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# Maternal plasma soluble ST2 concentrations are elevated prior to the development of early and late onset preeclampsia – a longitudinal study

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## Abstract

**Objective—**The objectives of this study were to determine: 1) the longitudinal profile of plasma-soluble ST2 (sST2) concentrations in patients with preeclampsia and those with uncomplicated pregnancies; 2) whether the changes in sST2 occur prior to the diagnosis of preeclampsia; and 3) the longitudinal sST2 profile of women with early *or* late preeclampsia.

**Materials and Methods—**This longitudinal nested case-control study included singleton pregnancies in the following groups: 1) uncomplicated pregnancies (n=160); and 2) those complicated by early (<34 weeks, n=9) and late ( ≥34 weeks, n=31) preeclampsia. sST2 concentrations were determined by enzyme-linked immunosorbent assays. Mixed-effects models were used for the longitudinal analysis.

**Results—**1) Plasma sST2 concentration profiles across gestation differed significantly among cases and controls ($p<0.0001$); 2) women with early preeclampsia had higher mean sST2 concentrations than controls >22 weeks of gestation; cases with late preeclampsia had higher mean concentrations >33 weeks of gestation (both $p<0.05$); and 3) these changes started approximately six weeks prior to clinical diagnosis.

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**Conclusions—**Maternal plasma sST2 concentrations are elevated six weeks prior to the clinical diagnosis of preeclampsia. An increase in maternal plasma concentration of sST2 may contribute to an exaggerated intravascular inflammatory response and/or the Th1/Th2 imbalance in some cases.

### Keywords

interleukin-1; interleukin-33; intravascular inflammation; prediction of preeclampsia; Th1/Th2 immune response

## Introduction

Preeclampsia, a syndrome largely evident during the third trimester, remains a major concern due to its association with maternal (1–6) and perinatal morbidity and mortality worldwide (7–17). The early (<34 weeks of gestation) and late ( ≥34 weeks of gestation) features of preeclampsia share clinical presentations of hypertension and proteinuria, but differ substantially in the severity of the disease, the rate of maternal and fetal/neonatal complications, and the severity of the placental lesions (18–27). Moreover, there is a difference in the underlying mechanisms implicated in the pathogenesis of early-onset versus late-onset preeclampsia (28) (i.e., maternal transcriptome (29), balance of angiogenic and antiangiogenic factors (30–54), oxidative stress (55–58), activation of coagulation and thrombic generation (59–61), and inflammation (22,60,62–64).

Preeclampsia is associated with a shift from T helper 2 (Th2)-associated anti-inflammatory cytokines indicating normal pregnancy to a predominant increase of T helper 1 (Th1)-associated pro-inflammatory cytokines (65–70). Cytokines produced by Th1 cells, such as interleukin (IL)-2 (68,71,72), interferon (IFN)-γ (67,71–73), and tumor necrosis factor (TNF)-α (74–77), have each been found to be higher in women with preeclampsia than in those with normal pregnancies. However, the information available regarding their role in early-onset and late-onset preeclampsia is scarce.

Suppressor of tumorigenicity 2 (ST2) is a member of the interleukin-1 receptor (IL-1R) family (78) and, together with its ligand IL-33, it is associated with a Th2 immune response via the production of anti-inflammatory cytokines, such as IL-4, IL-5, and IL-13 (79). The ST2 receptors comprise a membrane-anchored receptor (ST2L) and a soluble ST2 (sST2) receptor that act as decoys for IL-33 (80). This receptor is secreted by endothelial cells during inflammation (81–83). The binding of sST2 to IL-33 shifts the pro-inflammatory phenotype toward a Th1 response. Soluble ST2 concentrations are increased in the third trimester of normal pregnancy and, together with IL-33 and ST2L, might play an important role in maintaining the immunoregulation of normal pregnancy (83–86). Changes in sST2 concentrations were reported at the onset of disease in several pregnancy complications, including miscarriage (87), fetal inflammatory response syndrome (FIRS) (88), and preterm labor (86). Our group (85) and other investigators (84) showed that maternal plasma sST2 concentrations were significantly higher in women with preeclampsia than in those with normal pregnancies. Plasma concentrations of sST2 were higher in early-onset preeclampsia compared to the late onset of the disease and also in severe preeclampsia compared to mild

preeclampsia (85). However, due to the lack of information regarding the changes of sST2 concentrations throughout gestation in normal and preeclamptic pregnancies, we conducted a longitudinal study to determine 1) whether patients with preeclampsia have a different longitudinal profile of plasma sST2 concentration than those with uncomplicated pregnancies; 2) if the changes in sST2 occur prior to the diagnosis of preeclampsia; and 3) the longitudinal profile of sST2 between women who subsequently develop early-onset or late-onset preeclampsia.

