INTRODUCTION

Preeclampsia is a condition unique to human pregnancy. Occurring in 5-7% of pregnancies, it is the major cause of maternal and perinatal morbidity and mortality, but the pathogenesis of this disorder has not been clearly established.

Recently, an excessive maternal systemic inflammatory response to pregnancy has been proposed to be responsible for endothelial dysfunction leading to cellular activation and/or damage (1). Endothelial dysfunction is considered to be central in the pathogenesis of preeclampsia (2, 3). The inflammatory process is the adhesion of leukocytes to endothelial cells followed by transmigration of these cells into perivascular tissue. Leukocyte endothelial adhesion is governed largely by the interaction of adhesion molecules and their ligands on these cells. A number of the molecules which mediate leukocyte-endothelial adhesion have been identified; these include vascular cellular adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1) and E-selectin (4-6). In vitro studies have shown that the expression of these molecules on the endothelial surface is tightly regulated, and that this regulation may have a crucial role in the nature of leukocyte recruitment during the course of an inflammatory response (7).

Soluble forms of these molecules may be released to the circulation, and increased serum levels of these molecules may indicate endothelial dysfunction (8). Interestingly, several studies have reported that levels of these adhesion molecules appeared to be increased in the serum of pregnant women with preeclampsia (9-11). Indeed, abnormal levels of these adhesion molecules may be considered to be markers of preeclampsia (9). However, reports are not always in agreement. Lyall et al. (12) reported that serum levels of VCAM-1 and E-selectin were not significantly different between normal and preeclamptic pregnancies. Chaiworapongsa et al. (13) suggested that serum levels of ICAM-1 were no differences between normal and preeclamptic pregnancies.

In the present study, we compared the levels of soluble vascular cell adhesion molecule-1 (sVCAM-1), intercellular adhesion molecule-1 (sICAM-1) and E-selectin (sE-selectin) in sera of normal and preeclamptic pregnancies. We studied the serum levels of sVCAM-1, sICAM-1 and sE-selectin in normal pregnant women (n=63), mild preeclampsia (n=33) and severe preeclampsia (n=82). Concentrations of soluble adhesion molecules were determined with enzyme-linked immunoassay (ELISA). Serum concentrations of sVCAM-1 were significantly higher in both mild (p=0.004) and severe preeclampsia (p<0.000) than normal pregnancy. There were also significant differences in sVCAM-1 levels between mild and severe preeclampsia (p=0.002). sICAM-1 levels of severe preeclampsia were statistically different from those of normal pregnancy (p=0.038). Levels of sE-selectin were elevated in both mild (p=0.011) and severe preeclampsia (p=0.000) compared to normal pregnancy, but no statistical difference between the mild and severe preeclampsia (p=0.345). These results suggest 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.

Key Words: Preeclampsia; Cell Adhesion Molecules; Vascular Cell Adhesion Molecule-1, Interstitial Adhesion Molecule-1, E-Selectin

MATERIALS AND METHODS

Study subjects

The study population consisted of 63 women with normal pregnancy, 33 women with mild preeclampsia, and 82 women...
with severe preeclampsia. The clinical characteristics of the study groups are shown in Table 1. Cases complicated by chronic hypertension, diabetes, chronic renal disease and autoimmune disorders were not included in the study. 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 (14).

Severe preeclampsia was diagnosed on the basis of diastolic pressures being ≥ 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.

**Table 1. Clinical characteristics of normal pregnancy (NP), mild preeclampsia (MPE) and severe preeclampsia (SPE)**

| Characteristics                  | NP (n=63) | MPE (n=33) | SPE (n=82) | p   | p*   | p'   |
|----------------------------------|-----------|------------|------------|-----|------|------|
| Maternal age (yr)                | 30.8±3.0  | 29.8±3.6   | 30.8±4.0   | 0.558 | 1.000 | 0.551 |
| Gestational age at delivery (wk) | 39.2±1.0  | 37±2.9     | 35.3±4.2   | 0.005 | 0.000 | 0.041 |
| Birth weight (g)                 | 3372.2±382.3 | 2654.4±618.5 | 2167.3±855.4 | 0.000 | 0.000 | 0.024 |
| Maximum systolic blood pressure (mm Hg) | 127.9±10.5 | 147.3±17.3 | 162.8±15.9 | 0.000 | 0.000 | 0.036 |
| Maximum diastolic blood pressure (mm Hg) | 76.8±9.6 | 95.3±10.9 | 110.1±12.7 | 0.000 | 0.000 | 0.015 |
| Platelet count (x 10^3) (µL)     | 242.3±47.2 | 236.6±76.7 | 227.9±82.6 | 1.000 | 0.699 | 1.000 |

Data are given as mean±SD and were analyzed by ANOVA with multiple comparisons using the Bonferroni correction method. p, comparison between normal pregnancy and mild preeclampsia; p*, comparison between normal pregnancy ad severe preeclampsia; p', comparison between mild and severe preeclampsia.

