The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: informahealthcare.com/journals/ijmf20

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To cite this article: Piya Chaemsaithong, Tinnakorn Chaiworapongsa, Roberto Romero, Steven J. Korzeniewski, Tamara Stampalija, Nandor Gabor Than, Zhong Dong, Jezid Miranda, Lami Yeo & Sonia S. Hassan (2014) Maternal plasma soluble TRAIL is decreased in preeclampsia, The Journal of Maternal-Fetal & Neonatal Medicine, 27:3, 217-227, DOI: 10.3109/14767058.2013.806906

To link to this article: https://doi.org/10.3109/14767058.2013.806906

Published online: 13 Aug 2013.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE

http://informahealthcare.com/jmf
ISSN: 1476-7058 (print), 1476-4954 (electronic)

J Matern Fetal Neonatal Med, 2014; 27(3): 217–227
 DOI: 10.3109/14767058.2013.806906

informa healthcare

ORIGINAL ARTICLE

Maternal plasma soluble TRAIL is decreased in preeclampsia[1]

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Abstract

Objective: Preeclampsia (PE) is characterized by systemic intravascular inflammation. Women who develop PE are at an increased risk for cardiovascular disease in later life. Tumor necrosis factor related apoptosis-inducing ligand (TRAIL) has anti-atherosclerotic effects in endothelial cells and can mediate neutrophil apoptosis. Low soluble TRAIL (sTRAIL) and high C-reactive protein (CRP) concentrations are associated with an increased risk of future cardiovascular disease in non-pregnant individuals. The aim of this study was to determine whether maternal plasma concentrations of sTRAIL and CRP differ between women with PE and those with uncomplicated pregnancies.

Method: This cross-sectional study included women with an uncomplicated pregnancy ($n = 93$) and those with PE ($n = 52$). Maternal plasma concentrations of sTRAIL and CRP concentrations were determined by ELISA.

Results: 1) The median plasma sTRAIL concentration (pg/mL) was significantly lower and the median plasma CRP concentration was significantly higher in women with PE than in those with an uncomplicated pregnancy (25.55 versus 29.17; $p = 0.03$ and 8.0 versus 4.1; $p = 0.001$, respectively); 2) the median plasma concentration sTRAIL/CRP ratio was two-fold lower in women with PE than in those with an uncomplicated pregnancy ($p < 0.001$); and 3) women with plasma sTRAIL and CRP ratio in the lowest quartile were 8 times more likely to have PE than women with concentrations in the upper three quartiles (OR 8.9; 95% CI: 2.8–27.8).

Conclusion: Maternal plasma sTRAIL concentrations are lower (while those of CRP are higher) in women with PE than in those with uncomplicated pregnancies. These findings are consistent with the evidence of intravascular inflammation in this disorder.

Keywords

Apoptosis, coronary artery disease, C-reactive protein, endothelial cell, intravascular inflammation, neutrophil apoptosis

History

Received 16 April 2013
Accepted 16 May 2013
Published online 13 August 2013

Introduction

Preeclampsia (PE) is a multisystemic disorder defined clinically by the combination of new onset of gestational hypertension and proteinuria [1–16]. The condition has been termed ''toxemia of pregnancy'' because soluble factors have been implicated in its pathophysiology [1,17–20]. A disorder of deep placentation [21–26], resulting in failure of physiologic transformation of the spiral arteries has been proposed to lead to uteroplacental ischemia [27–29], which in turn, leads to the disease.

Intravascular inflammation [30–32] and endothelial cell dysfunction [33–44] are characteristic of PE, although intravascular inflammation has been reported in patients with other complications of pregnancy, such as preterm labor [45–47], preterm premature rupture of membrane (PROM) [48,49], and small for gestational age (SGA) [50–64]; failure of physiologic transformation of the spiral arteries has also been described in these three conditions [21,65–67]. A subset of patients with PE demonstrates an anti-angiogenic state. Plasma concentrations of the angiogenic factor, [placental growth factor (PlGF)], are decreased [68–77], and the anti-angiogenic factors [soluble vascular endothelial growth factor receptor-1 (sVEGFR-1), soluble endoglin (sEng)] are elevated both prior to [78–88] and at the time of the diagnosis [89–95]. Moreover, the concentration of these factors can be used to predict the outcome of the disease in patients presented to the obstetrical triage area [79,96–98].