## Materials and Methods

### Study design and participants

A longitudinal nested case-control study was performed that included 200 women with singleton pregnancies in the following groups: 1) normal pregnant women (n =160) and 2) patients who developed preeclampsia (n=40). Patients with preeclampsia were subdivided into early (<34 weeks, n=9) and late ( ≥34 weeks, n=31) groups according to the gestational age at delivery. Exclusion criteria included 1) patients with chronic hypertension, 2) known major fetal or chromosomal anomalies, and 3) multiple gestations. All women were enrolled in the prenatal clinic at the Sótero del Rió Hospital, Santiago, Chile, and followed until delivery.

A minimum of three samples were collected from all patients during pregnancy (ranging from 3–7 samples). Subjects were included only if their plasma samples were available at least once prior to 24 weeks of gestation. Plasma samples from each patient were selected once during the following seven intervals: 1) 6–14.9 weeks; 2) 15–19.9 weeks; 3) 20–24.9 weeks; 4) 25–27.9 weeks; 5) 28–31.9 weeks; 6) 32–36.9 weeks; and 7) 37 weeks of gestation or more. The earliest sample from each interval was used for sST2 profiling. Samples collected after the clinical diagnosis of preeclampsia were excluded.

### Clinical definitions

Preeclampsia was defined as hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least two occasions, 4 hours to 1 week apart) and as proteinuria ( ≥300 mg in a 24-hour urine collection or one dipstick measurement ≥2+) (89). Severe preeclampsia was defined as previously described (39). Patients with preeclampsia diagnosed before 34 weeks of gestation were defined as having early-onset preeclampsia, while late-onset preeclampsia was diagnosed after 34 weeks of gestation (90). Pregnant women were considered normal if they had no medical, obstetrical, or surgical complications and if they delivered a normal term ( ≥37 weeks) infant whose birthweight was appropriate for gestational age (10th–90th percentile) (91).

The collection and utilization of the samples were approved by the Human Investigation Committee of the Sótero del Rió Hospital, Santiago, Chile (a major affiliate of the Catholic University of Santiago), and by the Institutional Review Board of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, U.S. Department of Health and Human Services (NICHD/NIH/DHHS). Many of these samples were used in previous studies.

## Sample collection and sST2 immunoassay

Blood samples were collected into tubes containing EDTA. The samples were centrifuged for 10 min at 4°C and stored at −70°C. Laboratory personnel were blinded to the clinical diagnoses. Maternal plasma concentrations of sST2 were determined using sensitive and specific immunoassays (R&D Systems, Minneapolis, MN). All immunoassays utilized a sandwich enzyme-based technique and had been validated for plasma determinations of the analytes. The inter- and intra-assay coefficients of variation were 4.6% and 3.9%, respectively. The sensitivity of the assays was 17.5 pg/mL.

## Statistical analysis

### Cross-sectional analysis of the demographic and clinical characteristics data

—The Kolmogorov-Smirnov test was used to assess the distribution of the data. Since the data were not normally distributed, we used the Mann-Whitney U test to compare continuous variables between the groups. A Chi-squared or a Fisher's exact test was used for comparisons of categorical variables. Statistical analysis was performed using SPSS 19 (IBM Corp, Armonk, NY) and SAS 9.3 (SAS Inc., Cary, NC). A p value $< 0.05$ was considered statistically significant.

**Longitudinal analysis of plasma sST2 concentration—**The data collected in this study contain longitudinal measurements from the same individuals belonging to the two groups (preeclampsia and controls). An appropriate statistical method for longitudinal data analysis is the linear mixed-effects model, in which both fixed and random effects are allowed (92, 93). The inherent correlation (similarity) in the data for samples taken from the same individual is accounted for by a subject-specific coefficient in the model called random effect. Therefore, the baseline response (sST2 concentration), treated as a random effect, is allowed to differ from one subject to the next, yet the concentration profile (rate of change over time, i.e., gestational age) is assumed to be similar and, hence, modeled via polynomial terms of gestational age treated as fixed effects. The fixed effects included the group indicator variable (preeclampsia vs. controls), polynomial terms of the gestational age up to the third degree, nulliparity, and smoking. Body mass index (BMI), maternal age, and storage time were tested but did not improve the model fit as determined by a likelihood ratio test and, therefore, were not retained in the model. In addition, to allow the concentration profiles over time to be different between groups, the fixed effects in the model included interaction terms between polynomial components of gestational age and the group variable. With such an interaction model, the effect of the group variable is dependent on the gestational age; hence, we estimated the magnitude and significance of between-group differences in sST2 concentrations at every week of gestation.

