Published in final edited form as:

J Matern Fetal Neonatal Med. 2013 November ; 26(16): 1568–1575. doi:
10.3109/14767058.2013.783811.

Soluble TRAIL in Normal Pregnancy and Acute Pyelonephritis: a Potential Explanation for the Susceptibility of Pregnant Women to Microbial Products and Infection

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Abstract

Objective—Pregnancy is characterized by activation of the innate immune response demonstrated by phenotypic and metabolic changes in granulocytes and monocytes. This state of activation has been implicated in the pathophysiology of multiorgan dysfunction of pregnant women with acute viral or bacterial infection. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is one of the mediators responsible for neutrophil apoptosis. Gene deletion of TRAIL results in delayed neutrophil apoptosis and resolution of inflammation after the administration of bacterial endotoxin. The aim of this study was to determine if maternal plasma concentrations of the soluble form of TRAIL (sTRAIL) differ in women with uncomplicated pregnancy and those with acute pyelonephritis.

Method—A cross-sectional study was conducted to include women in the following groups: 1) non-pregnant (n=23); 2) uncomplicated pregnancies (n=93); and 3) pregnancies with acute pyelonephritis (n=23). Plasma concentrations of sTRAIL were determined by ELISA.

Results—1) Women with uncomplicated pregnancies had a lower mean plasma sTRAIL concentration (pg/mL) than non-pregnant women (31.5 ± 10.1 vs. 53.3 ± 12.5 ; $p < 0.001$); 2) plasma sTRAIL concentrations did not change as a function of gestational age (Pearson correlation = -0.1 ; $p=0.4$); 3) the mean plasma sTRAIL concentration (pg/mL) was significantly lower in pregnant women with acute pyelonephritis than in those with uncomplicated pregnancies (20.5 ± 6.6 vs. 31.5 ± 10.1 ; $p<0.001$); and 4) among patients with acute pyelonephritis, patients

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Declaration of Interest: The authors report no declarations of interest.

with bacteremia had a significantly lower mean plasma concentration of sTRAIL (pg/mL) than those without bacteremia (15.1 ± 4.8 vs. 24.7 ± 4.6 ; $p < 0.001$).

Conclusion—Women with uncomplicated pregnancies are associated with a significantly lower mean maternal plasma concentration of sTRAIL than that observed in non-pregnant women. Moreover, a further decrease of plasma sTRAIL concentration was observed in pregnant women with acute pyelonephritis, and this could account, at least in part, for the exaggerated intravascular inflammatory response previously reported in pyelonephritis during pregnancy.

Keywords

innate immunity; neutrophil apoptosis; non-pregnant; normal pregnancy; plasma; tumor necrosis factor-related apoptosis-inducing ligand

Introduction

Human pregnancy presents a unique immunological challenge [1–3]. Upregulation of the innate immune response and downregulation of the adaptive immune response serves to balance the risk of maternal infection and tolerance of the fetal semi-allograft [1,2]. Despite activation of the innate immune system, pregnant women are more susceptible to infection-related complications [1,4–7]. The Shwartzman reaction requires two separate exposures to endotoxin in non-pregnant animals [4]. In contrast, pregnant animals develop the Shwartzman reaction after a single injection of endotoxin [4]. This has been interpreted as evidence that normal pregnancy is characterized by a state of physiologic intravascular inflammation. Therefore, pregnancy can be considered a Shwartzman “preparative” condition [4,8]. Evidence suggests that leukocyte plays an important role and its number and activation state correlate with the severity of the generalized Shwartzman reaction [4,9].

During pregnancy neutrophils undergo phenotypic and metabolic changes in response to infection and acute inflammation [2,3,10–16]. The number of circulating neutrophils increases with advancing gestational age in normal pregnancy [17,18]. Impaired neutrophil apoptosis is associated with a systemic inflammatory response syndrome (SIRS) [19]. Jimenez *et al* proposed that while prolonged neutrophil survival may constitute an appropriate adaptive response, impairment of this process may contribute to systemic inflammatory injury and possibly a multiple organ dysfunction [19]. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a type II membrane bound tumor necrosis factor (TNF) family ligand [20,21], has been implicated in the pathogenesis of multiorgan failure during the course of infection and may govern the resolution of infection-induced inflammation through its actions in delaying neutrophil apoptosis [22–24]. While TRAIL and its receptors are found in the placenta and fetal membranes throughout gestation [25,26], few investigators have examined its relevance in normal and complicated pregnancy in the third trimester [25–28].