Women who develop PE are at an increased risk of cardiovascular disease in later life [99–109]. There are common risk factors for both conditions, such as hyperlipidemia [110–117], insulin resistance [110,111,116,118–120], obesity [110,111,117,121], and hypertension [110,111,117]. This suggests that an underlying mechanism of disease may predispose to both PE and cardiovascular disease. C-reactive protein (CRP) is a positive acute phase reactant protein that is

[1]Presented at the 33rd Annual Meeting Society for Maternal-Fetal Medicine, February 11–16, 2013, San Francisco, CA, USA

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produced by the liver in response to pro-inflammatory cytokines [122–124], and has pro-inflammatory and pro-atherogenic properties [125–131]. A solid body of evidence has shown that CRP is a major predictor of the subsequent risk of cardiovascular disease in non-pregnant subjects [132–145]. CRP is also known to be elevated in women with PE before [59,146–150] and at the time of diagnosis [151–155].

Tumor Necrosis Factor (TNF)-Related Apoptosis Inducing Ligand (TRAIL), a type II membrane bound tumor necrosis factor (TNF) family ligand [156,157], is a cytokine capable of inducing apoptosis. It has both anti-atherosclerotic and anti-inflammatory properties, and possibly promotes survival and proliferation of human vascular endothelial cells [158–163]. TRAIL has been implicated in the resolution of inflammation by removing both senescent circulating and activated tissue neutrophils [164–166].

While prior studies have reported that soluble TRAIL (sTRAIL) concentrations are reduced in the setting of cardiovascular disease [163,167–170], there is a paucity of information about the behavior of sTRAIL in pregnancy and PE [171]. The aim of this study was to determine whether maternal plasma sTRAIL concentrations differ between uncomplicated pregnancies and PE at the time of diagnosis.

Materials and methods

Study design

A cross-sectional study was conducted by searching the clinical database and bank of biologic samples of Wayne State University, Detroit Medical Center and the Perinatology Research Branch. The following group were included: 1) women with uncomplicated pregnancies ($n = 93$); and 2) women with PE ($n = 52$). Women with multiple gestations, affected by medical conditions (e.g. chronic hypertension, diabetes, renal disease), and those carrying fetus with congenital anomalies were excluded. All patients were enrolled at Hutzel Women's Hospital, Detroit, MI, USA and had venipuncture between 20 and 42 weeks.

PE was defined as hypertension (systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg on at least two occasions, 4 h to 1 week apart) and proteinuria ($\geq$300 mg in a 24-h urine collection or one urine dipstick measurement $\geq$2+) [172]. Severe PE was defined as previously describe [172]. Patients with PE were also sub classified as preterm (<37 weeks) and term ($\geq$37 weeks) according to the gestational age at diagnosis. Small for gestational age (SGA) was defined by ultrasonographic estimated fetal weight and birthweight <10th percentile for gestational age, according to the reference range proposed by Alexander et al. [173,174].

Women with an uncomplicated pregnancy were enrolled from either the Labor and Delivery unit (in cases of scheduled cesarean delivery) or the antenatal clinic, and were followed until the time of delivery. Uncomplicated pregnancy was defined as: (1) no medical, obstetrical, or surgical complications; (2) absence of labor at the time of venipuncture; and (3) delivery of a normal term ($\geq$37 weeks) infant whose birthweight was between the 10th and 90th percentile for gestational age. All women provided informed consent prior to the collection of plasma samples. The collection and utilization of samples for research purposes was approved by the Human Investigation Committee of Wayne State University and the IRB of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS. Many of these samples were used previously in studies of intravascular inflammation, soluble adhesion molecules, and cytokine biology in uncomplicated and complicated pregnancies.

Sample collection and human sTRAIL and CRP

Venipuncture was performed in the antenatal clinic or in the Labor and Delivery unit for women with uncomplicated pregnancies or at the time of diagnosis for women with PE. Blood was collected into tubes containing EDTA, centrifuged, and stored at $-70\,^{\circ}$C.