The *Imer* function from the *Ime4* package under the R statistical environment was used for mixed-effects model fitting. Significance of the coefficients was determined using the ANOVA method in the *Ime4* package, which performs a likelihood ratio test between the model fit with and without the coefficient of interest. All analyses were performed under the R statistical environment (www.r-project.org).

**Backward longitudinal analysis—**Backward longitudinal analysis was conducted to determine how many weeks prior to the diagnosis that the sST2 concentration in women with preeclampsia differed from the controls. Plasma samples from healthy pregnant women were matched for gestational age to those of patients with preeclampsia (in a 4:1 ratio). The samples from the matched controls of patients with preeclampsia, taken after the gestational age indicated at the time of diagnosis, were removed so that the distribution of gestational age values was similar between the disease and control groups. To test for the differences between groups as a function of time to the disease diagnosis, the same mixed-effects model used in the forward longitudinal analysis was applied.

## Results

### Demographic and clinical characteristics of the study groups

This study included a total of 1328 samples; of these samples, 1101 were obtained from women with uncomplicated pregnancies and 227 from those with preeclampsia. The demographic and clinical characteristics of the study groups are displayed in Table 1. Patients who developed preeclampsia had a significantly lower median maternal age, a higher median pre-pregnancy BMI, and a higher proportion of nulliparous women compared to those with normal pregnancies. There was no significant difference in the median gestational age at enrollment between patients who subsequently developed preeclampsia and those with normal pregnancies. The median gestational age at delivery and birthweight were lower in patients with preeclampsia than in those with normal pregnancies ($p < 0.001$ both; Table 1). Among women with preeclampsia, 27.5% (11/40) delivered neonates whose birthweights were less than the 10th percentile, 35% (14/40) delivered preterm before 37 weeks of gestation, 22% (9/40) delivered before 34 weeks of gestation, and 65% (26/40) had a severe preeclampsia.

### Plasma sST2 concentrations are increased prior to the clinical manifestation of preeclampsia: a longitudinal analysis

Plasma concentrations of sST2 were modeled using a linear mixed-effects model as described in the Methods section. Actual sST2 concentrations were in agreement with the prediction of the model (Figure S1).

Patients who subsequently developed preeclampsia presented a different profile of maternal plasma sST2 (concentration over time) compared to patients with normal pregnancies after adjusting for potential confounders ($p<0.0001$).

The mean maternal plasma sST2 concentrations were significantly higher in women who subsequently developed preeclampsia from 26 weeks of gestation onward than in women with normal pregnancies ($p<0.05$), and the magnitude of differences increased as term approached (Table 2, Figure 1).

The mean plasma sST2 concentrations were significantly increased ($p<0.05$) at an earlier stage of gestation (from 22 weeks onward) in patients who subsequently developed early-onset preeclampsia as opposed to those who developed late-onset preeclampsia (from 33 weeks onward) (Figure 2). Individual plasma sST2 concentration profiles of women with

normal pregnancies and those who subsequently developed preeclampsia are shown in Figure 3.

### Plasma sST2 concentration is increased 6 weeks prior to the clinical manifestation of preeclampsia (backward analysis)

We conducted a backward analysis to determine when the sST2 concentrations varied at any given time before diagnosis. The mean plasma sST2 concentration was significantly higher in patients who subsequently developed preeclampsia than in those with normal pregnancies at approximately 6 weeks before clinical diagnosis, after adjusting for covariates (all $p<0.05$; Table 3).

## Discussion

**Principal findings—**1) Maternal plasma sST2 concentration differs between patients destined to develop preeclampsia and those with a normal pregnancy from 27 weeks of gestation onward; 2) the change in the maternal plasma sST2 concentration of women with early-onset preeclampsia was observed at 22 weeks of gestation; and 3) in comparison to normal pregnant women, mean maternal plasma sST2 concentration was significantly higher approximately six weeks before the clinical onset of preeclampsia.

### Biology of ST2

ST2 is a member of the IL-1 receptor family; it was originally identified as being induced by serum or oncogene expression in mouse fibroblasts (94,95), and it does not bind IL-1α, IL-1β, or IL-1R antagonist (96–98). The two best-characterized isoforms are ST2L and sST2. The cellular activity of ST2 promotes a Th2 inflammatory response through ligation with IL-33 (99,100). The binding of IL-33 to ST2L initiates the production of Th2-associated cytokines (IL-4, IL-5, and IL-13) (101–109). IL-33 is considered an alarmin, as it can be expressed and released by the endothelial cells exposed to an insult (110,111). In addition to its conjoined activity with IL-33, ST2L has an anti-inflammatory property through the inhibition of Toll-like receptor (TLR) signaling (112–114). Macrophages from ST2 knockout mice produce more pro-inflammatory cytokines in response to lipopolysaccharide (LPS) than wild-type mice (115).

