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The Profiles of Soluble Adhesion Molecules in the "Great Obstetrical Syndromes"

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Abstract

Objective—The objective of this study was to determine the profiles of maternal plasma soluble adhesion molecules in patients with preeclampsia, small-for-gestational-age (SGA) fetuses, acute pyelonephritis, preterm labor with intact membranes (PTL), preterm prelabor rupture of the membranes (preterm PROM), and fetal death.

Materials and methods—A cross-sectional study was conducted to determine maternal plasma concentrations of sE-selectin, sL-selectin, and sP-selectin as well as sICAM-1, sVCAM-1, and sPECAM-1 in patients with 1) an uncomplicated pregnancy (control, n=100); 2) preeclampsia (n=94); 3) SGA fetuses (in women without preeclampsia/hypertension, n=45); 4) acute pyelonephritis (n=25); 5) PTL (n=53); 6) preterm PROM (n=24); and 7) fetal death (n=34). Concentrations of soluble adhesion molecules and inflammatory cytokines (tumor necrosis factor

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(TNF)-α and interleukin (IL)-8) were determined with sensitive and specific enzyme-linked immunoassays.

Results—In comparison to women with a normal pregnancy, 1) women with preeclampsia had higher median concentrations of sE-selectin, sP-selectin, and sVCAM-1, and a lower concentration of sL-selectin (all p-values <0.001); 2) patients with SGA fetuses had higher median concentrations of sE-selectin, sP-selectin, and sVCAM-1 (all p-values <0.05); 3) patients with a fetal death had higher median concentrations of sE-selectin and sP-selectin (all p-values <0.05); 4) patients with acute pyelonephritis had higher median plasma concentrations of sE-selectin, sICAM-1, and sVCAM-1 (all p-values < 0.001); 5) patients with preeclampsia and acute pyelonephritis, plasma concentrations of sVCAM-1, sE-selectin, and sP-selectin correlated with those of the pro-inflammatory cytokines TNF-α and interleukin (IL)-8 (all p-values <0.05); 6) patients with PTL had a higher median concentration of sP-selectin and a lower median concentration of VCAM-1 (all p-values <0.05); and 7) women with preterm PROM had lower median concentrations of sL-selectin and sVCAM-1 (all p-values <0.05).

Conclusions—The results of this study show that endothelial cell activation/dysfunction reflected by the plasma concentration of sE-selectin is not specific to preeclampsia but is present in pregnancies complicated by SGA fetuses, acute pyelonephritis, and fetal death. Collectively, we report that each obstetrical syndrome appears to have a stereotypical profile of soluble adhesion molecules in the peripheral circulation.

Keywords

preeclampsia; preterm labor; prelabor rupture of the membranes (PROM); pyelonephritis; small-for-gestational–age fetus

Introduction

Normal pregnancy is characterized by systemic intravascular inflammation as evidenced by phenotypic and functional activation of circulating granulocytes and monocytes measured by flow cytometry (1, 2) and also by an increase in plasma/serum concentrations of acute phase reactant proteins such as C-reactive protein (3, 4), fibrinogen (5–7), and complement split products (8–10). Central to the inflammatory process is endothelial activation (increased adhesion of endothelial cells to leukocytes), which may lead to endothelial cell dysfunction (decreased synthesis, release, and/or activity of endothelium-derived nitric oxide) (11–15). Changes of the endothelium in response to inflammation modify the leukocyte adhesion cascade, allowing leukocytes to attach to the endothelium and, subsequently, to transmigrate into the perivascular tissue (11, 13, 15–21).

Leukocyte-endothelial cell interactions are mainly mediated by cell adhesion molecules comprised of three families (selectins, integrins, and members of the immunoglobulin gene superfamily) (11, 13, 15–27). Pro-inflammatory cytokines change the expression of cell adhesion molecules that subsequently results in their shedding from the endothelium, leukocytes, or platelets (16, 22, 25, 28). Therefore, the soluble forms can be detected in the peripheral blood *in vivo* and in the supernatant during *in vitro* studies. The plasma

concentrations of these soluble adhesion molecules have been used as markers of endothelial, platelet, and leukocytic activation (29–32).

Intravascular inflammation is observed in the “great obstetrical syndromes,” which includes preeclampsia (1, 33–39), small-for-gestational-age (SGA) fetuses (40–48), acute pyelonephritis (2, 49–51), preterm labor with intact membranes (PTL) (52–54), and preterm prelabor rupture of the membranes (preterm PROM) (53–55). Previous studies have shown conflicting results about the profile of soluble adhesion molecules in preeclampsia (31, 32, 41–46, 56–110). Moreover, conclusions about the behavior of adhesion molecules require a comprehensive study of several obstetrical syndromes to ensure that changes are specific to each disease state. For example, the claim that preeclampsia is associated with endothelial cell activation based on an increase in plasma concentration of sE-selectin (31, 32, 43–45, 59, 62, 65, 68, 70, 71, 77, 80–82, 90, 94, 97, 103, 105, 110) would need to be revisited if similar findings could be observed in other obstetrical complications.

Therefore, this cross-sectional study was undertaken to determine whether the profiles of maternal plasma soluble adhesion molecules differ among patients with preeclampsia, SGA fetuses, acute pyelonephritis, PTL, preterm PROM, and fetal death.

Materials and Methods

Study design

A retrospective cross-sectional study was conducted. All samples were obtained from the Bank of Biological Materials of Wayne State University, the Detroit Medical Center, and the Perinatology Research Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (Detroit, MI). All patients were enrolled in the Labor and Delivery Unit or in the antenatal clinic at Hutzel Women’s Hospital (Detroit, MI). Women with the following characteristics were included: 1) normal pregnancy (n=100); 2) preeclampsia (n=94); 3) SGA fetuses (in women without preeclampsia/hypertension, n=45); 4) acute pyelonephritis (n=25); 5) PTL (n=53); 6) preterm PROM (n=24); and 7) fetal death (n=34). Women with multiple gestations and pregnancies affected by fetal chromosomal and/or structural anomalies were excluded. A subset of patients in this current study was included in a prior study (77).

All patients provided written informed consent, and the use of biological specimens and clinical data for research purposes was approved by the Institutional Review Boards of Wayne State University and NICHD.

Clinical definitions

Women who had a normal pregnancy met the following conditions: 1) venipuncture samples obtained between 20–42 weeks of gestation; 2) no medical, obstetrical, or surgical complications; and 3) delivery of a normal term (≥37 weeks of gestation) infant whose birth weight measured between the 10^{th} and 90^{th} percentiles for gestational age (114, 115).

Preeclampsia was defined as new-onset hypertension that developed after 20 weeks of gestation (systolic and/or diastolic blood pressure of ≥140 and/or ≥90 mmHg; measured on

at least two occasions, 4 hours to 1 week apart) and proteinuria (≥300 mg in a 24-hour urine collection, or two random urine specimens obtained 4 hours to 1 week apart containing ≥1+ protein by dipstick) (111). Severe preeclampsia was diagnosed according to criteria proposed by the American Congress of Obstetricians and Gynecologists (ACOG) (111, 112). Early-onset preeclampsia and late-onset preeclampsia were defined as cases diagnosed before and after 34 weeks of gestation, respectively (113).

An SGA fetus was defined as having a neonatal birth weight <10th percentile for gestational age (114). Patients with SGA fetuses were classified according to the umbilical artery Doppler velocimetry result (SGA fetus with an absent end-diastolic velocimetry (AEDV) and SGA fetus without an AEDV).