Concentrations of sTRAIL were measured using enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN). This assay employs the quantitative sandwich immunoassay technique. Briefly, recombinant human TRAIL standards and maternal plasma specimens were incubated in duplicate wells of the microtiter plates, which were pre-coated with monoclonal antibodies specific for TRAIL. During incubation, immobilized antibodies in the microtiter plate bound TRAIL which was present in both the standard and sample groups. After washing unbound substances, polyclonal antibodies to human TRAIL conjugated to an enzyme (horse-radish peroxidase) were added to the assay wells. Once the incubation period was complete, assay plates were washed to remove unbound antibody-enzyme reagents. Upon addition of a substrate solution (tetramathylbenzidine), color developed in the assay plates proportionally to the amount of TRAIL bound in the initial step. Microtiter plates were read using a programmable spectrophotometer (SpectraMax M5 Multi-Mode Microplate Reader, Molecular Devices, Sunnyvale, CA). The inter-and intra-assay coefficients of variation were 6.5% and 3.7%, respectively. The lowest maternal plasma sTRAIL concentration detectable was 8.2 pg/mL. Maternal plasma concentrations of CRP were also determined in 85 patients. For CRP, the inter-and intra-assay coefficients of variation were 10.66% and 2.96%, respectively. The lowest maternal plasma CRP concentration detectable was 0.048 ng/mL.

Statistical analysis

Normality of arithmetic data was assessed using the Kolmogorov–Smirnov test and visual plot inspection. Differences in frequency distributions of categorical variables were tested using the Chi-square or Fisher's exact test, where appropriate. Bivariate comparisons of arithmetic data were examined using a Mann–Whitney U test in the presence of non-normally distribute data. Multivariable general linear models were constructed to explore the effect of potentially confounding factors, selected based upon clinical knowledge (gestational age at venipuncture, maternal age, nulliparity, and race). These were entered into a ''full model,'' and variable reduction was considered to derive a ''final model'' based on the plausibility of regression coefficients, association between independent variables, and the magnitude of

change in the association between study group and group least squares geometric mean sTRAIL concentrations. Examined analytes were logarithmically transformed (base 2) to better meet the assumptions of linear regression. Multivariable logistic regression models were used to determine the magnitude of association between study group and the ratio of plasma sTRAIL/CRP, dichotomized as above or below the first quartile value calculated among patients with an uncomplicated pregnancy. Spearman correlation coefficients were also used to characterize the relationship between plasma concentrations of sTRAIL and CRP in each group. Statistical analysis was performed using SPSS 19 (IBM Corp, Armonk, NY) and SAS 9.3 (Cary, NC). A p value <0.05 was considered statistically significant.

Results

Demographic, clinical and obstetric characteristics are displayed in Table 1. The frequency of nulliparous women was greater in women with PE than in those with an uncomplicated pregnancy. Otherwise, there were no significant differences in characteristics between study groups ($p > 0.05$).

In women with PE, the median plasma sTRAIL concentration was significantly lower while that of CRP was significantly higher than in those with uncomplicated pregnancies ($p = 0.03$ and 0.001, respectively; Figure 1). Pre-specified subgroup analyses suggest that these differences may be confined to women with PE examined at <37 weeks of gestation. For this group, the median plasma sTRAIL concentration was 19% lower and the median CRP concentration was 53% greater than in those with uncomplicated pregnancies ($p = 0.03$ and 0.002, respectively; Figure 2). There were no significant differences in the median plasma sTRAIL and CRP concentrations between women with uncomplicated pregnancy at term and PE at term (Figure 3).

Multivariable adjustment for gestational age at venipuncture, maternal age, nulliparity, and race revealed that none of these factors were independently associated with plasma concentration of sTRAIL or CRP. The relationship between study group and either analyte also did not vary significantly as a function of gestational age at venipuncture ($p > 0.34$). Adjustment for BMI changed the group least squares means by less than 2%, and did not alter the statistical significance. Thus, the relationship between study group and either analyte was not confounded by any of the examined factors.

Among women with uncomplicated pregnancies, the plasma sTRAIL concentration was not correlated with plasma CRP concentrations (spearman correlation = 0.13; $p = 0.30$). Alternatively, among women with PE, plasma sTRAIL concentrations were negatively correlated with plasma CRP concentrations (spearman correlation = −0.28); however, the relationship did not reach the statistical significance ($p = 0.10$).

The plasma sTRAIL/CRP ratio demonstrated a greater magnitude of the difference between PE and uncomplicated pregnancy than either analyte individually. Specifically, the median ratio was approximately twofold lower in women with PE than in those with an uncomplicated pregnancy ($p < 0.001$; Figure 4). Women with a plasma sTRAIL/CRP ratio in the lowest quartile were eightfold more likely to have PE than in women with concentrations in the upper three quartiles [OR 8.0; 95% confidence interval (CI): 2.9–22.4]. Multivariable adjustment for maternal age, nulliparity, race, and gestational age at venipuncture slightly increased the magnitude of this association (OR 8.9; 95% CI: 2.8–27.8). Adjusting for BMI did not change the magnitude of association between PE and the lowest quartile ratio (OR 7.4; 95% CI: 2.0–26.1).