**RESULTS**

The clinical characteristics of the study groups are summarized in Table 1. There were no differences in the maternal age and platelet count among three groups. The gestational ages at delivery (p=0.005 for mild preeclampsia; p=0.000 for severe preeclampsia) and birth weights of the newborns (p=0.000) were significantly different between normal pregnancy and preeclampsia groups. As expected, the blood pressures were significantly higher in the preeclampsia groups than in normal pregnancy (p=0.000, respectively).

The serum concentrations of soluble adhesion molecules are shown in Fig. 1. Level of sVCAM-1 was significantly higher in both mild (960.71±364.7 ng/mL, p=0.004) and severe preeclampsia (1,576.75±451.5 ng/mL, p=0.000) compared with normal pregnancy (570.33±222.56 ng/mL) (Fig. 1A). Serum levels of sICAM-1 were not different statistically between the mild preeclamptic pregnancies (282.38±121.14 ng/mL, p=0.181) and normal pregnancies (243.27±57.56 ng/mL), but the concentration was higher in severe preeclampsia (291±108.73 ng/mL, p=0.038) compared with normal pregnancy (Fig. 1B). For sE-selectin level, the mean value was significantly elevated in both mild (52.40±27.42 ng/mL, p=0.011) and severe preeclampsia (61.94±36.8 ng/mL, p=0.000) compared with normal pregnancy group (33.94±16) (Fig. 1C). In preeclampsia groups, levels of sICAM-1 and sE-selectin were not different statistically between mild and severe preeclamptic pregnancies (p=1.000 for sICAM-1; p=0.345 for sE-selectin). Only sVCAM-1 level was different significantly between the mild and severe preeclampsia (p=0.002).
DISCUSSION

Preeclampsia is a pregnancy-specific disorder that is clinically characterized by hypertension, proteinuria and edema which remits after delivery. Despite the still unexplained pathogenesis, preeclampsia is thought to be resulted from generalized endothelial dysfunction (15). Recently, increased levels of cell adhesion molecules are believed to be indicators of endothelial dysfunction in preeclampsia (16). The cell adhesion molecules play a role in leukocyte-endothelial interaction and are divided into three groups according to their structure: selectins, integrins and members of the immunoglobulin gene superfamily. The selectins mediate the early steps ("rolling") of leukocyte adhesion to activated endothelial cell, while integrins and the immunoglobulin gene superfamily regulate the subsequent steps (firm adhesion followed by transmigration) (17).

VCAM-1 is a cell adhesion molecule and a member of the immunoglobulin superfamily (18). VCAM-1 has a single chain glycoprotein structure and functions as a transmembrane receptor in vascular endothelial cell membranes. VCAM-1 is present on a number of activated cells, including activated endothelial cells. 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 (19). For example, VCAM-1 expression on endothelial cells is induced by interleukin-1, interleukin-4, tumor necrosis factor-α, and interferon gamma (20). VCAM-1 is important for recruiting leukocytes to sites of inflammation because it mediates the adhesion of lymphocytes, monocytes, and eosinophils to endothelium (20). Our results indicated that circulating sVCAM-1 levels were significantly increased in severe preeclampsia compared with mild preeclampsia or normal pregnancy. Lyall et al. (21) were the first to show that sVCAM-1 was elevated in the serum of preeclamptic patients. Krauss et al. (9) also found significantly elevated levels of VCAM-1 in the plasma of pregnant women who subsequently developed preeclampsia, 3-15 weeks earlier before the onset of clinical symptoms. In contrast to these reports, Haller et al. (22) reported that ICAM-1 expression was increased in serum from preeclamptic patients but VCAM-1 expression was not.

ICAM-1 is a member of the immunoglobulin superfamily that mediates its functional activity through binding to leukocyte β2-integrins (23). The ICAM-1 molecule is functionally involved in the regulation of adhesion of leukocytes to the endothelium as well as leukocyte migration (24). The molecule expression is also essential for MHC (main histocompatibility complex) and non-MHC restricted cytotoxicity, interactions between T and B lymphocytes, and mitogen and antigen-induced lymphocyte proliferation (25). The shed soluble form (sICAM) is also present in plasma and interferes as a regulatory factor in ICAM-1/β2-integrin interactions (25). In this study, sICAM-1 levels were elevated in severe preeclamp-
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