Proposed roles of TRAIL in pregnancy include that it establishes immune tolerance at the feto-maternal interface [25,26] and induces smooth muscle cell apoptosis in the spiral arteries during implantation [28,29]. Recently, a higher serum concentration of sTRAIL was observed in patients with recurrent miscarriage than in those with uncomplicated pregnancy

at 12 weeks of gestation, supporting that sTRAIL may play a role in the pathogenesis of early pregnancy complications [30]. Yet, TRAIL has not been examined in the context of complications of pregnancy and in particular, in the presence of systemic inflammation which occur in the late second or third trimester, for instance acute pyelonephritis [31–35] (a common reason for hospitalization during pregnancy [36]). Moreover, pregnant women with acute pyelonephritis are more susceptible to infection related complications, such as acute respiratory distress syndrome (ARDS) [36–46], sepsis [36,47], septic shock [36,48,49], anemia [36], and transient renal dysfunction [50] than in non-pregnant women affected by this condition.

This study aims to determine whether maternal plasma sTRAIL concentrations during pregnancy differ from those in non-pregnant women and those of pregnant woman with acute pyelonephritis.

Materials and methods

Study design

A cross-sectional study was conducted by searching our clinical database and bank of biologic samples to include women in the following groups: 1) non-pregnant women; 2) uncomplicated pregnancies; and 3) pregnancies with acute pyelonephritis. The non-pregnant group consisted of women who had no history of acute or chronic inflammatory conditions. The uncomplicated pregnancy group included pregnant women between 20–42 weeks of gestation who: 1) had no medical, obstetrical or surgical complications; 2) were not in labor; and 3) delivered a normal term (≥ 37 weeks) infant whose birthweight was between the 10th and 90th percentile for gestational age. These women were enrolled from either Labor and Delivery unit (in cases of scheduled cesarean section) or the antenatal clinic, and followed until delivery. Acute pyelonephritis (n=23) during pregnancy was diagnosed in the presence of fever (temperature ≥ 38 °C), clinical signs (e.g. back pain), pyuria, and a positive urine culture for microorganisms. Women were grouped as follows: (1) acute pyelonephritis with positive urine culture only (without bacteremia); and (2) acute pyelonephritis with positive blood and urine cultures (with bacteremia).

All women provided written 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 Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, DHHS. Many samples were previously studied in the investigation of intravascular inflammation, angiogenesis and cytokine biology in normal and complicated pregnancies.

Sample collection and human sTRAIL

Venipuncture was performed in non-pregnant women, upon diagnosis of acute pyelonephritis and at 20–42 weeks of gestation upon enrollment for women with uncomplicated pregnancies. The blood was collected in EDTA tubes, centrifuged at 1300 g then stored at –70°C. The concentrations of sTRAIL were measured using enzyme-linked immunoassay (ELISA) (R&D Systems, Minneapolis, MN, USA). 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 pre-coated with monoclonal antibodies specific for TRAIL. During this incubation, the immobilized antibodies in the microtiter plate bound TRAIL present in both the standards and samples. After washing unbound substances, polyclonal antibodies to human TRAIL conjugated to an enzyme (horseradish peroxidase) were added to the assay wells. Once the incubation period was over, the assay plates were washed to remove unbound antibody-enzyme reagents. Upon addition of a substrate solution (tetramethylbenzidine), 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 USA). The inter- and intra-assay coefficients of variation (CVs) were 6.52% and 3.66%, respectively. The sensitivity of sTRAIL was 8.22 pg/mL; patients having concentrations below this threshold were considered to have had a value of 8.1 pg/mL (99% of the limit of detection).