Discussion

Principal findings

(1) women with PE had a significantly lower median plasma sTRAIL, sTRAIL/CRP ratio concentration, and a higher median CRP concentration than in those with uncomplicated pregnancies; (2) there was no correlation between plasma concentrations of sTRAIL and CRP; and (3) women with a median plasma sTRAIL/CRP ratio in the lowest quartile were 8 times more likely to have PE than in those with concentrations in the upper three quartiles.

Potential mechanisms by which decreased plasma sTRAIL concentrations may confer an increased risk of PE are its anti-inflammatory and anti-atherosclerotic effects in endothelial cells and its involvement in systemic intravascular inflammation [164–166].

Table 1. Clinical characteristics of uncomplicated pregnancy versus preeclampsia.

	Uncomplicated pregnancy ($n = 93$)	Preeclampsia ($n = 52$)	p Value
Age (years)	24 (21, 29)	23 (19, 29)	0.32
Race			
African American	69 (74.19)	39 (75)	0.63
Caucasian	13 (13.98)	8 (15.38)	
Hispanic	5 (5.38)	4 (7.69)	
Asian	6 (6.45)	0	
Other	0	1 (1.92)	
Nulliparity (%)	28 (30.1)	35 (67.3)	<0.001
Pre- pregnancy body mass index (BMI; kg/m^2)	24.74 (21.42 to 31.01)*	26.68 (24.06 to 30.27)†	0.28
Gestational age at venipuncture (weeks)	33.71 (28.86 to 38.93)	31.86 (29.18 to 37.54)	0.44
Gestational age at delivery (weeks)	39.29 (38.57 to 40.36)	32.29 (29.93 to 37.57)	<0.001
Birthweight (grams)	3360 (3085 to 3634.5)	1725 (1150 to 2635)	<0.001

Values are presented as median (interquartile range).
*missing data $N = 49$, †Missing data $N = 31$.