Soluble ST2 is identical to the extracellular region of ST2L, except for additional nine amino acids present at the C terminus of the molecule (116, 117). This molecule is expressed in the embryonic tissues, mammary tumors and fibroblasts (94,95,117), alveolar epithelial cells (118), brain, small bowel cells, placenta (84,119), endothelial cells in various tissues (81,83,120,121), and cardiomyocytes (118). Soluble ST2 acts as a decoy that binds IL-33 and prevents its intracellular signaling, shifting the inflammatory response to a Th1 type.

Elevated circulating sST2 concentration has been observed in various conditions characterized by 1) intravascular inflammation, such as LPS-induced lung acute inflammation (119,122–124), dengue fever (125–127), myocardial infarction (128–131), heart failure (132,133), atherosclerosis (134), sepsis (124,135), trauma (124); and in 2)

disorders associated with an abnormal Th2 immune response (105,136,137), such as systemic lupus erythematous (138), atopic dermatitis (139,140), idiopathic pulmonary fibrosis (141), acute eosinophilic pneumonia (142), and asthma (143–146).

## Changes in soluble ST2 during pregnancy

This longitudinal study describes for the first time the changes observed in maternal plasma sST2 concentrations during normal pregnancy. The concentrations of sST2 are relatively constant until 30 weeks of gestation, from which they increase steadily until delivery (Figure 2). This pattern of increased concentration toward the end of pregnancy is similar to previous reports regarding the changes of cytokine concentrations, e.g., IL-6, IL-8, IL-12, and TNF-α during gestation (147–150). It has been proposed that the increase in the pro-inflammatory cytokines during the third trimester may be associated with physiological changes toward the onset of parturition (151–158). An additional etiology for the elevation of sST2 during the third trimester, after 30 weeks of gestation, is a change in the volume of maternal circulation. It may be that a sense of volume overload promotes the release of sST2 endothelial cells (81,128,132). This may be inferred from studies by Bartunek et al. that demonstrated increased endothelial cell production of sST2 in cases of volume overload in patients with diastolic cardiac dysfunction(81).

## The inflammatory phenotype of patients with preeclampsia

Preeclampsia is associated with a systemic maternal inflammatory response (159,160) almost akin to sepsis (161). Indeed, we and other investigators have described changes in the metabolic activity of leukocytes (161,164–166), oxidative stress (55–58), and cytokine profiles (22,60,62,64). These changes were described mainly during the clinical presentation of the disease. Preeclampsia is characterized by an improper inflammatory response initiated and maintained by cytokines such as IL-1β, TNF-α, IL-6, IL-8, and IL-17, which are secreted from Th1 and Th17 cells (162,163). Previous flow cytometry studies have demonstrated that women with preeclampsia exhibit a change in the phenotype and in the metabolic activity of immune cells consistent with leukocyte activation, which is higher than that of normal pregnancy (161,164–166). In addition, the changes in the inflammatory response differ between early-onset and late-onset preeclampsia (167,168). Indeed, higher cytokine concentrations of IL-12, TNF-α, and IL-1β were reported in patients with early-onset versus late-onset preeclampsia (167).

## Changes in sST2 in preeclampsia

Our group and other investigators reported an increase of circulating sST2 in the maternal plasma of patients with preeclampsia in comparison to those with normal pregnancies (84,85,169). In addition, women with early-onset preeclampsia had higher sST2 concentrations than those with late onset of this syndrome. The sources for such elevation in sST2 in the maternal circulation among women with preeclampsia were either placental or of the vascular endothelium in response to the exaggerated maternal inflammatory state associated with this syndrome (161,165,170–172). Indeed, the maternal concentration of pro-inflammatory cytokines are higher in patients with early-onset preeclampsia (173–175) and severe preeclampsia (174,176,177) than in women with normal pregnancies. Pro-inflammatory cytokines such as TNF-α and IL-1β, activate endothelial cells; for *in vitro*

studies, investigators were able to stimulate vascular endothelial cells to secrete sST2 into the supernatant (81,83). Since sST2 has been associated with heart failure and volume overload in the vasculature, one cannot but wonder whether the maternal hemodynamic changes of the cardiovascular system in women with preeclampsia may also contribute to the elevation of sST2 concentration observed in this syndrome.