Acute pyelonephritis was diagnosed in the presence of fever (temperature ≥38°C), clinical signs or symptoms of an upper urinary tract infection (e.g., flank pain, costovertebral angle tenderness), pyuria, and a positive urine culture for microorganisms (115, 116). Women with acute pyelonephritis were classified as follows: 1) acute pyelonephritis with a positive urine culture only (without bacteremia) and 2) acute pyelonephritis with positive blood and urine cultures (with bacteremia).

Preterm labor with intact membranes was defined as the presence of premature uterine contractions leading to cervical changes and resulting in preterm delivery. Preterm PROM was diagnosed as amniorrhexis in a preterm gestation leading to preterm delivery. Fetal death was defined as death of the fetus after 20 weeks of gestation, confirmed by ultrasound (all fetal deaths were unexplained).

Sample collection and immunoassay

Venipuncture was performed upon the diagnosis of each pregnancy complication or upon enrollment at 20–42 weeks of gestation for women who had an uncomplicated pregnancy. Blood was collected in tubes containing EDTA. Following centrifugation, samples were stored at −70°C. The concentrations of soluble adhesion molecules were measured using an enzyme-linked immunosorbent assay (ELISA). The plasma concentrations of TNF-α and IL-8 were also determined using sensitive and specific immunoassays. All immunoassay kits were purchased from R&D Systems (Minneapolis, MN, USA), except sPECAM-1, which was purchased from Diaclone Research (Cedex, France). Table 1 displays the sensitivity and the inter-assay and intra-assay coefficients of variation for each assay.

Doppler velocimetry of the uterine and umbilical arteries

Pulse-wave and color Doppler ultrasound (Acuson, Sequoia, Mountain View, CA, USA) examinations of the uterine and umbilical arteries were performed by trained personnel for a subset of patients at the time of diagnosis of an SGA fetus. Uterine artery Doppler velocimetry was defined as abnormal if the mean resistance index (average of right and left) was above the 95th percentile for gestational age (117). Umbilical artery Doppler velocimetry was defined as abnormal if either the pulsatility index (PI) was above the 95th percentile for gestational age (118) or if waveforms were abnormal (absent or reverse end-diastolic velocities) (119). The inter- and intra-observer coefficients of variation of the

umbilical and uterine arteries were 0.81 (for both arteries), and 0.85 (umbilical artery) and 0.91 (uterine artery), respectively.

Statistical analysis

Normality of continuous variables was assessed using the Kolmogorov-Smirnov test and visual inspection of histograms. The chi-square test was used to evaluate the differences in proportions. Spearman's rank correlation coefficients were used to determine the relationship between the plasma soluble adhesion molecules and the plasma pro-inflammatory cytokine concentrations. For concentrations below the detection limit, 99% of the lowest detectable concentration across all samples was used. Group-level differences in concentrations were evaluated using the Kruskal-Wallis test, and pairwise comparisons were performed using the Mann-Whitney U test. An alternative analysis was performed using linear models with adjustment for gestational age at sampling. A p-value of <0.05 was considered significant. Analysis was performed using the R statistical language and environment (www.r-project.org).

Results

Clinical characteristics of the study population

The demographic, clinical, and obstetrical characteristics of the study population are displayed in Table 2. The median maternal age, rate of nulliparity, ethnicity, and median gestational age at sample collection and at delivery, as well as birth weight, differed among the study groups ($p<0.05$ for all comparisons).

Among patients with preeclampsia, 76% (71/94) had preterm preeclampsia, 50% (47/94) had early-onset preeclampsia, and 38% (36/93) had preeclampsia with an SGA neonate. The rate of bacteremia was 52.2% (12/23) and the most common microorganism identified was *Escherichia coli* (7/12).

The soluble adhesion molecules, except sICAM-1, were detected in the maternal plasma of all patients. Soluble ICAM-1 was undetectable in 14 (3.7%) samples. Among women with uncomplicated pregnancies, maternal plasma sP-selectin, sL-selectin, sICAM-1, and sPECAM-1 did not correlate with gestational age at sampling (all p-values >0.05).

Plasma soluble adhesion molecules in patients with preeclampsia

The median maternal plasma concentrations of sE-selectin, sP-selectin, and sVCAM-1 were significantly higher among patients with preeclampsia compared to those with a normal pregnancy [preeclampsia (ng/mL): sE-selectin: 64.2 (46.1–81.4); sP-selectin: 116.2 (92.6–156.8); and sVCAM-1: 744.1 (641.1–986.7) versus normal pregnancy (ng/mL): sE-selectin: 45.1 (33.9–53.3); sP-selectin: 92.6 (72.4–111.1); and sVCAM-1: 507.8 (451.8–593.7); all p-values <0.001]. Additionally, patients with preeclampsia had a significantly lower median plasma sL-selectin concentration (ng/mL) compared to the controls [559.3 (444.9–671.2) versus 669.7 (583.4–830.4); p-value <0.001]. The median plasma concentrations of sICAM-1 and sPECAM-1 did not change significantly between these two groups (all p-values ≥ 0.05) (Table 3A, Table 4, and Figures 1–6 and Supplementary Figure S1).

There were no significant differences in the median plasma concentration of soluble adhesion molecules among patients with preeclampsia based on the severity of preeclampsia (all p-values ≥0.05) (please see Supplementary material). The median plasma sE-selectin, sP-selectin, and sVCAM-1 concentrations in patients with preeclampsia were positively correlated with the plasma concentrations of the liver enzyme serum glutamic oxaloacetic transaminase (SGOT) [sP-selectin: Spearman's rho=0.22, p-value=0.04; sE-selectin: Spearman's rho=0.24, p-value =0.03; and sVCAM-1: Spearman's rho=0.30, p-value =0.007]. By contrast, the plasma sVCAM-1 concentration had a significantly negative correlation with the platelet count [Spearman's rho= −0.24, p-value=0.02).

Plasma soluble adhesion molecules in patients with small-for-gestational-age fetuses

The median maternal plasma concentrations of sE-selectin, sP-selectin, and sVCAM-1 were significantly higher in patients with SGA neonates compared to those with normal pregnancies [women with SGA neonates (ng/mL): sE-selectin: 54.5 (36.8–76.8); sP-selectin: 121.5 (94.1–145.4); and sVCAM-1: 595.3 (510.5–719.7) versus normal pregnancy (ng/mL): sE-selectin: 45.1 (33.9–53.3); sP-selectin: 92.6 (72.4–111.1); and sVCAM-1: 507.8 (451.8–593.7); all p-values <0.05]; (Table 3A, Table 4, and Figures 1–6, Supplementary Figure S2). However, the median plasma concentrations of sL-selectin, sICAM-1, and sPECAM-1 did not differ significantly between patients with SGA fetuses and those with normal pregnancies (all p-values ≥0.05). Among SGA patients, the median plasma concentration of sVCAM-1 was increased in those who had an AEDV than in patients without an AEDV, but this difference failed to reach statistical significance [SGA with AEDV: 670.1 (629.2–719.7) versus SGA without AEDV: 566.3 (460.6–730.2); p=0.05]. Moreover, a plasma sVCAM-1 concentration had a significant positive correlation with the mean uterine artery resistant index (RI) [Spearman's rho=0.5; p-value <0.03].

