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ORIGINAL ARTICLE

Endocan, a putative endothelial cell marker, is elevated in preeclampsia, decreased in acute pyelonephritis, and unchanged in other obstetrical syndromes

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Abstract

Objective: Endocan, a dermatan sulphate proteoglycan produced by endothelial cells, is considered a biomarker for endothelial cell activation/dysfunction. Preeclampsia is characterized by systemic vascular inflammation, and endothelial cell activation/dysfunction. Therefore, the objectives of this study were to determine whether: (1) plasma endocan concentrations in preeclampsia differ from those in uncomplicated pregnancies; (2) changes in plasma endocan concentration relate to the severity of preeclampsia, and whether these changes are specific or observed in other obstetrical syndromes such as small-for-gestational age (SGA), fetal death (FD), preterm labor (PTL) or preterm prelabor rupture of membranes (PROM); (3) a correlation exists between plasma concentration of endocan and angiogenic (placental growth factor or PlGF)/anti-angiogenic factors (soluble vascular endothelial growth factor receptor or sVEGFR-1, and soluble endoglin or sEng) among pregnancies complicated by preeclampsia; and (4) plasma endocan concentrations in patients with preeclampsia and acute pyelonephritis (both conditions in which there is endothelial cell activation) differ.

Method: This cross-sectional study included the following groups: (1) uncomplicated pregnancy ($n = 130$); (2) preeclampsia ($n = 102$); (3) pregnant women without preeclampsia who delivered an SGA neonate ($n = 51$); (4) FD ($n = 49$); (5) acute pyelonephritis (AP; $n = 35$); (6) spontaneous PTL ($n = 75$); and (7) preterm PROM ($n = 64$). Plasma endocan concentrations were determined in all groups, and PlGF, sEng and VEGFR-1 plasma concentrations were measured by ELISA in the preeclampsia group.

Results: (1) Women with preeclampsia had a significantly higher median plasma endocan concentration than those with uncomplicated pregnancies ($p = 0.004$); (2) among women with preeclampsia, the median plasma endocan concentration did not differ significantly according to disease severity ($p = 0.1$), abnormal uterine artery Doppler velocimetry ($p = 0.7$) or whether diagnosis was made before or after 34 weeks gestational age ($p = 0.3$); (3) plasma endocan concentration in women with preeclampsia correlated positively with plasma anti-angiogenic factor concentrations [sVEGFR-1: Spearman rho 0.34, $p = 0.001$ and sEng: Spearman rho 0.30, $p = 0.003$]; (4) pregnancies complicated by acute pyelonephritis with bacteremia had a lower median plasma endocan concentration than pregnancies complicated by acute pyelonephritis without bacteremia ($p = 0.004$), as well as uncomplicated pregnancies ($p = 0.001$); and (5) there was no significant difference in the median plasma endocan concentration between uncomplicated pregnancies and those complicated by FD, delivery of an SGA neonate, PTL or preterm PROM (other members of the "great obstetrical syndromes"; each $p > 0.05$).

Conclusion: Median maternal plasma endocan concentrations were higher preeclampsia and lower in acute pyelonephritis with bacteremia than in uncomplicated pregnancy. No significant difference was observed in the median plasma endocan concentration between other great

Keywords

Endothelial cell activation, endothelial dysfunction, fetal death, preterm labor, small-for-gestational age, soluble endoglin, soluble vascular endothelial growth factor receptor-1

History

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obstetrical syndromes and uncomplicated pregnancies. The difference in the direction of change of endocan in preeclampsia and acute pyelonephritis with bacteremia may be consistent with the view that both disease entities differ in pathogenic mechanisms, despite their associations with systemic vascular inflammation and endothelial cell activation/dysfunction.

Introduction

The traditional view of the pathogenesis of preeclampsia is that uteroplacental ischemia induces the production of soluble factors (or toxins) that, when released into the maternal circulation, are responsible for the clinical manifestations of the disease [1–9]. These factors are thought to cause intravascular inflammation [10–16], endothelial cell dysfunction [17–25], increased thrombin generation [26–35] and platelet aggregation [3,28,35–39].