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 an unpaired Student's T-test or Mann-Whitney U test, where appropriate. One-way analysis of variance (ANOVA) with post-hoc Dunnett T3 tests were utilized to examine the differences in mean sTRAIL concentrations across groups. Multivariable general linear models were constructed to examine the effect of potentially confounding factors selected based upon clinical knowledge. These were entered into a 'full model', and variable reduction was performed 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 predicted geometric mean sTRAIL concentration. Statistical analysis was performed with SPSS 19 (IBM Corp, Armonk, NY) and SAS version 9.3 (Cary, NC). A p value < 0.05 was considered statistically significant.

Results

Demographic, clinical and obstetric characteristics are displayed in Table I by study group: 1) non-pregnant women (n=23); 2) pregnant women who had an uncomplicated pregnancies (n=93); and 3) pregnant women with acute pyelonephritis (n=23). The frequency of nulliparous women was greater in non-pregnant group than in the uncomplicated pregnancy and pregnancy with acute pyelonephritis groups. Otherwise, there were no significant differences in characteristics between study groups.

sTRAIL was detected in 97.8% (136/139) of samples. Pregnant women with acute pyelonephritis had a lower mean $\pm$ SD plasma sTRAIL concentration (pg/mL) than women with uncomplicated pregnancies (20.5 ± 6.6 vs. 31.5 ± 10.1 ; $p < 0.001$; Figure 1). The mean $\pm$ SD plasma sTRAIL concentration (pg/mL) was significantly lower in the uncomplicated

pregnancy than in the non-pregnant group. (31.5 ± 10.1 vs. 53.3 ± 12.5 ; $p < 0.001$; Figure 1). These differences remained significant after adjusting for nulliparity; other potentially confounding factors (maternal age and race) were not significantly associated with sTRAIL concentrations, and their inclusion in a multivariable model did not alter the magnitude or significance of its association with study group (least squares mean sTRAIL for each group changed by $< 1\%$ following multivariable adjustment).

Among pregnant patients, plasma sTRAIL concentrations were not associated with gestational age at venipuncture ($\beta = -0.0008$, $p = 0.75$), after holding study group constant. Among women with acute pyelonephritis (Table II), the mean plasma sTRAIL concentration was significantly lower in those with bacteremia than in those without bacteremia (15.1 ± 4.8 vs. 24.7 ± 4.6 ; $p < 0.001$; Figure 2). Adjustment for maternal age, race, nulliparity and gestational age at venipuncture did not alter the magnitude or significance of this relation.

Discussion

Principal findings of the study

1) The mean plasma sTRAIL concentration was lower in pregnant than in non-pregnant women; 2) pregnant women with acute pyelonephritis had a lower mean plasma sTRAIL concentration than in those with uncomplicated pregnancies; and 3) among pregnant women with acute pyelonephritis, those with bacteremia had a lower mean plasma sTRAIL concentration than those without bacteremia.

Biology of TRAIL

TRAIL, or Apo2L, is a membrane protein which is the third pro-apoptotic member other than tumor necrosis factor (TNF) and FAS of the TNF family [20,21,51,52]. TRAIL can induce apoptosis signals through death domains. Binding of TRAIL to its death receptors, TRAIL-R1 or TRAIL-R2, results in the formation of death-inducing signaling complex (DISC). Fas associated death domain (FADD) translocates and recruits pro-caspase-8 and -10 to DISC result in apoptosis [53–58]. In contrast, binding of TRAIL to TRAIL-R3/Decoy receptor 1 (DcR1) [59–63] or TRAIL-R4/DcR2 [62,63] cannot induce an apoptotic signal, therefore, both are considered decoy receptors. TRAIL can also bind to osteoprotegerin (OPG), a protein involved in bone remodeling that acts through ligands other than TRAIL, with a low affinity [64,65]. TRAIL is expressed predominantly in the spleen, lung, prostate, immune cells (e.g. neutrophils, monocytes, lymphocytes, dendritic cells, natural killer cells, macrophage), endothelial cells, syncytiotrophoblasts, cytotrophoblasts and decidual cells [20,25,26,59,61,66]. The soluble form of TRAIL also elicits apoptosis signals similar to that of the cell surface TRAIL [67,68].