Plasma soluble adhesion molecules in patients with a fetal death

Patients with a fetal death had higher median maternal plasma concentrations of sE-selectin and sP-selectin than women with normal pregnancies [fetal death (ng/mL): sE-selectin: 53.3 (37.2–64.0); sP-selectin: 119.2 (86.3–171.2) vs. normal pregnancy (ng/mL): sE-selectin: 45.1 (33.9–53.3); and sP-selectin: 92.6 (72.4–111.1); all p-values <0.05]. No significant differences were observed in the median concentrations of sL-selectin, sVCAM-1, sICAM-1, and sPECAM-1 between patients with a fetal death and a normal pregnancy (Table 3A, Table 4, and Figures 1–6, Supplementary Figure S3).

Plasma soluble adhesion molecules in patients with acute pyelonephritis

Patients with acute pyelonephritis had higher median plasma concentrations of sE-selectin, sVCAM-1, and ICAM-1 compared to the controls [acute pyelonephritis (ng/mL): sE-selectin 99.1 (76.8–175.2), sVCAM-1: 671.3 (543.7–713.4), sICAM-1 442.8 (332.6–622.2) versus normal pregnancy (ng/mL): sE-selectin 45.1 (33.9–53.3) ; sVCAM-1: 507.8 (451.8–593.7);sICAM-1: 266.7(217.6–312.8); all p-values < 0.001] (Table 3B, Table 4, and Figures 1–6, Supplementary Figure S4. The median concentration of sL-selectin was lower in patients with acute pyelonephritis compared to the controls, yet the result did not reach statistical significance (potentially due to a small sample size). No significant differences were observed in the concentrations of sP-selectin and sPECAM-1 between patients with

acute pyelonephritis and normal pregnancy (all p-values ≥0.05) (Table 3B, Table 4, and Figure 1–6, Supplementary Figure S4).

Among patients with acute pyelonephritis, those with bacteremia had a significantly high median maternal plasma concentration of sE-selectin, sVCAM-1, and sICAM-1 ($p<0.01$) than those without bacteremia (Table 5).

The correlation of soluble adhesion molecules and pro-inflammatory cytokines in patients with preeclampsia and acute pyelonephritis

In patients with preeclampsia, plasma sVCAM-1 concentration had a significant positive correlation with TNF-α and IL-8 concentrations (Spearman's rho=0.36 and 0.29; p-value <0.05, for both groups). The correlation coefficients were stronger in patients with acute pyelonephritis (TNF-α: Spearman's rho =0.57; p-value=0.003; and IL-8: Spearman's rho=0.43; p-value=0.038) compared to those with preeclampsia.

Plasma sE-selectin and sP-selectin concentrations were positively correlated with plasma IL-8 concentrations in patients with both preeclampsia and acute pyelonephritis. Furthermore, the correlations were stronger in patients with acute pyelonephritis than in those with preeclampsia (preeclampsia: sE-selectin: Spearman's rho=0.23; p-value=0.03; sP-selectin: Spearman's rho=0.28; p-value=0.007; acute pyelonephritis: sE-selectin: Spearman's rho=0.41; p-value =0.045; and sP-selectin: Spearman's rho=0.5; p-value=0.02).

Plasma soluble adhesion molecules in patients with preterm labor and intact membranes

Patients with PTL who delivered preterm had a higher median concentration of sP-selectin and a lower median concentration of sVCAM-1 compared to those with normal pregnancies [PTL (ng/mL): sP-selectin: 102.5 (83.2–133.3) and sVCAM-1: 454.0 (402.6–529.7) versus normal pregnancy (ng/mL): sP-selectin: 92.6 (72.4–111.1) and sVCAM-1: 507.8 (451.8–593.7); all p-values <0.05]. No significant differences were observed in the median concentrations of sE-selectin, sL-selectin, and sICAM-1 between patients with preterm labor and intact membranes and the controls (all p-values ≥0.05) (Table 3B, Table 4, and Figure 1–6, Supplementary figure S5). The plasma concentration of sPECAM-1 was not measured in the PTL group.

Plasma soluble adhesion molecules in patients with preterm prelabor rupture of the membranes

Women with preterm PROM had lower median concentrations of sL-selectin and sVCAM-1 than patients who had a normal pregnancy [preterm PROM (ng/mL): sL-selectin: 518.1 (429.1–638.7) and sVCAM-1: 445.3 (376.2–472.6) versus normal pregnancy (ng/mL): sL-selectin: 669.7 (583.4–830.4) and sVCAM-1: 507.8 (451.8–593.7); all p-values <0.05]. No significant differences were observed in the median concentrations of sE-selectin, sL-selectin, and sICAM-1 between patients with preterm PROM and the controls (Table 3B, Table 4, and Figures 1–6, Supplementary Figure S6). The plasma concentration of sPECAM-1 was not measured in patients with preterm PROM.

Discussion

Principal findings of the study

1) Women with preeclampsia had higher median concentrations of sE-selectin, sP-selectin, and sVCAM-1 and a lower median concentration of sL-selectin compared to women who had a normal pregnancy. This is evidence of endothelial, leukocytic, and platelet activation in this syndrome; 2) there was a significant positive correlation between the plasma sE-selectin, sP-selectin, and sVCAM-1 concentrations in patients with preeclampsia and the liver enzyme SGOT, a marker of multi-organ involvement in preeclampsia. This suggests that endothelial and platelet activation participate in the hepatic damage that occurs in preeclampsia; 3) patients with SGA fetuses had higher median concentrations of sE-selectin, sP-selectin, and sVCAM-1 compared to the controls; 4) patients with acute pyelonephritis had higher median plasma concentrations of sE-selectin, sVCAM-1, and sICAM-1 compared to the controls; 5) plasma sVCAM-1, sE-selectin, and sP-selectin concentrations had moderate correlations with pro-inflammatory cytokines (TNF-α and IL-8) in patients with preeclampsia and acute pyelonephritis. These correlations were stronger in acute pyelonephritis than in preeclampsia; 6) patients with preterm labor and intact membranes had a higher median concentration of sP-selectin and a lower median concentration of sVCAM-1 compared to the controls; 7) women with preterm PROM had lower median concentrations of sL-selectin and sVCAM-1 compared to the controls; and 8) patients with a fetal death had higher median concentrations of sE-selectin and sP-selectin compared to the controls.

Overall, the results of this study suggest that each obstetrical syndrome is characterized by a stereotypical profile of soluble adhesion molecules in the maternal plasma.

Soluble adhesion molecules and endothelial activation/dysfunction

The endothelium is a single cell layer that lines the interior surface of the blood and lymphatic vessels. Its fundamental functions include maintenance of vascular tone, hemostasis, fluid filtration, cell adhesion, and neutrophil recruitment (11, 13, 19, 21, 120). During an inflammatory response, the endothelium undergoes activation/dysfunction. Endothelial cell activation refers to increased adhesive properties of the endothelium to leukocytes in response to biomechanical stimuli (121–123) or cytokines (124–130). In endothelial cell dysfunction, there is an impaired endothelial cell-dependent relaxation (11, 13, 15), and this was initially observed in a human *in vivo* model of essential hypertension (131). Endothelial cell activation can lead to an endothelial dysfunction, and the major link between these processes is the leukocyte adhesion cascade (11, 13, 15–21).

The leukocyte adhesion cascade is central to the development of an inflammatory response and is a regulated, multi-step process consisting of capture, rolling, slow rolling, firm adhesion, adhesion strengthening, intramural crawling, and paracellular/transcellular migration of the leukocyte (11, 13, 16–21). The leukocyte-endothelial cell interactions are predominantly mediated by cell adhesion molecules comprised of three families (selectins, integrins, and members of the immunoglobulin gene superfamily) (16, 17, 19, 22–27). The selectin family is mainly responsible for the rolling of the leukocyte on the surface of the

endothelium and includes three members: E-selectin, L-selectin, and P-selectin (11, 13, 16–27). ICAM-1, VCAM-1, and PECAM-1 are ligands for leukocyte integrins and belong to the immunoglobulin superfamily. These molecules are important for adhesion, arrest, and transmigration of leukocytes (11, 13, 16–21, 23, 25).