Generalized endothelial cell activation/dysfunction is considered to be central to the pathophysiology of preeclampsia [9,17]. Considerable effort has been made to identify circulating markers of endothelial cell activation/dysfunction in the circulation of normal pregnant women and those with preeclampsia – this has included coagulation factors produced by endothelial cells, such as Von Willebrand factor [40–44], cellular ''cements'' (e.g. cellular fibronectin, which is also almost exclusively located in the endothelium) [45–56], endothelial cell adhesion molecules (e.g. E-selectin and vascular cell adhesion molecule-1) [57–67] and anti-endothelial cell antibodies [68–70]. However, none of these makers have been proven to be specific to preeclampsia, and can be elevated in other conditions [71–80]. Thus, a major challenge has been the to identify a biomarker specific to endothelial cell activation/dysfunction and preeclampsia.

Endocan, also known as endothelial specific molecule-1 (ESM-1), is a proteoglycan detectable in the circulation that has been proposed to be a new endothelial cell marker. This protein is elevated in serum of patients with sepsis who have endothelial cell activation/dysfunction [81,82]. Similarly, the serum concentrations of endocan are elevated in lung, breast, hepatocellular [83] and renal cancers [84–86] as well as acute myeloid leukemia [87], conditions associated with endothelial activation/dysfunction [72,74,76,88–94].

The objectives of this study were to determine: (1) whether plasma endocan concentrations in PE differ from those of uncomplicated pregnancy; (2) whether changes the plasma endocan concentration relate to the severity of preeclampsia, and whether these changes are specific or observed in other obstetrical syndromes such as small-for-gestational age (SGA), fetal death (FD), preterm labor (PTL) or preterm prelabor rupture of membranes (PROM); (3) if a correlation exists between the plasma concentration of endocan and angiogenic/anti-angiogenic factors among pregnancies complicated by PE; and (4) whether plasma endocan concentrations in patients with preeclampsia and acute pyelonephritis (both conditions in which there is endothelial cell activation) differ.

Materials and methods

Study design

A cross-sectional study was designed to include patients in the following groups: (1) uncomplicated pregnancy ($n = 130$); (2) preeclampsia ($n = 102$); (3) pregnant women without pre-eclampsia or hypertension who delivered a small-for-gestational age neonate ($n = 51$); (4) fetal death ($n = 49$); (5) acute pyelonephritis ($n = 35$); (6) preterm labor with intact membranes ($n = 75$); and (7) preterm PROM ($n = 64$). All participants provided written informed consent for the collection and use of samples for research purposes under the protocols approved by, the Institutional Review Boards of Wayne State University and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services (NICHD/NIH/DHHS).

Clinical definitions

Preeclampsia was defined as new onset hypertension (systolic and/or diastolic blood pressure of $\geq$140 and/or $\geq$90 mm Hg) that developed after 20 weeks of gestation, measured on at least two occasions, 4 h to 1 week apart and proteinuria ($\geq$300 mg in a 24-h urine collection, or two random urine specimens obtained 4 h to 1 week apart containing $\geq$1 + protein by dipstick) [95]. Severe PE was diagnosed according to criteria proposed by the American Congress of Obstetricians and Gynecologists (ACOG) [95,96]. Early and late-onset preeclampsia was defined as cases diagnosed before and after 34 weeks of gestation, respectively [97].

The uncomplicated pregnancy group comprised of women with: (1) no medical, obstetrical or surgical complications; (2) a singleton gestation; (3) no labor; and (4) a normal term ($\geq$37 weeks) infant delivered at term whose birth weight was between the 10th and 90th percentile for gestational age [98]. Acute pyelonephritis was diagnosed in the presence of fever (temperature $\geq$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 [99,100]. An SGA neonate was defined as birth weight <10th percentile for gestational age [98]. Fetal death was defined as death of the fetus after 20 weeks of gestation, confirmed by ultrasound. All fetal deaths were unexplained. Spontaneous PTL was defined by the presence of preterm labor leading to preterm delivery. Pre-term PPROM was diagnosed as amniorrhexis in preterm gestations that were followed by preterm delivery.

Maternal plasma concentrations of endocan, placental growth factor, sVEGFR-1 and endoglin

Maternal blood was collected into tubes containing ethylenediaminetetraacetic acid (EDTA), centrifuged and stored at −70 °C until assayed. Maternal plasma concentrations of intact endocan were measured with an immunoassay following the manufacturers' instructions (USCN Life Science Inc., Wuhan, Hubei, PRC or Cloud-Clone Corp., Houston, TX). Maternal plasma concentrations of placenta growth factor (PIGF), soluble endoglin (sEng) and soluble vascular endothelial growth factor receptor (sVEGFR)-1 were determined by sensitive and specific immunoassays obtained from R&D

Systems (Minneapolis, MN). The sensitivity and coefficients of variation for these assays are described in Table 1. Validation of these assays has been previously described [101].