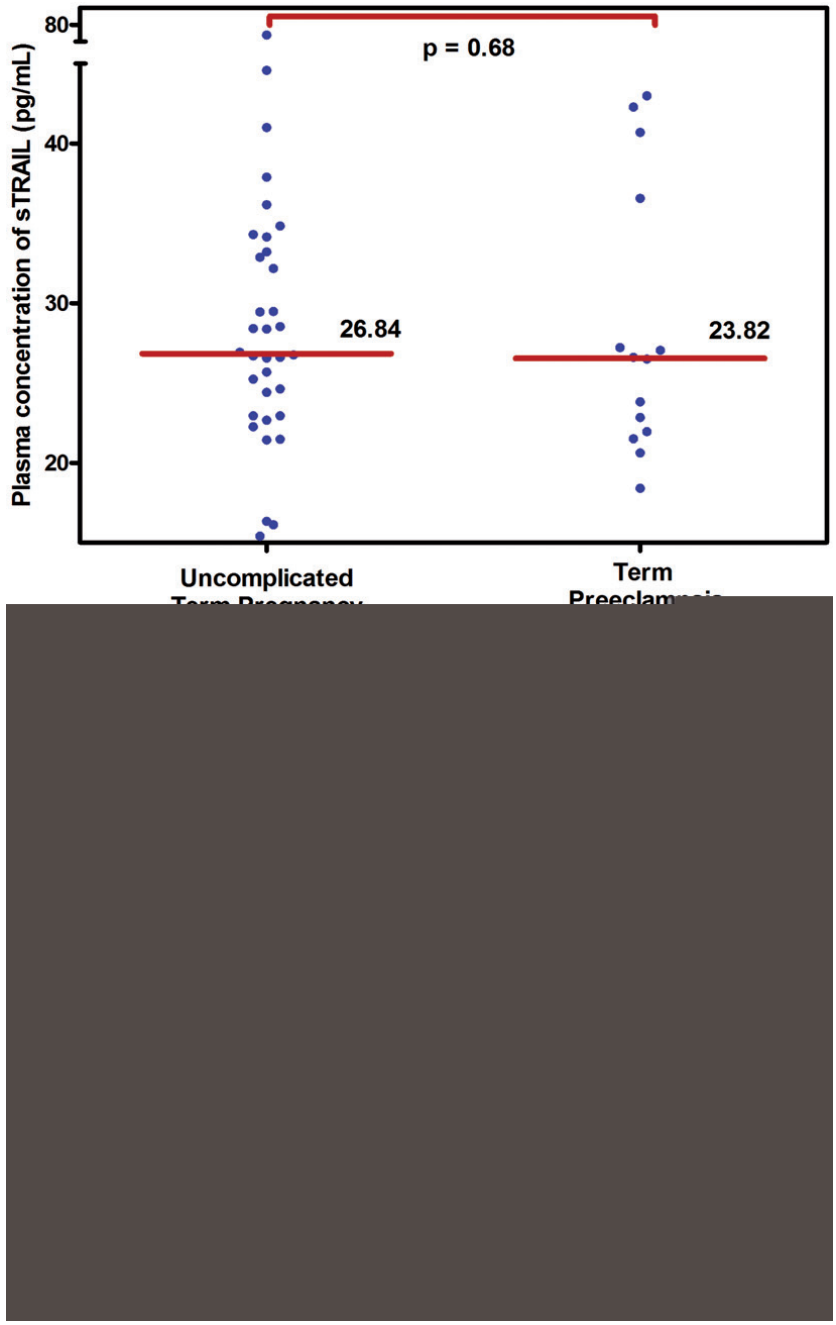

Figure 1. Median plasma sTRAIL and CRP concentrations in women with uncomplicated pregnancy and preeclampsia. Women with preeclampsia had a significantly lower median (IQR) plasma sTRAIL concentration (pg/mL) than those with uncomplicated pregnancy [25.55 (20.62–36.11) versus 29.17 (25.24–36.28); $p = 0.03$]. For CRP, women with preeclampsia had a significantly higher median (IQR) plasma CRP concentration (ng/mL) than those with uncomplicated pregnancy [8 (5.3–1.7) versus 4.1 (1.2–8.6); $p = 0.001$].

Biology of TRAIL

TRAIL interacts with four high-affinity transmembrane receptors and one soluble receptor belonging to the TNF receptor family. TRAIL-receptor 1 (TRAIL-R1)/Death receptor 4 (DR4) [175] and TRAIL-R2/DR5 [176–179] are capable of inducing a pro-apoptotic signal through: 1) intracellular death domain (DD), which; in turn recruits procaspase-8 to activate death-inducing signaling complex (DISC), followed by the cleavage and activation of effector caspases 3, 6 and 7 (so called extrinsic or mitochondrial independent pathways) [180–183]; and 2) activation of Bcl-2 interacting protein domain (BID) by the engagement of mitochondria (so called the intrinsic pathway) [184,185]. In contrast, binding of TRAIL to TRAIL-R3/Decoy receptor 1 (DcR1) [176,177,179,186,187] or TRAIL-R4/DcR2 [186,187] cannot induce an apoptotic signal, and thus, both are considered decoy receptors. TRAIL can also bind to osteoprotegerin (OPG), a protein involved in bone remodeling which acts through ligands other than TRAIL [188,189]. The soluble form of TRAIL also elicits apoptosis signals similar to that of the cell surface TRAIL [190,191].

TRAIL and its receptors are expressed in a variety of human tissues, most predominantly in immune cells (e.g. lymphocytes, monocytes, dendritic cells, natural killer cells, neutrophils, macrophages) [156,164,176,179,186,192], human endothelial cells [60,75], the placenta, and fetal membranes [193,194]. The proposed functions of TRAIL in pregnancy are to establish immune tolerance at the feto-maternal interface [193,194] and induce smooth muscle cell apoptosis in the spiral arteries [195,196].