Unlike other death receptor ligands of the TNF family, TRAIL is unique because it induces apoptosis of transformed cells (i.e. cancer) but not in the majority of normal cells [69,70]. The presence of decoy receptors for TRAIL in normal (but not in tumor cells) could partly explain why most normal cells are resistant to TRAIL-induced apoptosis [61,71]. This unique property has led to investigation using recombinant TRAIL for therapy, especially in the field of oncology [72,73]. In addition to apoptotic signaling, TRAIL can also elicit non-

apoptotic signals such as NF- κ B [51,74,75], extracellular signal-regulated kinase (ERK) [51,52,69,76] and c-Jun NH2-terminal kinase (JNK) pathways depending on cell types [51,52,57,62,66,77]. The biological significance of NF- κ B activation by TRAIL however, has not been fully elucidated [78].

TRAIL knock-out mice develop normally and do not develop tumors spontaneously (52). However, they are more susceptible to metastasis of implanted tumors (Renca tumor cell, mammary carcinoma and fibrosarcoma) [79,80]. Recently, TRAIL has been implicated in the pathophysiology of autoimmune disease, since TRAIL-deficient mice have increased numbers of immature thymocytes, impaired thymic deletion, and develop collagen-induced arthritis and streptozocin-induced diabetes [81].

sTRAIL is detectable in the serum/plasma of healthy individuals [82–84], and is increased in patients with autoimmune diseases (such as systemic sclerosis, systemic lupus erythematosus (SLE), rheumatoid arthritis) [82,85,86] and viral infection such as human immunodeficiency virus (HIV) [87]. In contrast, serum/plasma concentrations of sTRAIL are decreased in patients with ischemic heart disease [88,89].

Roles of TRAIL at feto-maternal interface

TRAIL and its receptors (TRAIL-R) can be detected in the placenta and fetal membranes throughout gestation [25,26]. TRAIL receptor expression in villous trophoblasts changes with advancing gestational age (TRAIL-R1 and TRAIL-R2 increase, while TRAIL-R3 and TRAIL-R4 decrease) [25,26]. Immunohistochemistry studies have reported that TRAIL expression is more prominent in syncytiotrophoblasts than cytotrophoblasts [25,26], whereas the distribution of the TRAIL receptor differs depending on the type of receptor. TRAIL-R1 and TRAIL-R2 were mainly localized in cytotrophoblasts, while TRAIL-R3 and TRAIL-R4 (decoy receptors) were confined to syncytiotrophoblasts [25,26]. Since syncytiotrophoblasts are in direct contact with maternal blood containing immune cells, the distribution of TRAIL and its receptors on syncytiotrophoblast may confer protection of trophoblasts against immune cells [27]. Moreover, the TRAIL receptor can be translocated inside cells. For example, in a model of villous cytotrophoblast culture, the administration of recombinant TRAIL did not increase trophoblast apoptosis, but relocated TRAIL-R2 from the cytoplasm into the nucleus. This phenomenon may explain the resistance of trophoblasts to TRAIL-induced apoptosis [90]. In contrast, TNF- α treatment enhanced TRAIL-induced apoptosis by relocating TRAIL-R2 from the nucleus to the plasma membrane [90].

Plasma concentration of sTRAIL in women with uncomplicated pregnancies

The study reported herein is the first to demonstrate that the mean plasma concentration of sTRAIL is significantly lower in pregnant than in non-pregnant women. Moreover, its concentration in women with uncomplicated pregnancies remains largely unchanged throughout the second half of pregnancy. The lack of correlation between plasma concentrations of sTRAIL and gestational age in this study is consistent with the findings of Zauli *et al.*, who reported that serum concentrations of sTRAIL were stable from 12 to 16 weeks of gestation [91]. In contrast, others have shown that the amniotic fluid concentration of sTRAIL is significantly higher at term than those in midtrimester [27].