Doppler velocimetry

Color Doppler was used to identify blood vessels, and spectral Doppler to calculate Doppler indices in the uterine arteries. The examinations were performed at the time of diagnosis according to methods previously described [15,102,103]. The uterine artery resistance index (RI) was used as a measure of vascular impedance in the uterine circulation. A mean RI (average of left and right) of $<$ or $\geq$95th percentile for gestational age was used to determine normal and abnormal uterine artery Doppler velocimetry, respectively [104].

Statistical analysis

Normality of data was assessed using the Kolmogorov–Smirnov test and visual plot inspection. The Kruskal–Wallis test with *post-hoc* analysis by Mann–Whitney *U*-tests was used to compare continuous variables. Comparison of proportions was performed using χ^2 or Fisher's exact tests. Spearman's rank correlation coefficient was used to assess the relationship between plasma endocan, angiogenic (PIGF) and anti-angiogenic factor [(sEng and sVEGFR)-1] concentrations as well as maternal age, gestational age at blood draw, gestational age at delivery and neonatal birth weight. General linear models were constructed to examine the relevance of potential confounders including gestational age at venipuncture, maternal age, African American race and history of smoking status. Endocan concentrations were log-transformed. Multivariable analysis also controlled for the false discovery rate (FDR) in light of the performance of multiple tests. A probability value of $<$0.05 (2-tailed) was considered significant. Statistical tests were performed with Statistical Package for the Social Sciences version 19 (SPSS Inc., Chicago, IL).

Table 1. Sensitivities and coefficients of variation of the assays used in this study.

Analytes	Sensitivity	Inter-assay coefficient of variation (%)	Intra-assay coefficient of variation (%)
Endocan (ng/ml)	89.5	6.2	10.2
Soluble endoglin (ng/ml)	0.08	2.0	4.0
Soluble vascular endothelial growth factor receptor (pg/ml)	16.97	1.4	3.9
Placenta growth factor (pg/ml)	9.52	6.02	4.8

Results

The demographic, clinical and obstetric characteristics of the study population are displayed in Table 2. Endocan was detected in the maternal plasma of all patients. Among women with uncomplicated pregnancies, maternal plasma endocan concentrations did not correlate with maternal age ($p = 0.5$), gestational age at venipuncture ($p = 0.2$), gestational age at delivery ($p = 0.9$) or birth weight of the neonate ($p = 0.8$).

Maternal plasma endocan concentrations in pre-eclampsia

The median plasma endocan concentration (ng/ml) in patients with preeclampsia was significantly higher than that of women with uncomplicated pregnancies (22.5, IQR 13.8–44.4 versus 18.2, IQR 10.6–28.0; $p = 0.004$; Figure 1). Subgroup analysis performed among women with preeclampsia revealed that the median plasma endocan concentration (ng/ml) did not significantly differ according to: disease severity (mild preeclampsia 17.5, IQR 10.5–34.1 versus severe preeclampsia 22.6, IQR 15.3–45.6; $p = 0.1$); the presence of abnormal uterine artery Doppler velocimetry (normal: 21.4, IQR 14.2–51.0 versus abnormal: 22.3, IQR 13.3–41.0; $p = 0.7$); or if diagnosis was made before or after 34 weeks gestational age (early onset: 24.0, IQR 17.1–45.0 versus late-onset: 22.0, IQR 12.0–43.0; $p = 0.3$). Maternal plasma endocan concentration correlated positively with plasma sVEGFR-1 (Spearman's rho 0.34; $p = 0.001$) and sEng (Spearman's rho 0.30; $p = 0.003$), but not with the concentration of PlGF ($p = 0.3$).

Table 2. Clinical and obstetric characteristics of normal and complicated pregnancies.