## The longitudal profile of sST2 and other biomarkers in preeclampsia

Plasma concentration of sST2 in preeclampsia was strongly correlated with plasma concentrations of anti-angiogenic factors (sVEGFR-1 and sEng) and inversely correlated with the angiogenic placental growth factor (PlGF) (85). The performance of sST2 in identifying patients with preterm preeclampsia was equivalent to that of angiogenic (PlGF) and anti-angiogenic (sVEGFR-1, sEng) factors and their ratios (PlGF/sVEGFR-1, PlGF/sEng) (85). Although the mean plasma sST2 concentration was reported to be significantly increased prior to the onset of preeclampsia (84), the current study extends these observations by demonstrating the profile of plasma sST2 concentration changes throughout pregnancy. Soluble ST2 concentrations were higher toward the end of pregnancy for women with normal pregnancies and for preeclamptic women, although a higher magnitude was seen in early-onset preeclampsia. We also showed that women with early-onset preeclampsia had a higher, earlier increase of plasma sST2 concentration than those with late-onset preeclampsia. The finding that plasma sST2 concentration increased six weeks prior to the diagnosis of preeclampsia is similar to other biomarkers (178). An increase in sVEGFR-1 concentration was demonstrated 6–10 weeks before clinical manifestations (31,178–184). A lower plasma PlGF/sVEGFR-1 ratio was detected in women who developed preterm and term preeclampsia at 20 weeks and at 14 weeks before the clinical diagnosis, respectively (182). A plasma ratio of PlGF/sVEGFR-1 below the 2.5th percentile at 20–23 weeks of gestation was also strongly predictive of delivery before 34 weeks with an increasing number of histological lesions consistent with maternal underperfusion (185), a major placental lesion found in women with preeclampsia (160). Similarly, a lower plasma PlGF/sEng ratio was observed in women with preeclampsia at 20 weeks and at 10 weeks before the clinical diagnosis for preterm and term preeclampsia (182). We were able to identify that sST2 increases significantly in the maternal plasma about six weeks prior to the onset of the syndrome, similar to other biomarkers of this disease. It is not clear whether this observation reflects the systemic maternal changes (hemodynamic, immune system, and endothelial dysfunction) prior to the onset of preeclampsia, or whether this elevation in sST2 concentration has a role in shifting the maternal immune response to the Th1 type (by inhibiting IL-33) associated with preeclampsia (65,67,69).

## Strengths and limitations

This study is the first to demonstrate the different profiles of plasma sST2 concentrations in relation to gestational age in women with a normal pregnancy and in those with preeclampsia as well as between early-onset and late-onset preeclampsia. Its observational nature precludes us from any conclusions regarding causality and specific mechanisms that may derive from this study.

## Conclusions

Our study demonstrates the change in plasma sST2 concentration throughout gestation. Women who subsequently developed preeclampsia have a higher sST2 concentration when compared to healthy pregnant women. This change is observed approximately six weeks prior to the clinical manifestation of preeclampsia. Patients with early-onset preeclampsia showed a substantial change in the maternal plasma sST2 concentration beginning at 22 weeks of gestation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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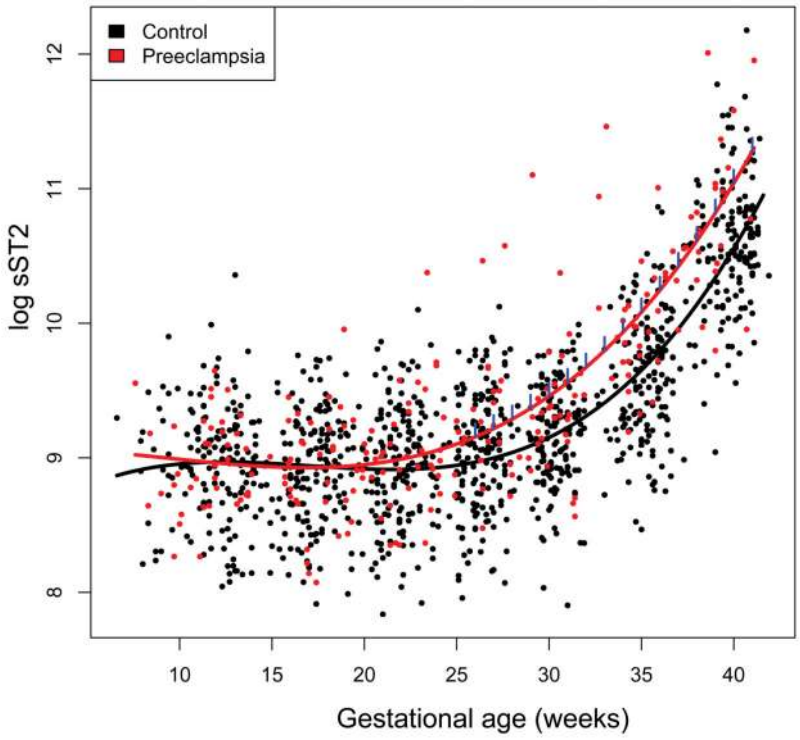