Recently, Agostinis *et al* [30] demonstrated that maternal serum concentrations of sTRAIL in patients with recurrent miscarriage were higher than in normal pregnant women at 12 weeks of gestation [30]. Moreover, they found that soluble recombinant TRAIL inhibits human first-trimester-derived trophoblastic cell migration and adhesion to decidual endothelial cells and fibronectin *in vitro* [30]. However, this study was unable to determine whether elevated sTRAIL concentrations caused, or was a consequence of miscarriage. Furthermore, it is noteworthy that the sTRAIL concentration which inhibited migration and adhesion of trophoblast to decidual endothelial cells is similar to that found in the serum of pregnant women with uncomplicated pregnancies [91].

Our results suggest that lower maternal plasma concentrations of sTRAIL in women with uncomplicated pregnancies than non-pregnant women may explain, at least in part, the neutrophilia observed in normal pregnancy [17,18]. The pathophysiologic significance and mechanisms of lower plasma sTRAIL concentrations in women with uncomplicated pregnancies requires further investigation.

Plasma concentration of sTRAIL in pregnancies with acute pyelonephritis

TRAIL may be involved in regulation of the immune response against infection, since it is expressed on almost every type of immune cell (e.g. neutrophils, monocytes, macrophages, CD4⁺ T cells, NK cells, and dendritic cells) [92–94]. Although most studies have examined the role of TRAIL in viral infections such as HIV [87,95,96], cytomegalovirus [97], influenza [98,99], reovirus [100] and respiratory syncytial virus [101], this protein is also involved in regulation of inflammatory response to bacterial infections [102]. Indeed, TRAIL and its receptors have been implicated in the removal of senescent circulating neutrophils and activated tissue neutrophils, leading to resolution of inflammation [23,24]. In an animal model of endotoxin-induced acute lung injury and zymosan-induced peritonitis, TRAIL-knock-out mice had an enhanced inflammatory response with increased neutrophil numbers and reduced neutrophil apoptosis in bronchoalveolar and peritoneal lavage fluid, respectively [24]. Similarly, in an animal model of pneumococcal-induced pneumonia, TRAIL knock-out mice had significantly decreased lung bacterial clearance and survival when compared to wild type mice [103]. The alveolar macrophage cell death in these mice shifted from apoptosis towards necrosis, [103]. Moreover, the inflammatory response [tumor necrosis factor, IL-6, chemokine (C-X-C motif) ligand 1, and interferon gamma] in the lungs was increased, indicating that TRAIL regulates the inflammatory response elicited by bacterial infection [103]. In an animal model of pneumococcal-induced meningitis, TRAIL knock-out mice had prolonged inflammation, impaired coordination, decreased motor strength, and increased neuronal cell death than in wild-type mice [104]. Moreover, intrathecal administration of recombinant TRAIL corrected these deficits [104]. Taken together, these observations suggest that TRAIL is involved in inflammatory signaling cascades and is a protective cytokine against an exaggerated proinflammatory response during the course of acute infection [23].

Our findings that pregnant women with acute pyelonephritis (especially those with bacteremia) had a lower mean plasma concentration of sTRAIL than those with uncomplicated pregnancies are consistent with previous experimental models demonstrated

that TRAIL is a protective cytokine against bacterial infection [23,24,103,104]. The decrease in plasma concentrations of sTRAIL in the setting of acute infection may be associated with an increased inflammatory response to bacterial products, probably due to delayed neutrophil apoptosis. This hypothesis may partly explain why pregnant women with acute pyelonephritis are more susceptible to complications such as systemic inflammatory response syndrome (SIRS) or ARDS than non-pregnant women. Moreover, maternal plasma sTRAIL concentration is related to the severity of bacterial infection.

Strengths and limitations

This is the first study to examine differences in maternal plasma concentrations of sTRAIL among non-pregnant women, women with uncomplicated pregnancy and those with acute pyelonephritis. Due to the cross-sectional nature of the study, a temporal relationship of the changes in plasma sTRAIL concentrations and the development of acute infection during pregnancy could not be established.

Conclusions

Maternal plasma concentrations of sTRAIL are lower in women with uncomplicated pregnancies than in non-pregnant women and are further decreased among pregnant women with acute pyelonephritis, particularly in those with evidence of bacteremia. Low plasma sTRAIL concentration could account, at least in part, for the exaggerated intravascular inflammatory response previously reported in pyelonephritis during pregnancy.