	Uncomplicated pregnancy ($n = 130$)	Pre-eclampsia ($n = 102$)	SGA ($n = 51$)	Fetal death ($n = 49$)	Acute pyelonephritis ($n = 35$)	PTL ($n = 75$)	PPROM ($n = 64$)	p value
Age (years)	25 (21–29)	23.5 (19.8–30)	24 (20–29)	26 (20–30)	22 (19–25)	22.5 (19–26)	26 (21–32)	0.002
Nulliparity (%)	35 (26.9%)	63 (61.8%)	26 (50.9%)	19 (38.8%)	12 (34.3%)	39 (40.6%)	17 (26.6%)	$<$0.001
Race								
African American	102 (78.5%)	83 (81.4%)	44 (86.3%)	42 (85.7%)	27 (77.1%)	60 (80%)	57 (89.1%)	0.55
Caucasian	15 (11.5%)	11 (10.8%)	4 (7.8%)	3 (6.1%)	5 (14.3%)	9 (12.3%)	6 (9.4%)	
Hispanic	7 (5.4%)	5 (4.9%)	1 (2.0%)	3 (6.1%)	3 (8.6%)	3 (4%)	1 (1.6%)	
Others	6 (4.6%)	3 (2.9%)	2 (3.9%)	1 (2%)	0	1 (1.3%)	0	
Smoking	22 (16.9%)	14 (13.7%)	15 (29.4%)	16 (32.7%)	5 (14.3%)	27 (28.1%)	34 (53.1%)	$<$0.001
GA at venipuncture (weeks)	38 (31.4–39.1)	36.1 (31.5–38.6)	36.9 (32.7–38.4)	31 (24.8–36.6)	31.4 (25.3–36.4)	29.9 (25.1–32.3)	30.6 (27.6–32.1)	$<$0.001
GA at delivery (weeks)	39.3 (38.4–40.3)	36.1 (32.3–38.6)	37.1 (33.6–38.6)	31 (25.9–36.7)	39.4 (38.4–40.7)	30 (25–34)	31.6 (29.3–33.1)	$<$0.001
Birth weight (g)	3352 (3118–3633)	2280 (1455–2835)	2050 (1500–2380)	1380 (535–2263)	3210 (2690–3600)	1785 (865–2623.8)	1580 (1142–2055)	$<$0.001

Data presented as median (interquartile range) or number (percentage). GA, gestational age; SGA, small for gestational age; PTL, spontaneous preterm labor with intact membranes; PPROM, preterm prelabor rupture of membranes.