In response to pro-inflammatory cytokines, specific adhesion molecules are shed from the surface of the endothelium, and they can be detected in the peripheral circulation (16, 22, 25, 28). High concentrations of such soluble forms of E-selectin have been interpreted as evidence of endothelial activation/dysfunction. In contrast, high concentrations of sL-selectin inhibit the attachment of leukocytes to the endothelium; therefore, low sL-selectin is indicative of leukocyte activation (132). Previous studies have shown that soluble adhesion molecules could be used as markers in various inflammatory conditions such as sepsis (14, 133, 134), acute pancreatitis (135, 136), rheumatoid arthritis (137–139), and cancer metastasis (140, 141).

Preeclampsia is associated with the activation of platelets, leukocytes, and endothelial cells

Preeclampsia is one of the great obstetrical syndromes (142–152) and is characterized by utero-placental insufficiency (151, 153–175), an imbalance between angiogenic and anti-angiogenic factors in the maternal plasma (37, 38, 46, 47, 151, 176–211), increased thrombin generation (212–221), platelet aggregation (214, 221–226), endothelial cell dysfunction (51, 110, 156, 161, 227–236), and exaggerated intravascular inflammation (1, 33–39).

Central to the inflammatory response are the adhesion molecules that mediate leukocyte-endothelial cell interactions (11, 13, 15–21). These molecules are also important for the development of early placentation and successful physiological transformation of the spiral arteries (237–246). However, in preeclampsia, the cytotrophoblasts fail to up-regulate expression of the immunoglobulin superfamily adhesion receptors (i.e., VCAM-1, PECAM-1); therefore, these cytotrophoblasts fail to mimic a vascular adhesion phenotype (168, 247–249). Additionally, the expression of adhesion molecules on cultured endothelial cells is stimulated by factors in the maternal circulation, e.g., pro-inflammatory cytokines that could be detected in patients with preeclampsia (29, 250). Due to the systemic inflammatory response (1, 33–39), endothelial activation/dysfunction (51, 110, 156, 161, 227–236), and the hypercoagulable state in preeclampsia (212–226), adhesion molecules are shed from the surface of cells, and their soluble forms can be detected in the peripheral circulation (16, 22, 25, 28).

The profiles of soluble adhesion molecules have been examined in patients with preeclampsia, yet the results are conflicting (31, 32, 41–46, 56–110). In this study, we simultaneously determined the behavior of the six adhesion molecules in preeclampsia and found higher median concentrations of sE-selectin, sVCAM-1 (both reflect activation of the endothelium), and sP-selectin (indicative of platelet activation) and a lower concentration of sL-selectin (represents leukocyte activation). Moreover, plasma sE-selectin, sP-selectin, and sVCAM-1 concentrations were correlated with the severity of liver injury in patients with preeclampsia as well as with pro-inflammatory cytokines (TNF-α and IL-8).

SGA pregnancy is associated with endothelial and platelet activation

A pregnancy with an SGA fetus is another great obstetrical syndrome (142, 149, 150) and shares common pathophysiological mechanisms with preeclampsia, such as utero-placental ischemia (155, 157, 158, 163, 169, 170, 173), abnormal placentation (111, 153, 154, 251–260), an imbalance between angiogenic and anti-angiogenic factors in the maternal plasma (46, 47, 185, 187, 190, 193–197, 199, 210, 261), platelet changes (262), and increased oxidative stress (232, 263–269). However, despite the shared pathophysiology, it is still unknown why some women go on to develop preeclampsia with or without an SGA fetus, whereas other women have only SGA fetuses. It was initially thought that endothelial involvement is systemic in preeclampsia and localized only to the utero-placental unit in SGA pregnancies (270). However, other investigators have reported enhanced endothelial (42–47) and neutrophil (40, 41, 48) activation in women with SGA fetuses, suggesting that there is a systemic maternal inflammatory response.

Herein, we report that patients with an SGA fetus had significantly higher plasma sE-selectin, sP-selectin, and sVCAM-1 concentrations than those who had a normal pregnancy. These results are indicative of the presence of endothelial and platelet activation in pregnancies with SGA fetuses. Our findings are similar to those reported by Johnson et al. (44) and Coata et al. (45) who showed that patients with SGA fetuses had higher sE-selectin and sVCAM-1 concentrations compared to the controls. Collectively, these observations suggest that patients with SGA fetuses have endothelial activation/dysfunction, and the profiles of the soluble adhesion molecules of these patients differ from those observed in pregnancies complicated by preeclampsia.

Pyelonephritis is associated with the activation of the endothelium

Acute pyelonephritis is a frequent cause of maternal systemic inflammation (271–276). Previous studies investigating the behavior of cytokines (277), chemokines (278), and complement (49, 279) in preeclampsia and acute pyelonephritis showed that both conditions were associated with intravascular inflammation (2, 34). However, transcriptomic analysis of the peripheral blood of patients with pyelonephritis (280) and preeclampsia (281) demonstrated differences in the inflammatory response (pyelonephritis was associated with increased expression of genes involved in innate immunity and decreased expression of genes involved in lymphocyte function (280), whereas the transcriptional profile of peripheral whole blood in preeclampsia demonstrated differential expression of genes involved in coagulation, immune regulation, the growth/developmental process, host defense, and tight junctions in the blood-brain barrier (281).

In the study herein, we present evidence indicating that acute pyelonephritis was associated with higher plasma concentrations of sE-selectin, sVCAM-1, and sICAM-1 compared to a normal pregnancy. The concentrations of sE-selectin, sVCAM-1, and sICAM-1 were associated with the degree of severity (bacteremia). Moreover, the magnitude of the differences was significantly greater in acute pyelonephritis than in preeclampsia. These findings demonstrate marked endothelial activation in acute pyelonephritis. Also, the dramatic rise in the sICAM-1 concentration was detected only in acute pyelonephritis, suggesting that sICAM-1 is more specific to acute pyelonephritis than to other obstetrical

conditions such as preeclampsia. In support of this finding, previous studies that used immunohistochemistry have shown increased expression of ICAM-1 in the kidneys with pyelonephritis (282, 283) and various glomerulonephritis (284–286). Additionally, elevated concentrations of sICAM-1 (a marker of endothelial activation/dysfunction) are well-documented in human models of sepsis (133, 134, 287–299). An unexpected finding was the lack of a demonstrable decrease in the plasma concentration of sL-selectin, a marker for leukocyte activation. We believe that the sample size of patients in the pyelonephritis group account for this observation, given the strong evidence for leukocyte activation derived from studies with flow-cytometry (2). Overall, more studies are needed to further explore the role of soluble adhesion molecules in patients with acute pyelonephritis.