**Figure 1.**

Longitudinal profiles of plasma sST2 concentration. Maternal plasma concentration of sST2 (log, base e, thereof) in women with normal pregnancy (black dots) and those who subsequently developed preeclampsia (red dots). The gestational age dependence of the sST2 concentration in women with normal pregnancy (black line) and those with preeclampsia (red line) was estimated using a linear mixed-effect model and a third degree polynomial function. The blue vertical lines on the preeclampsia curve denote statistical significance of the difference between the two groups at the corresponding gestational age according to a linear mixed-effects model adjusting for covariates (gestational age at venipuncture, nulliparity, and smoking).

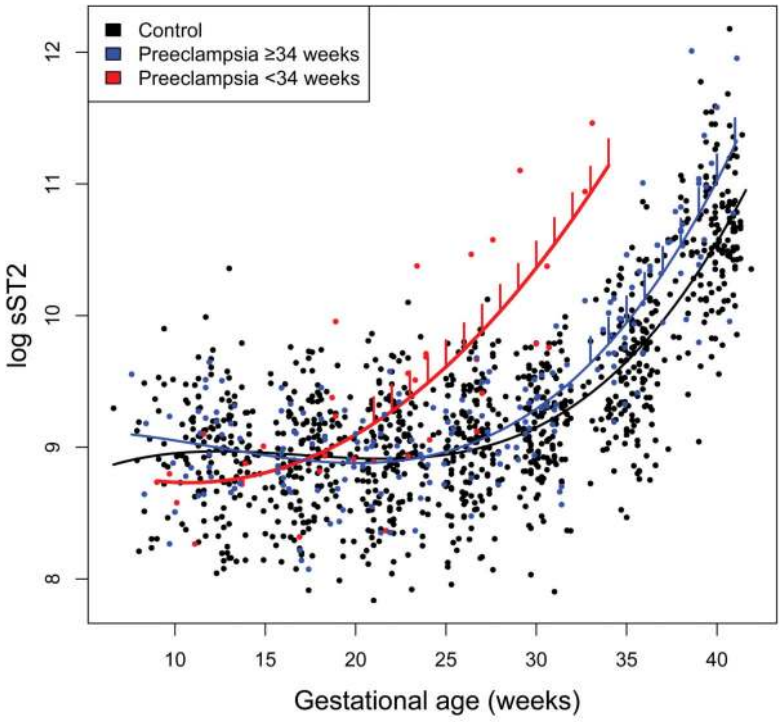
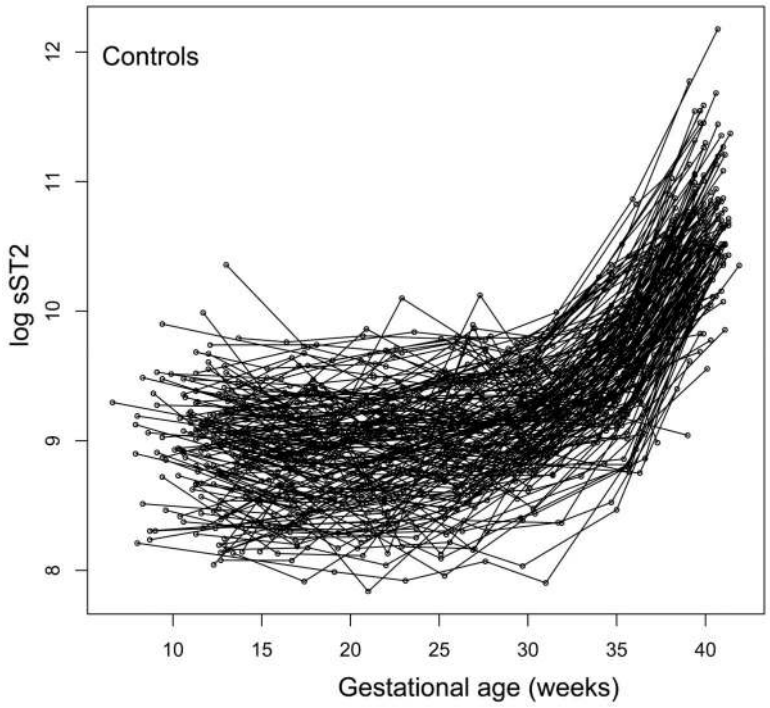



**Figure 2.**

Longitudinal profiles of plasma sST2 concentration in early-onset and late-onset preeclampsia. Maternal plasma concentration of sST2 (log, base e, thereof) in women with normal pregnancy (black dots), early-onset preeclampsia (delivered < 34 weeks of gestation; red dots), and late-onset preeclampsia (blue dots). The gestational-age dependence of the sST2 concentration in women with normal pregnancy (black line), the early-onset preeclampsia group (red line), and the late-onset preeclampsia group (blue line) was estimated using a linear mixed-effect model and a third degree polynomial function. The vertical lines on the preeclampsia curve denote statistical significance of the difference between the preeclampsia and normal pregnancy at the corresponding gestational age according to a linear mixed-effects model, adjusting for covariates (gestational age at venipuncture, nulliparity, and smoking).