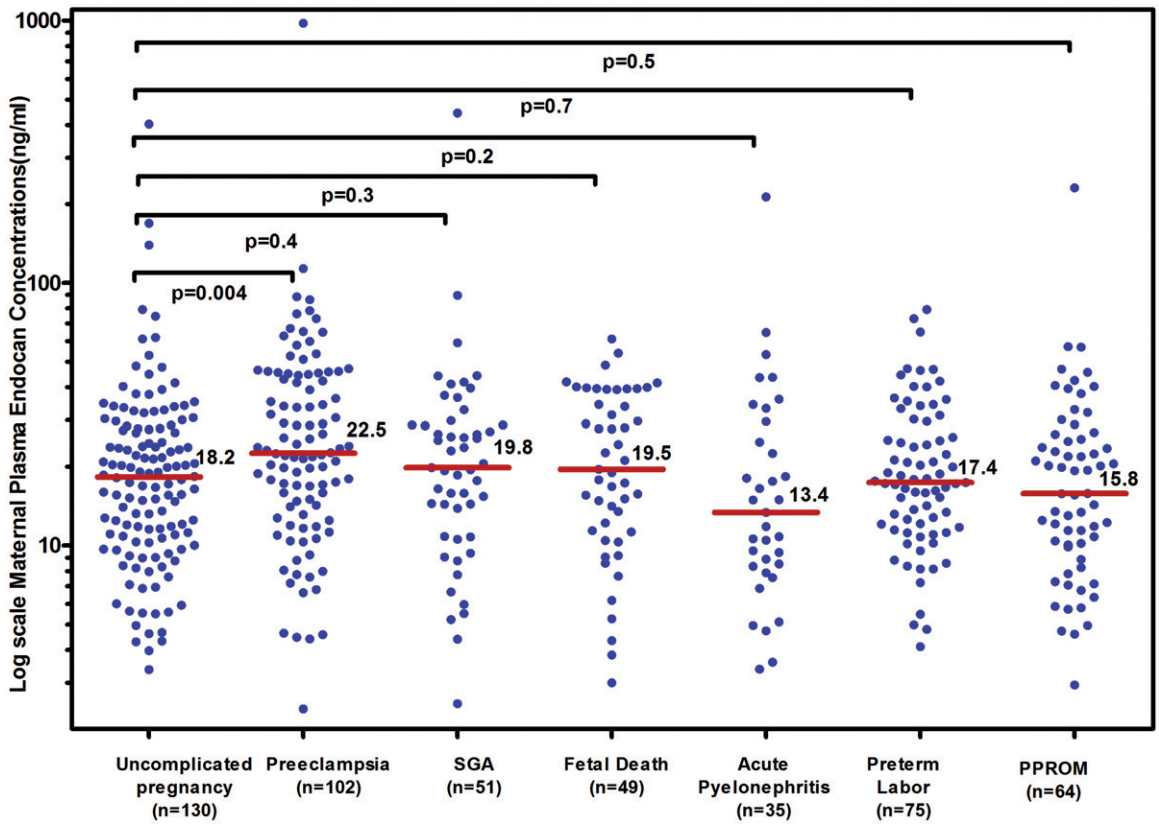

Figure 1. The median plasma endocan concentration in uncomplicated pregnancy, preeclampsia, pregnancies complicated by the delivery of a small-for-gestational age newborn (SGA), fetal death, acute pyelonephritis, preterm labor and preterm pre-mature rupture of membranes (PPROM). There were significant differences among groups; $p = 0.01$. The median plasma endocan concentration (ng/ml) between uncomplicated pregnancies; 18.2 (IQR 10.6–28.0) and other groups were as follows: preeclampsia (22.5, IQR 13.8–44.4; $p = 0.004$), SGA (19.8, IQR 10.8–28.8; $p = 0.4$); fetal death (19.5, IQR 11.3–39.2; $p = 0.3$); acute pyelonephritis (13.4, IQR 8.3–29.6; $p = 0.2$); preterm labor (17.4, IQR 11.8–29.7; $p = 0.7$); and preterm PROM (15.8, IQR 10.0–26.0; $p = 0.5$).

Maternal plasma endocan concentration in pregnancies with acute pyelonephritis

The median plasma endocan concentration (ng/ml) was lower in pregnancies complicated by acute pyelonephritis than in uncomplicated pregnancies, but this was not statistically significant (13.4, IQR 8.3–29.6 versus 18.2, IQR 10.6–28.0; $p = 0.2$). There was no significant difference observed between the median plasma endocan concentration (ng/ml) in pregnancies complicated by acute pyelonephritis without bacteremia and uncomplicated pregnancies (18.1, IQR 9.5–35.2 versus 18.2, IQR 10.6–28.0; $p = 0.7$; Figure 2). The median plasma concentration of endocan (ng/ml) in pregnancies complicated by acute pyelonephritis with bacteremia was significantly lower than that of those without bacteremia (8.4, IQR 4.5–13.8 versus 18.1, IQR 9.5–35.2; $p = 0.004$; Figure 2) and lower than that of women with uncomplicated pregnancies (8.4, IQR 4.5–13.8 versus 18.2, IQR 10.6–28.0; $p = 0.001$). The prevalence of acute respiratory distress syndrome (ARDS) among pregnancies complicated by acute pyelonephritis in this study was 2.9% (1/35). The plasma endocan concentration of the patient who developed ARDS was 13.4 ng/ml.

The median maternal plasma concentration of endocan (ng/ml) was significantly lower in patients with acute pyelonephritis in patients with preeclampsia (13.4, IQR 8.3–29.6 versus 22.5, IQR 13.8–44.4; $p = 0.005$).

Maternal plasma endocan concentration in fetal death, SGA, preterm labor and preterm PROM

There were no significant differences in the median plasma endocan concentrations (ng/ml) among women with uncomplicated pregnancies (18.2, IQR 10.6–28.0) and those with FD (19.5, IQR 11.3–39.2; $p = 0.3$), delivery of an SGA neonate (19.8, IQR 10.8–28.8; $p = 0.4$), spontaneous PTL (17.4, IQR 11.8–29.7; $p = 0.7$) or preterm PPROM (15.8, IQR 10.0–26.0; $p = 0.5$; Figure 1).

Multivariable adjustment with correction for the FDR did not alter the unadjusted determinations of statistical significance. Log endocan concentrations were significantly higher among women with preeclampsia than in those with uncomplicated pregnancies ($p < 0.01$), adjusting for gestational age at venipuncture, maternal age, nulliparity, race, smoking status and BMI. Similarly adjusting for potential confounders, log endocan concentrations were significantly lower among women with acute pyelonephritis with bacteremia than among those with acute pyelonephritis without bacteremia ($p < 0.01$) or uncomplicated pregnancies ($p < 0.01$).