The profiles of soluble adhesion molecules in preterm labor with intact membranes and preterm prelabor rupture of the membranes

We report herein that preterm labor was associated with a higher median concentration of sP-selectin but with a lower median concentration of sVCAM-1 than normal pregnancy. On the other hand, patients with preterm PROM had lower median concentrations of sL-selectin and sVCAM-1 compared to the controls. The profiles of the soluble adhesion molecules reflected platelet and leukocytic activation in preterm labor with intact membranes and in leukocyte activation in preterm PROM; however, under both conditions, no marked endothelial activity was observed. Previous studies that examined the behavior of soluble adhesion molecules in the maternal plasma/serum yielded conflicting results (300–304). For example, Chen et al, (304) showed that women with preterm delivery (spontaneous preterm labor or preterm PROM) had higher serum sICAM-1 and sVCAM-1 concentrations than patients with a normal term pregnancy, whereas no change was observed in the sE-selectin concentration. On the other hand, Bartha et al, (303) found no significant differences in the concentrations of sE-selectin, sVCAM-1, and sICAM-1 between patients who had spontaneous preterm labor and those with a normal term pregnancy. Even though the results from previous studies and of those reported herein are inconsistent, maternal intravascular inflammation (52–55) and platelet activation (305, 306) have been demonstrated in preterm labor and preterm PROM. Additionally, data from epidemiological studies showed that women with preterm deliveries are at an increased risk for future cardiovascular diseases (307–312), suggesting that there is some degree of endothelial dysfunction. Therefore, larger studies are needed to further examine the behavior of soluble adhesion molecules in different patient populations with preterm labor and preterm PROM.

The profiles of soluble adhesion molecules in patients with an unexplained fetal death

The observations of this study reflect platelet activation in the maternal circulation of cases with a fetal demise, as women with an unexplained fetal death had a higher median concentration of sP-selectin than those with a normal pregnancy. This is consistent with a previous study that reported a higher plasma sCD40L (marker of platelet activation) concentration in mothers with fetal demise than in those with normal pregnancies (313). Also, the concentrations of sP-selectin were higher in non-pregnant women with a history of venous thromboembolism and fetal death than in those with a history of thromboembolism but no fetal death (314). Collectively, these results suggest that there is a subclinical activation of the hemostatic system in women with fetal death.

Herein, we also report that patients with an unexplained fetal death had a higher median concentration of sE-selectin than women with a normal pregnancy, reflecting activation of the endothelium. Activation of the endothelium and platelets can occur in the setting of an inflammatory response (315, 316); yet, the role of inflammation in unexplained fetal death remains to be elucidated. A previous study reported that women with unexplained fetal death had a higher concentration of plasma C5a (a potent pro-inflammatory mediator (317, 318)) than women with a normal pregnancy (319). These observations are important as C5a can increase the expression of adhesion molecules on the endothelium and activate neutrophils (317, 320, 321), which, in turn, can activate platelets by secreting cathepsin G (322). Moreover, experimental evidence suggests that complement activation requires the stimulation of platelets, which is associated with the expression of P-selectin (323–326). Therefore, additional studies are needed to elucidate the link between inflammation and activation of the hemostatic system, endothelium, and leukocytes in patients with an unexplained fetal death.

Strengths and Limitations

This is the first study to simultaneously investigate the profile of six soluble adhesion molecules in pregnancies complicated by preeclampsia, SGA fetuses, acute pyelonephritis, preterm labor with intact membranes, preterm PROM, and fetal death.

Limitations include those stemming from the small sample size of some of the groups (i.e. pyelonephritis). Additionally, our study population is consistent with mainly African American patients, and there is a concern that our findings may not be applicable to other ethnic groups. However, in term of ethnic risk for pregnancy complications, African-American women are at markedly increased risk for preterm delivery, preeclampsia and cardiovascular diseases (327, 328). Second, there are differences in adhesions molecules concentrations in various ethnic groups. Indeed, Miller et al, found that females of African origin (Caribbean and West African) had significantly lower concentrations of sICAM-1, sVCAM-1, and sP-selectin than White women in England (329). Similar results were found by Akolekar et al, who reported that the concentrations of plasma P-selectin in women with a normal pregnancy between 11–13 weeks of gestation were lower in Blacks and Orientals than in White women (330). However, the effect of ethnicity on soluble adhesion molecules throughout pregnancy and in the great obstetrical syndromes was not studied yet, and it is beyond the scope of the current study. This may affect the generalization of our results to the entire obstetrical population; nevertheless, our findings are important and are relevant to the ethnic group with the highest risk for such complications. Further studies are needed to address the effect of ethnicity on the profile of the different.

Conclusions

Endothelial activation/dysfunction is present not only in preeclampsia but also in other obstetrical syndromes such as pregnancy complicated by an SGA fetus, acute pyelonephritis, and an unexplained fetal death. Collectively, we report that each obstetrical syndrome appears to have a stereotypical profile of soluble adhesion molecules in the peripheral circulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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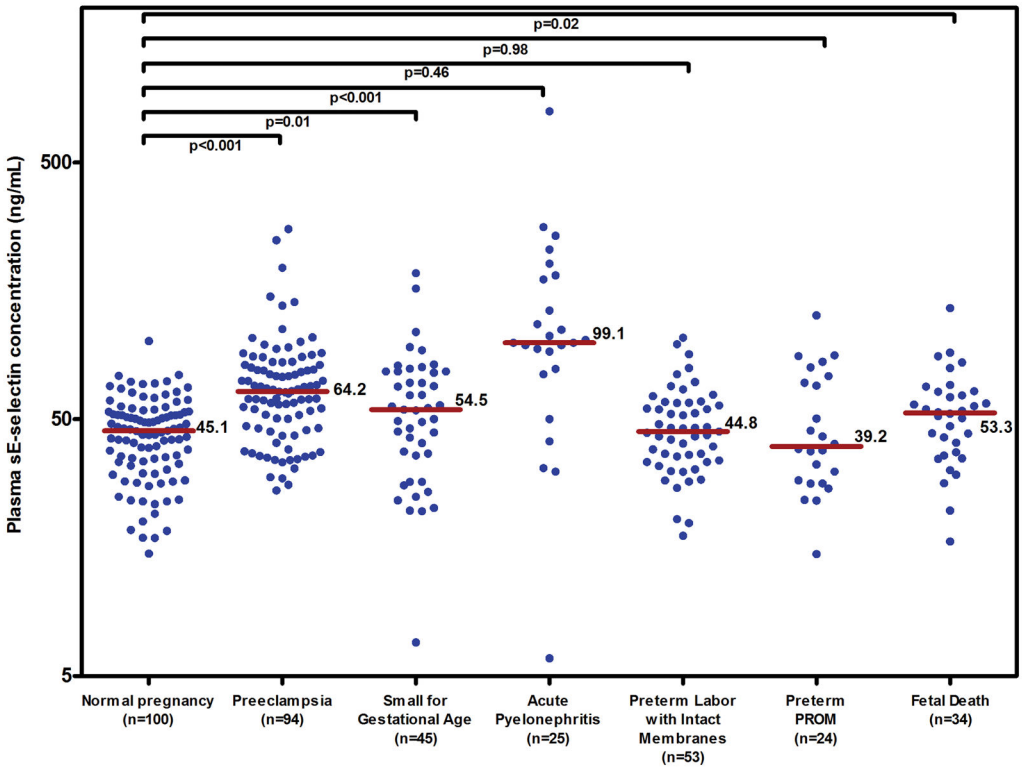

Figure 1.
Plasma sE-selectin concentration (ng/mL)