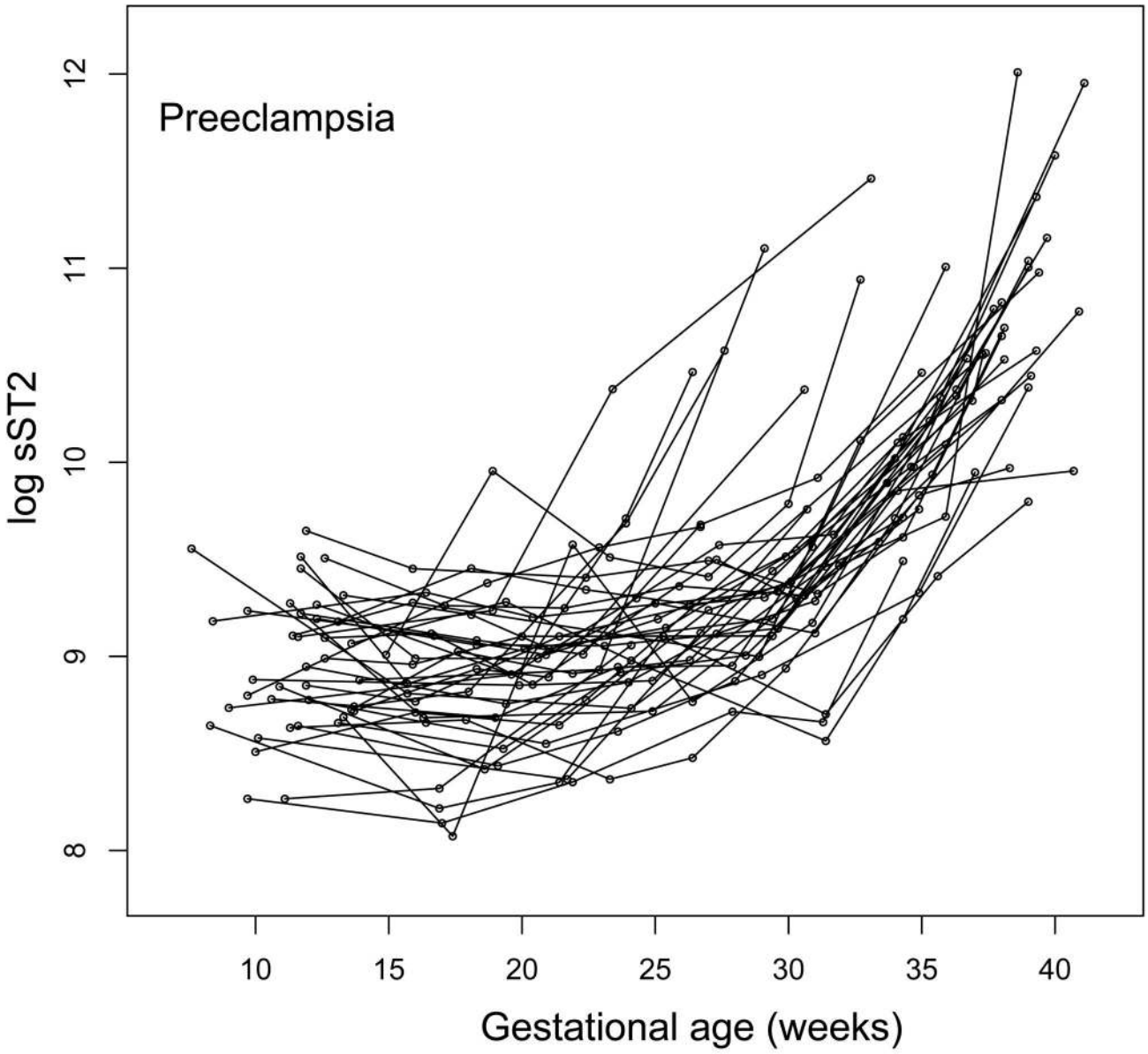



**Figure 3.**

Individual longitudinal plasma sST2 concentration profiles. sST2 plasma concentration (log, base e, thereof) in women with normal pregnancy (n=160) and those who subsequently developed preeclampsia (n=40) is shown as a function of gestational age. Each line corresponds to one patient.