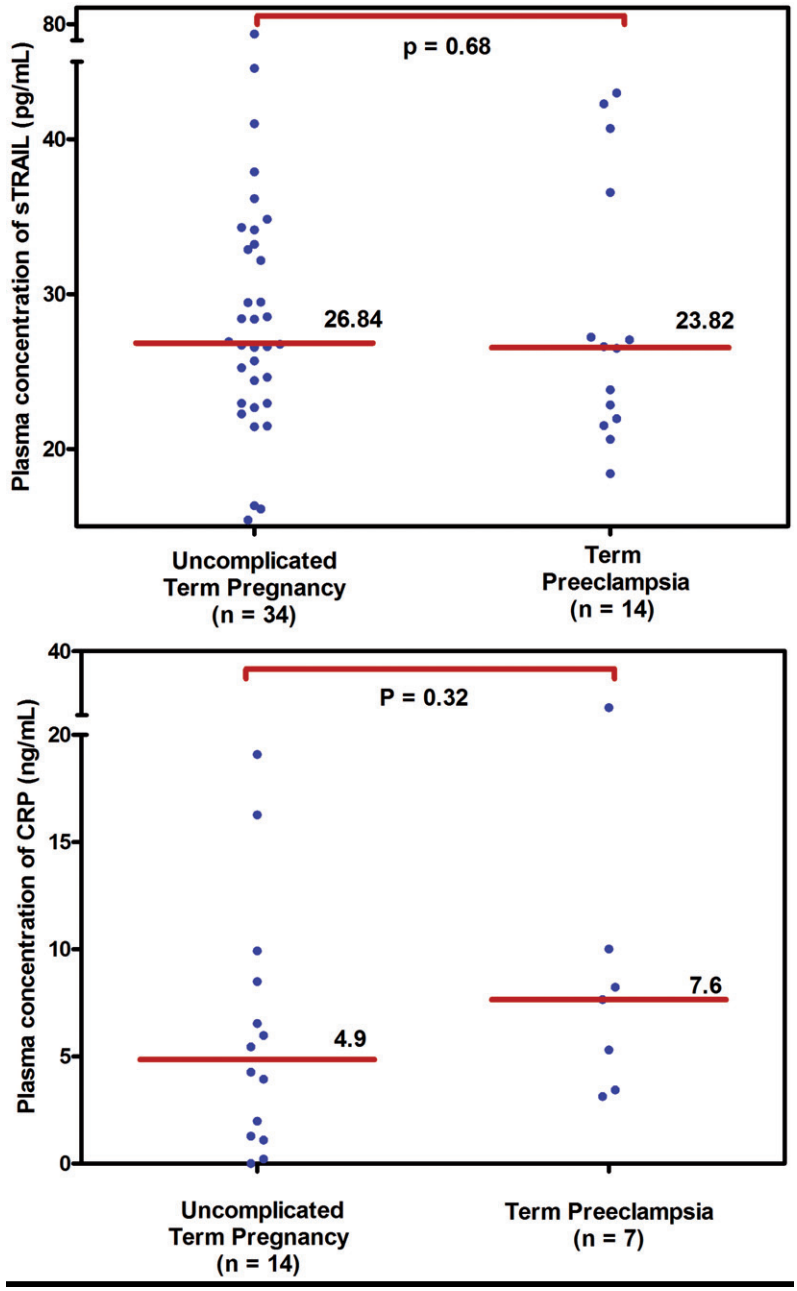

Figure 2. Median plasma concentrations of sTRAIL and CRP in women with uncomplicated preterm gestations and preterm preeclampsia. Women with preterm preeclampsia had a significantly lower median (IQR) plasma concentration (pg/mL) of sTRAIL than those with uncomplicated preterm gestations [24.76 (19.81–35.45) versus 30.50 (26.41–39.23) $p = 0.03$]. For CRP, women with preterm preeclampsia had a significantly higher median (IQR) plasma concentration (ng/mL) than those with uncomplicated preterm gestations [8.7 (5.5–19.7) versus 4.1 (0.9–8.8); $p = 0.002$].

TRAIL is capable of inducing apoptosis in macrophages and neutrophils, therefore, a disturbance in this process may result in prolonged neutrophil survival, and contribute to a further systemic inflammatory response and possible multiple organs dysfunction [164,192,197]. The anti-inflammatory and anti-atherosclerotic properties of TRAIL are demonstrated by the down-regulation of proadhesive inflammatory cytokines (CCL8, CXCL10) in models of human endothelial cell culture [162]. Systemic TRAIL administration also markedly reduce the development and extension of atherosclerotic plaques in apolipoprotein E-null diabetics mice by inducing macrophage and neutrophil cell death [192,198,199], and increasing vascular smooth muscle cell content [198]. TRAIL modulates the production of prostaglandin E_2 (PGE_2), prostaglandin I_2 (PGI_2) and nitric oxide (NO) [159]. Such factors regulate vascular tone, promote endothelial cell survival and migration, inhibit platelet adhesion and aggregation, and inhibit leukocyte adherence, supporting the antithrombotic and anti-inflammatory effects of TRAIL in endothelial cells [159–161]. Moreover, TRAIL and ApoE-deficient mice have a significantly greater mean area of atheromatous lesions in the aorta than ApoE-deficient mice controls when fed with a regular chow or western diet for 8 weeks [200]. Taken all together, TRAIL is a protective cytokine against inflammation and also has a protective role in vascular endothelial cells.