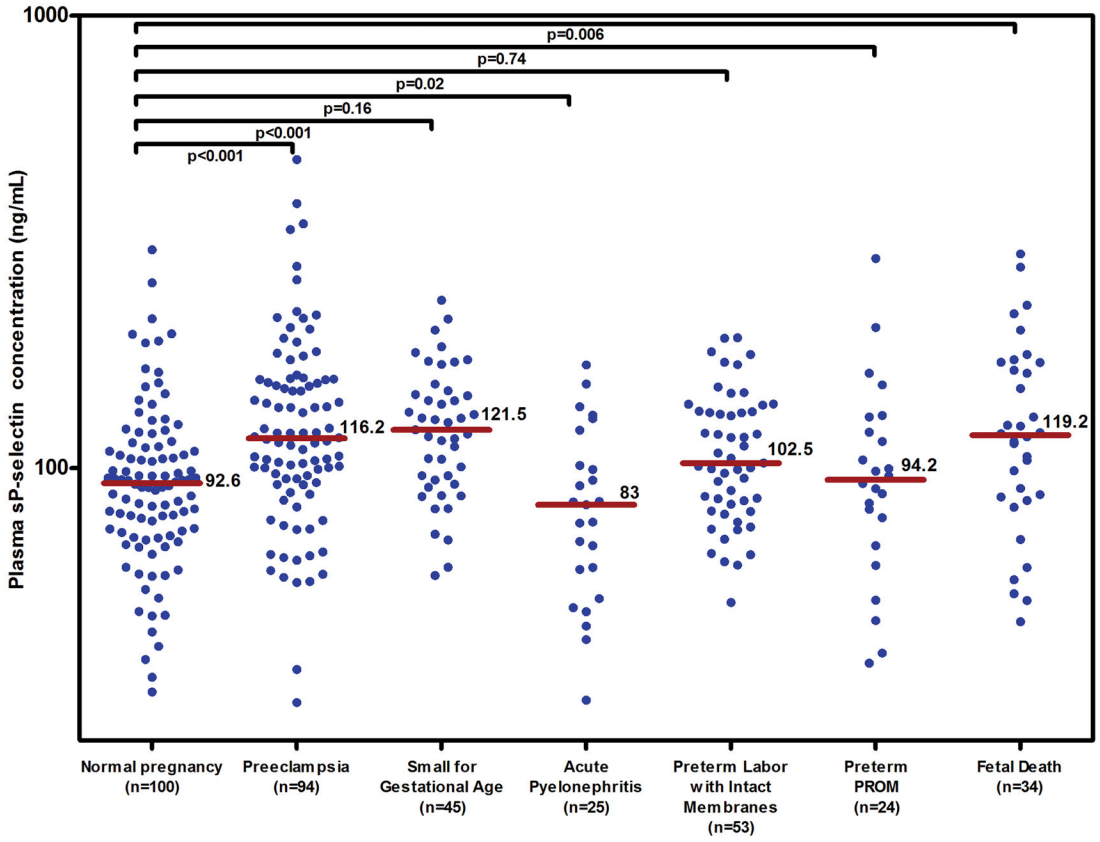

Figure 2.
Plasma sP-selectin concentration (ng/mL)

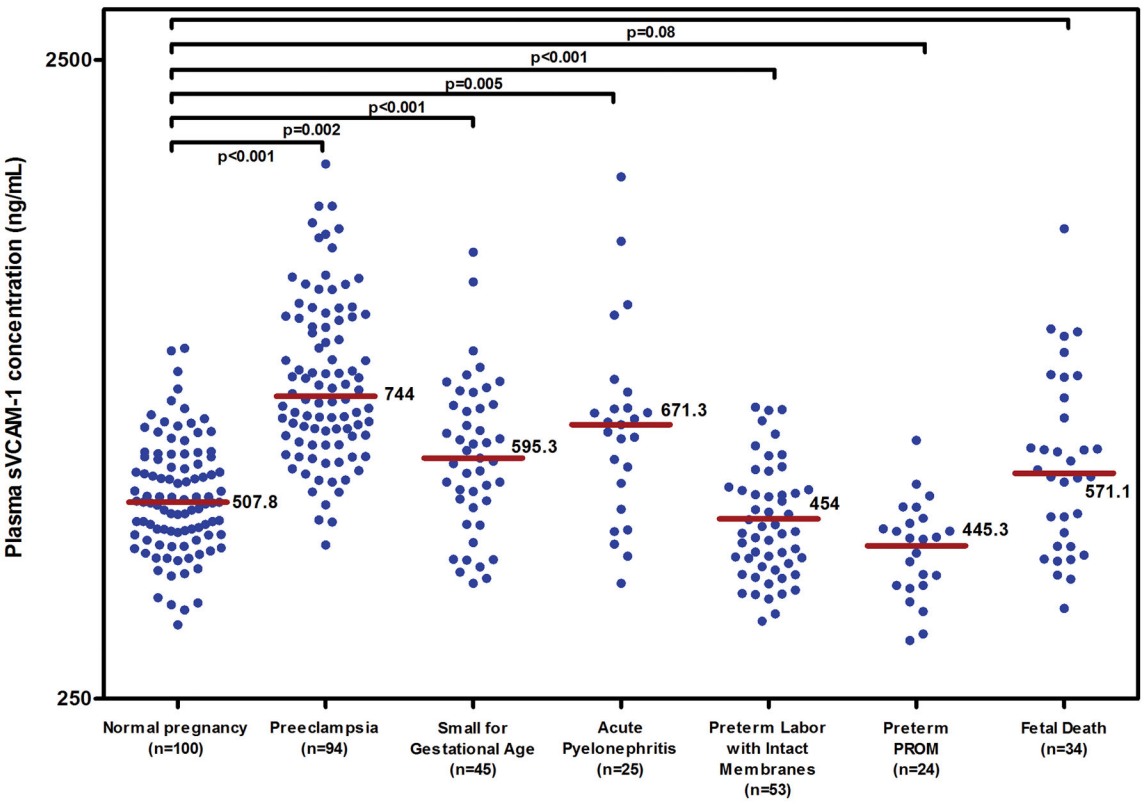

Figure 3.
Plasma sVCAM-1 concentration (ng/mL)

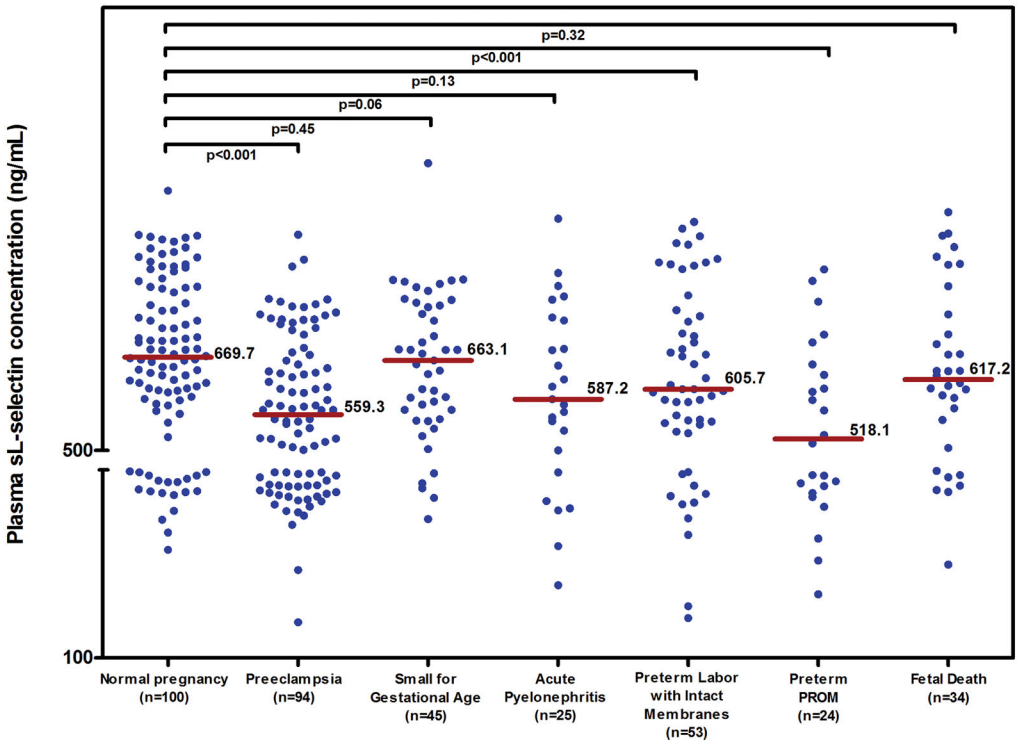

Figure 4.
Plasma sL-selectin concentration (ng/mL)