Acknowledgments

This project has been funded in whole or in part with Federal funds from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN275201300006C.

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Figure 1. The mean maternal plasma sTRAIL concentration in non-pregnant women, uncomplicated pregnancy and pregnancy with acute pyelonephritis

Women with uncomplicated pregnancy had a significantly lower mean maternal plasma sTRAIL concentration than non-pregnant women (mean $\pm$ SD: 31.5 $\pm$ 10.1 pg/mL vs. mean $\pm$ SD: 53.3 $\pm$ 12.5 pg/mL; $p < 0.001$). Pregnant women with acute pyelonephritis had a significantly lower mean maternal plasma sTRAIL concentration than those with uncomplicated pregnancy (mean $\pm$ SD: 20.5 $\pm$ 6.6 pg/mL vs. mean $\pm$ SD: 31.5 $\pm$ 10.1 pg/mL; $p < 0.001$).

Figure 2. The mean maternal plasma sTRAIL concentration in pregnancy with acute pyelonephritis without bacteremia and those with bacteremia

Pregnant women with acute pyelonephritis who had bacteremia had a significantly lower mean maternal plasma concentration of sTRAIL than those without bacteremia (mean $\pm$ SD: 15.1 ± 4.8 pg/mL vs. mean $\pm$ SD: 24.7 ± 4.6 pg/mL; $p < 0.001$).

Table I

Clinical characteristics by study group: 1) non-pregnant, 2) uncomplicated pregnancy, and 3) pregnancy with acute pyelonephritis

	Non-pregnant women (n=23)	Uncomplicated pregnancy (n=93)	P	Pregnancy with acute pyelonephritis (n=23)	P*	P**
Age (years)	26.6 ± 5.2	24.7 ± 4.8	0.33	24.9 ± 6.2	1.0	0.786
Nulliparity	14 (60.9)	28 (30.1)	0.01	6 (26.1)	0.7	0.02
Smoking	2 (12.5)	16 (17.4)	0.63	3 (13)	0.62	0.96
Race						
African American	14 (60.9)	69 (74.2)	0.32	16 (69.6)	0.4	0.4
Caucasian	7 (30.4)	13 (14)		4 (17.4)		
Hispanic	1 (4.3)	5 (5.4)		3 (13)		
Other	1 (4.3)	6 (6.5)		0 (0)		
Storage time (years)	10.7 ± 1.0	11 ± 0.7	0.53	11.1 ± 0.7	0.62	0.23
Gestational age at venipuncture (weeks)		33.1 ± 5.8		32 ± 4.8	0.39	
Gestational age at delivery (weeks)		39.5 ± 1.3		38.4 ± 2.8	0.08	
Birthweight (grams)		3368.4 ± 354.7		3079.1 ± 641.8	0.05	

Values are presented as mean ± SD or N (%)

p compared between non-pregnant women and uncomplicated pregnancy.

p* compared between uncomplicated pregnancy and pregnancy with acute pyelonephritis.

p** compared between non-pregnant women and pregnancy with acute pyelonephritis

Table II

Clinical characteristics by culture status among women in the acute pyelonephritis study group.

	Urine culture positive alone (n=13)	Urine and blood culture positive (n=10)	P
Age (years)	24.92 ± 5.8	24.9 ± 7.1	0.99
Nulliparity	5 (38.5)	1 (10)	0.12
Smoking	2 (15.4)	1 (10)	0.70
Race			
African American	9 (69.2)	7 (70)	0.91
Caucasian	2 (15.4)	2 (20)	
Hispanic	2 (15.4)	1 (10)	
Other	0 (0)	0 (0)	
Gestational age at venipuncture (weeks)	32.99 ± 4.96	30.7 ± 4.42	0.26
Gestational age at delivery (weeks)	37.96 ± 3.18	38.94 ± 2.23	0.41
Birthweight (grams)	3009.5 ± 756.72	3169.6 ± 476.71	0.57

Values are presented as mean ± SD or n (%).