Maternal plasma sTRAIL and CRP concentrations in patients with preeclampsia

In the study reported herein, women with PE had a significantly lower median plasma sTRAIL concentration than in those with uncomplicated pregnancies. The decrease

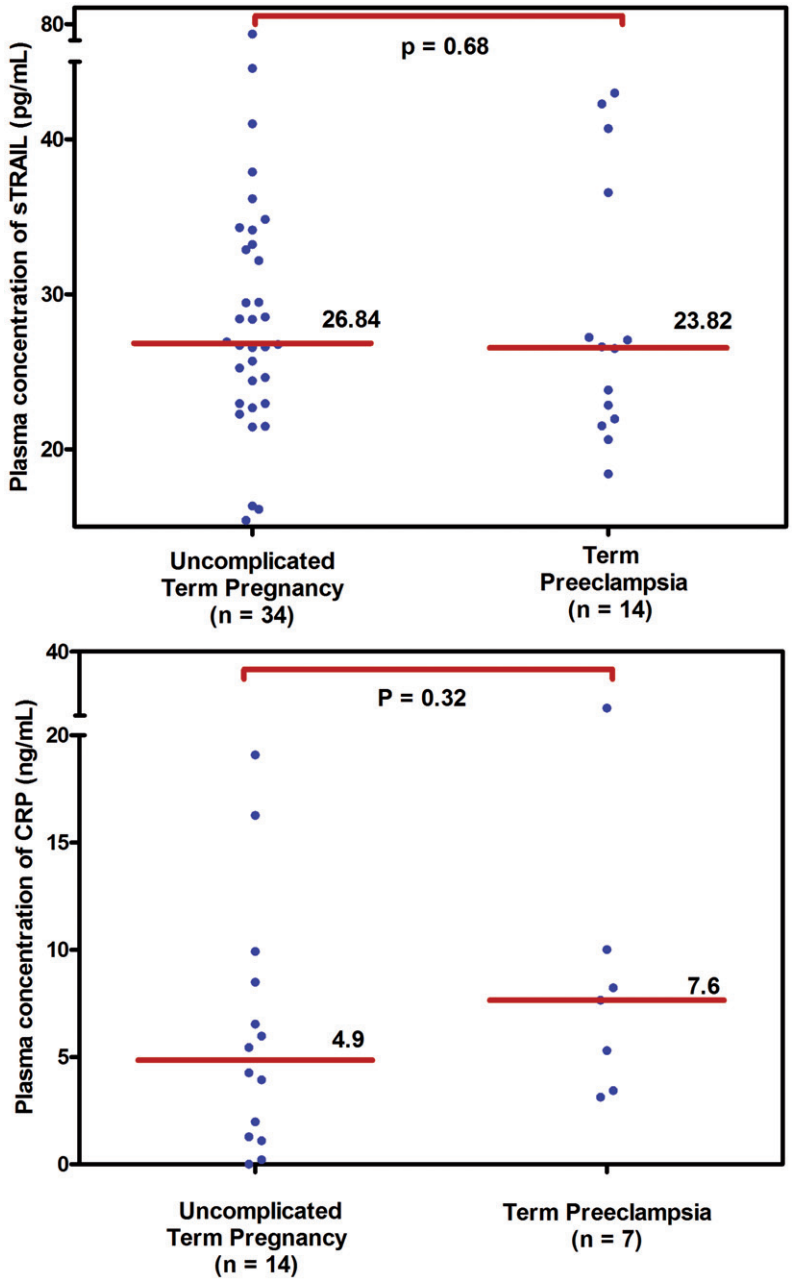

Figure 3. Median plasma concentrations of sTRAIL and CRP in women with uncomplicated term pregnancy and term preeclampsia. There was no significant difference in the median (IQR) plasma sTRAIL (pg/mL) and CRP (ng/mL) concentrations between these two groups [26.84 (22.95–33.45) versus 23.82 (20.62–34.24); $p = 0.68$ and 4.9 (1.2–8.8) versus 7.6 (3.4–10); $p = 0.32$, respectively].

in plasma sTRAIL concentrations in patients with PE may be associated with prolonged neutrophil survival, and thus, an enhanced systemic inflammatory response.