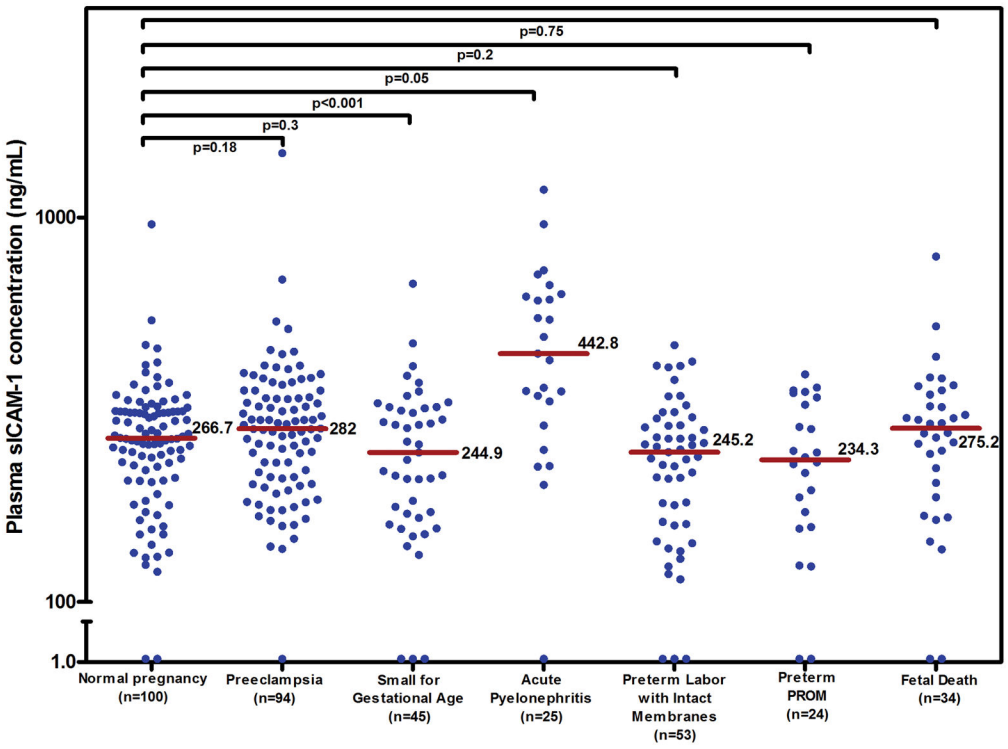

Figure 5.
Plasma sICAM-1 concentration (ng/mL)

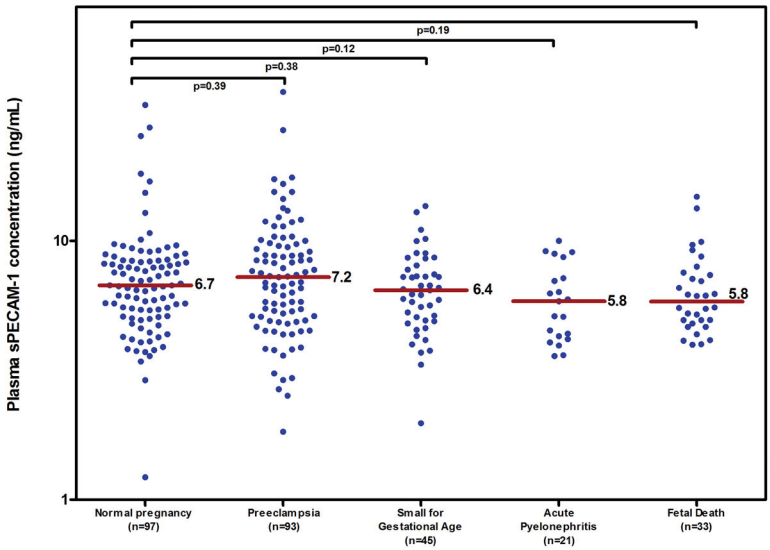

Figure 6.
Plasma sPECAM-1 concentration (ng/mL)

Table 1

Sensitivity and coefficient of variation (CV) of the immunoassay kits

Analyte	Sensitivity	Inter-assay CV	Intra-assay CV
soluble E-selectin	0.331(ng/mL)	9.07	2.77
soluble L-selectin	0.799(ng/mL)	4.54	1.46
soluble P-selectin	0.72 (ng/mL)	5.96	4.18
soluble VCAM-1	3.171(ng/mL)	8.66	5.00
soluble ICAM-1	1.058 (ng/mL)	6.89	2.85
soluble PECAM-1	0.049(ng/mL)	11.70	2.07
IL-8	5.82 (pg/mL)	6.27	5.36
TNF-α	0.329 (pg/mL)	6.60	5.95

ICAM-1: intercellular adhesion molecule-1; IL: interleukin; PECAM-1: platelet endothelial cell adhesion molecule-1; TNF: tumor necrosis factor; VCAM-1: vascular cell adhesion molecule-1

Table 2

Demographic, clinical and obstetric characteristics of the study population

	Normal Pregnancy (n = 100)	Preeclampsia (n = 94)	Small for Gestational Age (n = 45)	Acute Pyelonephritis (n = 25)	Preterm Labor with Intact Membranes (n=53)	Preterm PROM (n=24)	Fetal Death (n=34)	P value
Age (years)	25 (21–30)	24 (20.8–30)	25 (20–31)	22 (20.5–31)	21 (19–26.5)	28 (22–32.8)	24.5 (20–29.3)	0.04
Nulliparity	25% (25/100)	61.7% (58/94)	35.6% (16/45)	28% (7/25)	41.5% (22/53)	16.7% (4/24)	40.6% (13/32)**	<0.001
Race								
• **African-American**	63% (63/100)	64.9% (61/94)	80% (36/45)	72% (18/25)	88.7% (47/53)	91.7% (22/24)	88.2% (30/34)	
• **Caucasian**	11% (11/100)	11.7% (11/94)	15.6% (7/45)	16% (4/25)	9.4% (5/53)	8.3% (2/24)	2.9% (1/34)	0.007
• **Hispanic**	21% (21/100)	21.3% (20/94)	2.2% (1/45)	8% (2/25)	-	-	6% (2/34)	
• **Other**	5% (5/100)	2.1% (2/94)	2.2% (1/45)	4% (1/25)	1.9% (1/53)	-	2.9% (1/34)	
Gestational age at venipuncture (weeks)	34 (28.3–38.4)	33.8 (29.3–36.8)	33.5 (30.1–37.5)	31.5 (25.7–35.8)	30.4 (25.5–33)	30.1 (25.1–31.9)	30.1 (24.9–35.4)	<0.001
Gestational age at delivery (weeks)	39.1 (38.4–40.1)	34.2 (30.5–37.2)	35 (30.9–37.6)	39.2* (37.3–40.3)	35.1 (27.8–37.1)	30.2 (25.3–31.9)	30.1 (24.7–35.5)	<0.001
Birthweight (grams)	3,375 (3,158–3,800)	1,830 (1,320–2,733)	1,980 (1,045–2,325)	3,215* (2,770–3,583)	2,353 (1,005–2,775)	1,295 (655–1,988)	1,106 (513–2,031)	<0.001

