infurther longitudinal studies.

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Conflict of Interest Statement

The authors indicate no potential conflicts of interest.

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