Zauli et al. [171] reported no significant differences in maternal serum sTRAIL concentrations at 12 weeks of gestation between patients with uncomplicated pregnancies and those who subsequently developed hypertensive disorders of pregnancy [171]. The apparent discrepancy can be explained by differences in the timing of venipuncture, or methodological differences (including variation in study population and laboratory methods). The observation that CRP concentrations are higher in women with PE than in those with uncomplicated pregnancies at the time of diagnosis is consistent with previous studies [59,146–155], and may partly explain prior observations that patients with PE are at an increased risk of cardiovascular events in later life [99–109].

Taken together, our findings suggest that the lower maternal plasma concentration of sTRAIL and the sTRAIL/CRP ratio in women with PE may reflect an exaggerated intravascular inflammatory response in such patients. However, further investigation is necessary to determine whether this finding is a reflection of the severity of inflammation or is specific to PE. Moreover, lower plasma sTRAIL concentrations and higher plasma CRP concentrations in women with PE may be contributing factors to future cardiovascular disease in these women.

Strengths and limitations

This is the first study to evaluate plasma concentrations of sTRAIL and CRP in women with uncomplicated pregnancies and those with PE. Due to the cross-sectional design, temporal relationships between sTRAIL, CRP and the clinical diagnosis of preeclampsia could not be established.

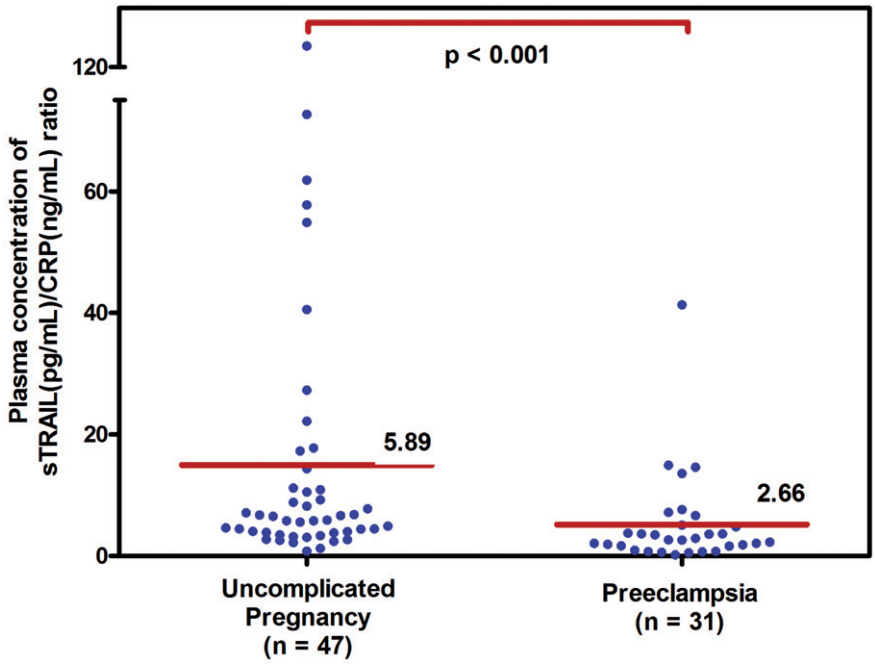

Figure 4. The median plasma concentration of sTRAIL/CRP ratio (pg/ng) ratio in women with uncomplicated pregnancy and preeclampsia. Women with preeclampsia had a significantly lower median (IQR) plasma sTRAIL/CRP ratio concentration (pg/ng) than those with uncomplicated pregnancy. [2.66 (1.63–5.1) versus 5.89 (3.82–11.19); $p < 0.001$]. Plasma sTRAIL/CRP ratio could not be calculated in 7 patients who had CRP below the limit of detection.

Conclusions

Among women with PE, maternal plasma sTRAIL concentrations are lower, while those of CRP are higher than in those with uncomplicated pregnancies. These findings are consistent with the presence of intravascular inflammation in women with PE.

Declaration 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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