* data not available in 5 cases;

** data not available in 2 cases;

PROM – prelabor rupture of membranes; numbers in () either expressed as percentage or Interquartile range

Data is presented as percent (number), median (interquartile range)

Table 3

The concentrations of soluble adhesion molecules in patients with preeclampsia, small for gestational age and fetal death compared to normal pregnancy

	Normal pregnancy (n=100)	Preeclampsia (n=94)	P value	Small for gestational age (n=45)	P value	Fetal Death (n=34)	P value
Soluble E-selectin (ng/mL)	45.1 (33.9–53.3)	64.2 (46.4–81)	<0.001	54.5 (36.8–76.8)	0.01	53.3 (37.2–64)	0.02
Soluble L-selectin (ng/mL)	669.7 (583.4–830.4)	559.3 (444.9–671.2)	<0.001	663.1 (567.8–787.3)	0.45	617.2 (503.9–765.8)	0.32
Soluble P-selectin (ng/mL)	92.6 (72.4–111.1)	116.2 (93.3–156.2)	<0.001	121.5 (94.1–145.4)	<0.001	119.2 (86.3–171.2)	0.006
Soluble VCAM-1 (ng/mL)	507.8 (451.8–593.7)	744 (644.7–983.8)	<0.001	595.3 (510.5–719.7)	0.002	571.1 (433.3–739.9)	0.08
Soluble ICAM-1 (ng/mL)	266.7 (217.6–312.8)	282.0 (211.1 –340.4)	0.18	244.9 (169.7–319.1)	0.3	275.2 (204.2–323.2)	0.75
Soluble PECAM-1 (ng/mL)	6.7 * (5.1–8.4)	7.2 ** (5.1–9.6)	0.39	6.4 (4.9–7.7)	0.38	5.8 ** (4.9–7.4)	0.19

NOTE: P value (obstetrical condition vs. normal pregnancy); ICAM-1: intercellular adhesion molecule; PECAM-1: platelet endothelial cell adhesion molecule; VCAM-1: vascular cell adhesion molecule;

* data not available in 3 cases;

** data not available in 1 case

Data is presented as median (interquartile range).

Table 4

Summary of the differences in soluble adhesion molecules concentration in patients with normal pregnancy and those with preeclampsia, small for gestational age, acute pyelonephritis, preterm labor and intact membranes, preterm PROM and fetal death

Soluble Adhesion Molecules	Preeclampsia (n=94)	Small for Gestational Age (n=45)	Acute Pyelonephritis (n=25)	Preterm Labor with Intact Membranes (n=53)	Preterm PROM (n=24)	Fetal Death (n=34)
Soluble E-selectin (ng/mL)	↑(+,+)	↑(+,+)	↑(+,+)	↔	↔	↑(+,+)
Soluble L-selectin (ng/mL)	↓(+,+)1)	↔	↓(−,+)	↓(−,+)	↓(+,+)	↔
Soluble P-selectin (ng/mL)	↑(+,+)	↑(+,+)	↔	↑(+,−)	↔	↑(+,+)
Soluble VCAM-1 (ng/mL)	↑(+,+)	↑(+,+)	↑(+,+)	↓(+,−)	↓(+,+)2)	↑(−,+)
Soluble ICAM-1 (ng/mL)	↔	↔	↑(+,+)	↔	↔	↔
Soluble PECAM-1 (ng/mL)	↔	↔	↔	not measured	not measured	↔

ICAM-1: intercellular adhesion molecule-1; PECAM-1: platelet endothelial cell adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1; ↑ :a higher median concentration than in normal pregnancy, ↓ :a lower median concentration than in normal pregnancy, ↔: no significant change in the median concentration.

(+/−,+/−) positive/negative test by wilcoxon test (p-value <0.05) and positive/negative test by linear model with adjustment for gestational age as needed (p-value<0.05);

1) differences are higher earlier in gestation (significant interaction between gestational age and group);

2) differences are higher later in gestation (significant interaction between gestational age and group).

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Table 5

The concentrations of soluble adhesion molecules in patients with preterm labor and intact membranes, preterm PROM and acute pyelonephritis compared to normal pregnancy

	Normal Pregnancy (n=100)	Preterm Labor with Intact Membranes (n=53)	P value	Preterm PROM (n=24)	P value	Acute pyelonephritis (n=25)	P value
Soluble E-selectin (ng/mL)	45.1 (33.9–53.3)	44.8 (34.6–57.8)	0.46	39.2 (28.7–70.5)	0.98	99.1 (78.6–175.2)	<0.001
Soluble L-selectin (ng/mL)	669.7 (583.4–830.4)	605.7 (542.4–761.2)	0.13	518.1 (429.1–638.7)	<0.001	587.2 (500.2–750.9)	0.06
Soluble P-selectin (ng/mL)	92.6 (72.4–111.1)	102.5 (83.2–133.3)	0.02	94.2 (75.1–122.5)	0.74	83 (59.7–101.3)	0.16
Soluble VCAM-1 (ng/mL)	507.8 (451.8–593.7)	454 (402.6–529.7)	0.005	445.3 (376.2–472.6)	<0.001	671.3 (543.7–713.4)	<0.001
Soluble ICAM-1 (ng/mL)	266.7 (217.6–312.8)	245.2 (161.6–288.2)	0.05	234.3 (167.6–329.5)	0.2	442.8 (332.6–622.2)	<0.001
Soluble PECAM-1 (ng/mL)	6.7 * (5.1–8.4)	not measured	-	not measured	-	5.8 *** (4.3–7.2)	0.12

NOTE: P value (obstetrical condition vs. normal pregnancy); ICAM-1: intercellular adhesion molecule; PECAM-1: platelet endothelial cell adhesion molecule; PROM: prelabor rupture of membranes; VCAM-1: vascular cell adhesion molecule;

* data not available in 3 cases;

*** data not available in 4 cases.

Data is presented as median (interquartile range)

Table 6

The concentrations of soluble adhesion molecules in patients with acute pyelonephritis in the presence or absence of bacteremia

	Acute pyelonephritis without bacteremia (n=11)	Acute pyelonephritis with bacteremia (n=12)	P value
Soluble E-selectin (ng/mL)	78.6 (32.3–97.2)	178.4 (100.7–251.5)	<0.001
Soluble L-selectin (ng/mL)	587.2 (489.2–687.2)	631.3 (549.6–790.9)	0.61
Soluble P-selectin (ng/mL)	84.2 (49.1–101.3)	79.5 (62–119.9)	0.79
Soluble VCAM-1 (ng/mL)	576.4 (456.7–654.1)	734.1 (689.2–1025.2)	<0.001
Soluble ICAM-1 (ng/mL)	353.6 (332.6–442.8)	627.1 (562.9–724.6)	0.004
Soluble PECAM-1 (ng/mL)	4.8 (3.9–7.5)	6.3 (5.1–9.1)	0.13

ICAM-1: intercellular adhesion molecule; PECAM-1: platelet endothelial cell adhesion molecule; VCAM-1: vascular cell adhesion molecule

Data is presented as median (interquartile range).