Discussion

Principal findings of the study

(1) The median plasma endocan concentration was higher in preeclampsia than in uncomplicated pregnancies; however,

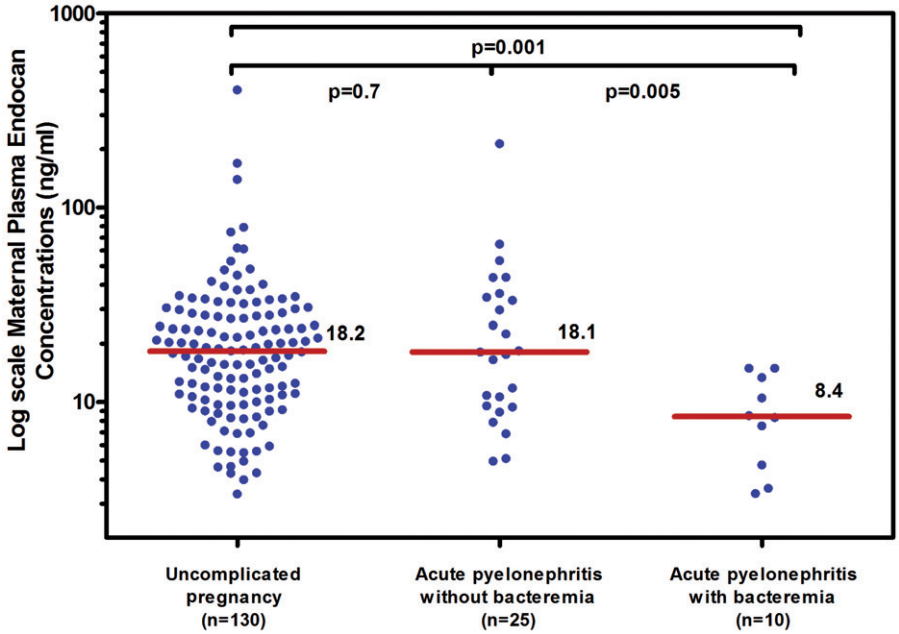

Figure 2. The median plasma endocan concentration of uncomplicated pregnancies, pregnancies complicated by acute pyelonephritis without bacteremia and pregnancies complicated by acute pyelonephritis with bacteremia. There was significant difference in the median plasma endocan concentration (ng/ml) among groups ($p = 0.001$). Pregnancies complicated by acute pyelonephritis with bacteremia (8.4, IQR 4.5–13.8) had a lower median plasma concentration of endocan than those without bacteremia (18.1, IQR 9.5–35.2; $p = 0.005$) and lower than those with uncomplicated pregnancies (18.2, IQR 10.6–28.0; $p = 0.001$). There was no significant different in the median plasma endocan concentration between pregnancies complicated by acute pyelonephritis without bacteremia (18.1, IQR 9.5–35.2) and those with uncomplicated pregnancy (18.2, IQR 10.6–28.0; $p = 0.7$). Kruskal–Wallis and Mann–Whitney *U*-tests were performed for comparisons.

there was no relationship between the plasma concentration of endocan and the severity of preeclampsia; (2) there was a positive correlation between the plasma concentration of endocan and sVEGFR-1 and sEng plasma concentrations among women with preeclampsia; (3) contrary to what was expected, the median plasma concentration of endocan was lower in patients with acute pyelonephritis than in those with preeclampsia; a subgroup analysis demonstrated a significantly lower median endocan concentration in acute pyelonephritis with bacteremia than in those without bacteremia and in those with uncomplicated pregnancies; and (4) endocan was not elevated in other obstetrical syndromes, such as fetal death, SGA, preterm labor and preterm PROM, suggesting that an elevation of maternal plasma endocan occurs selectively in patients with preeclampsia.

Endothelial cell activation and dysfunction in health and disease

The endothelium is a monolayer that lines all blood vessels. The functions of the endothelium are to maintain vascular tone, prevent cell adhesion, promote thromboresistance and regulate smooth muscle vessel wall proliferation [105,106]. Many of these properties are mediated by nitric oxide (NO), which is produced by the endothelium [from L-arginine by the action of endothelial NO synthase (also called eNOS)] [107–116]. This gas diffuses to the vascular smooth muscle cells and activates guanylate cyclase, which leads to cGMP-mediated vasodilatation [106,107,117]. Physiologic regulators of eNOS expression include shear stress [118–122], but other factors can activate this enzyme, including bradykinin, adenosine, vascular endothelial growth factor and serotonin [112,123–128].

The concept of endothelial cell activation was formulated by investigators examining the behavior of endothelial cells in culture, and was coined to describe the increased adhesive properties of these cells to white blood cells when endothelial cells are exposed to biomechanical stimuli [129–131] or cytokines [132–138]. The molecular basis for the increased adhesiveness was the expression of cell surface adhesion molecules, such as VCAM-1, ICAM-1 and endothelial cell adhesion molecule (also known as E-selectin or ELAM) [139,140]. Nitric oxide generated from endothelium (as a result of the activity of nitric oxide synthase) can reduce endothelial cell activation through inhibition of NFκ-B [139,141–143].

The term ''endothelial cell dysfunction'' was introduced by physiologists and cardiologists who were originally studying impaired endothelial cell-dependent relaxation, and demonstrated that this feature was present in patients with essential hypertension [144]. Endothelial cell dysfunction has been defined as decreased synthesis, release and/or activity of endothelium-derived nitric oxide induced by hypercholesterolemia [140,145], smoking [140,146–148] or oxidative stress [140,149–152].

Endothelial cell activation may lead to endothelial cell dysfunction [140], and both can induce vasoconstriction, platelet aggregation, leukocyte adhesion, low-density lipoprotein oxidation and matrix metalloproteinase protein activation [140]. Thus, endothelial cell activation/dysfunction can lead to atherosclerosis/vascular disease [153–156]. Pregnancy represents a physiological state in which there appears to be endothelial cell activation as a consequence of physiologic intravascular inflammation [157]. It is unclear if endothelial cell activation and dysfunction have different molecular fingerprints; indeed, they appear to coexist. Preeclampsia is considered to be characterized by endothelial cell activation/dysfunction [17–24], and this condition is associated with a significant increase in the maternal circulating concentrations of sE-selectin [57,58,60,158,159] and sVCAM-1 [57,60,158,160,161], which are markers of endothelial cell activation/dysfunction [136,162]. However, there is no increase in the concentration of sICAM-1 and sPECAM-1 [57,60,163,164], indicating that there are some unique features of endothelial cell activation/dysfunction in preeclampsia. When assessing the profile of adhesion molecules, we have found that patients with acute pyelonephritis have

an increase in sICAM-1, sE-selectin and sVCAM-1 [60], suggesting that there are subtle differences in the adhesion molecule profile in patients with pyelonephritis and pre-eclampsia, both of which are characterized by intravascular inflammation [12,157].

What is endocan?

Endocan is a dermatan sulphate proteoglycan first isolated from the human umbilical vein endothelial cell (HUVEC) cDNA library by Lassalle et al. [165]. This protein is found in endothelial cells and in the epithelium the lung and kidney [166]. Pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β can up-regulate mRNA expression of endocan in endothelial cells [167]. Endocan can inhibit the interaction between intercellular adhesion molecule-1 (ICAM-1) and the integrin (lymphocyte function-associated antigen-1) LFA-1 on leukocytes [168,169], then modulate several leukocyte functions, including adhesion to the endothelium and transmigration [168,170,171]. In addition, endocan can stimulate endothelial cell proliferation and migration induced by epidermal growth factor (EGF), Hepatocyte growth factor/scatter factor (HGF/SF) and vascular endothelial growth factor (VEGF) A and-C [172–174]. This has been attributed to the dermatan sulfate moieties of endocan [172,173,175].

We decided to study the behavior of endocan in normal pregnancy and pregnancy complications due to the claim that this was an endothelial cell marker [81]. Previous reports indicated that serum endocan concentrations were elevated in patients with sepsis and septic shock [81]. Sepsis is considered to represent a state in which there is endothelial cell activation/dysfunction. In these conditions, activated leukocytes roll, adhere and extravasate following interaction between the integrin leukocyte function-associated antigen (LFA-1) and intercellular adhesion molecule (ICAM-1) on surface of these activated leukocytes [176].

Plasma endocan concentration is increased in pre-eclampsia

'We found that plasma endocan concentrations was increased in patients with preeclampsia, and this increase correlated with the increase in plasma anti-angiogenic factors concentrations, but not with the severity of disease. Preeclampsia is characterized by excessive maternal systemic vascular inflammation, as demonstrated by the phenotypic and metabolic characteristics of neutrophils and monocytes [10,12,177,178], as well as the increased concentration of cytokines [63,65,179–197], chemokines [63,65,198–203], other inflammatory mediators [63,185,189,190,192,204–213], as well as acute phase protein reactants [193,204,214–225] and the decreased concentration of negative acute phase protein reactants [225,226]. The increased cytokine concentration in pre-eclampsia may be responsible for the elevation in endocan.

The relationship between the increased concentrations of maternal plasma endocan and that of anti-angiogenic factors (sVEGFR-1 and endoglin) in preeclampsia suggests that there may be convergence of the inflammatory process, and the abnormal anti-angiogenic profile observed in the disease [227]. The lack of correlation between the concentrations of PlGF and endocan is unexpected, given that VEGF (another angiogenic factor in the same family as PIGF) can stimulate endocan mRNA expression and release from endothelial cells [228].

Plasma endocan concentration is lower in pregnant women with acute pyelonephritis

Scherpereel et al. [81] demonstrated that the serum endocan concentrations in patients with sepsis and a systemic inflammatory response were significantly higher than that of non-pregnant patients. Our findings herein are different, as we observed that the median plasma endocan concentration was lower in pregnancies complicated by acute pyelonephritis than in non-pregnant patients. This is a puzzling observation, given that our systematic studies of the behavior of cytokines [229], chemokines [230], complement [231,232] in acute pyelonephritis and preeclampsia suggest that both conditions are associated with a pro-inflammatory state. However, studies of the transcriptome of peripheral blood in patients with preeclampsia [233] and pyelonephritis [234] suggest that the molecular details of the inflammatory response differ. Further work is required to understand the similarities and differences in the systemic and local inflammatory response in these two conditions. Interestingly, systemic infection in non-pregnant subjects is associated with an increase in the concentration of sVEGFR-1 in non-pregnant animals [235] and humans [236]. However, in pregnant subjects with acute pyelonephritis, the median plasma concentrations of anti-angiogenic factors (VEGFR-1 and sEng), similar to endocan, are not significantly higher than that of uncomplicated pregnancy [229]. In addition, endocan behaves in a different direction of change in preeclampsia compared to the changes observed in acute pyelonephritis with bacteremia. This is consistent with the view that there may be a fundamental difference in the nature of the inflammatory response in microbial- and ''danger signal''-induced inflammation [237].

TNF-α, which stimulates the production of endocan [167], is increased in the peripheral blood of patients with sepsis [238–241]. In addition to demonstrating a high concentration of TNF-α in plasma during maternal sepsis [242], our group also showed a higher concentration of this cytokine in pregnancies complicated by acute pyelonephritis than uncomplicated pregnancies [229]. Therefore, a lower plasma endocan concentration in pregnancies complicated by acute pyelonephritis as a whole, and especially those complicated by bacteremia, was unexpected.

One study reported that, among patients with major trauma, those with lower circulating concentrations of endocan are at increased risk for acute lung injury supporting a protective effect of this protein [243]. The presence of endocan may inhibit leukocyte recruitment, and this protects against lung injury [168]. There was no evidence in our study that patients with pyelonephritis had a higher rate of acute lung injury, although it is well-known that pregnant women with pyelonephritis are at an increased risk for ARDS [244–249].

Strengths and limitations

This is the first study to focus on the changes in plasma concentrations of endocan in preeclampsia, acute pyelonephritis and other ''great obstetrical syndromes''. The cross-sectional nature of this study does not enable us to make inferences about temporal changes before diagnosis of the diseases.

Conclusion

Maternal plasma endocan concentrations were higher in pregnancies complicated by preeclampsia and lower in pregnancies complicated by acute pyelonephritis with bacteremia when compared to uncomplicated pregnancies. Patients with SGA, fetal death, preterm labor or preterm PROM did not have demonstrable changes in maternal plasma concentrations of endocan when compared to uncomplicated pregnancies.

Declaration of interest

The authors declare no conflicts of interest. This research was supported, in part, by the Perinatology Research Branch, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services (NICHD/NIH); and, in part, with Federal funds from NICHD, NIH under Contract No. HHSN275201300006C.

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