## Table 1

Demographic and clinical characteristics of the study groups

| | Normal pregnancy (n=160) | Preeclampsia (n=40) | p |
|---|---|---|---|
| Maternal age (years) | 24 (20–30) | 20.5 (19–25) | 0.02 |
| Pre-pregnancy body mass index (BMI) (kg/m$^2$) | 23.9 (21.6–26.8) | 25.7 (23.5–29.2) | 0.005 |
| Smoking | 23 (14.4) | 2 (5) | 0.55 |
| Nulliparity | 71 (44.4) | 26 (65) | 0.02 |
| Previous preeclampsia | 2 (1.3) | 5 (12.5) | 0.04 |
| Gestational age at enrollment (weeks) | 9.4 (8–11.4) | 10 (8.7–11.4) | 0.3 |
| Gestational age at delivery (weeks) | 40 (39.2–40.7) | 38 (34.8–39.3) | <0.001 |
| Birthweight (g) | 3415 (3190–3560) | 2980 (1990–3537) | <0.001 |

Data expressed as median (interquartile range) and number (percentage)

## Table 2

Magnitude and significance of differences in sST2 concentration between patients with preeclampsia and those with normal pregnancies according to gestational age. The magnitude of differences is expressed as percentage changes [(preeclampsia-control)/control * 100] and significance p-values was obtained from linear mixed-effects models.

| GA | sST2 (pg/mL) | | Percentage difference | p-value |
|---|---|---|---|---|
| | Preeclampsia | Control | | |
| 10 | 7294.5 | 7368.0 | −1.0 | 0.91 |
| 11 | 7192.7 | 7436.7 | −3.3 | 0.67 |
| 12 | 7098.0 | 7466.2 | −4.9 | 0.48 |
| 13 | 7013.9 | 7462.6 | −6.0 | 0.37 |
| 14 | 6943.6 | 7432.7 | −6.6 | 0.32 |
| 15 | 6890.4 | 7383.4 | −6.7 | 0.31 |
| 16 | 6857.5 | 7321.7 | −6.3 | 0.33 |
| 17 | 6848.0 | 7254.4 | −5.6 | 0.40 |
| 18 | 6865.6 | 7188.0 | −4.5 | 0.50 |
| 19 | 6914.0 | 7129.0 | −3.0 | 0.65 |
| 20 | 6997.5 | 7083.5 | −1.2 | 0.86 |
| 21 | 7121.1 | 7057.6 | 0.9 | 0.89 |
| 22 | 7290.6 | 7057.5 | 3.3 | 0.62 |
| 23 | 7513.3 | 7089.4 | 6.0 | 0.37 |
| 24 | 7797.6 | 7160.3 | 8.9 | 0.19 |
| 25 | 8154.4 | 7277.8 | 12.0 | 0.079 |
| 26 | 8596.9 | 7450.8 | 15.4 | 0.028 |
| 27 | 9142.0 | 7690.2 | 18.9 | 0.0087 |
| 28 | 9811.1 | 8009.2 | 22.5 | 0.0024 |
| 29 | 10631.5 | 8424.5 | 26.2 | 0.0006 |
| 30 | 11638.5 | 8957.7 | 29.9 | 0.0001 |
| 31 | 12878.3 | 9636.8 | 33.6 | <0.0001 |
| 32 | 14411.2 | 10498.9 | 37.3 | <0.0001 |
| 33 | 16317.3 | 11593.7 | 40.7 | <0.0001 |
| 34 | 18703.8 | 12988.2 | 44.0 | <0.0001 |
| 35 | 21715.6 | 14774.8 | 47.0 | <0.0001 |
| 36 | 25550.7 | 17081.5 | 49.6 | <0.0001 |
| 37 | 30482.1 | 20088.8 | 51.7 | <0.0001 |
| 38 | 36891.6 | 24054.3 | 53.4 | <0.0001 |
| 39 | 45318.7 | 29351.6 | 54.4 | <0.0001 |
| 40 | 56535.2 | 36531.0 | 54.8 | <0.0001 |
| 41 | 71660.5 | 46416.4 | 54.4 | 0.0001 |

## Table 3

The differences in plasma sST2 concentration between normal pregnancy and preeclampsia as a function of the number of weeks before clinical diagnosis. The magnitude of differences (expressed as fold change between cases and controls) and corresponding significance p-values were estimated using linear mixed-effect models.

| | Preeclampsia vs Controls | |
|---|---|---|
| Weeks before clinical diagnosis | Fold change | P value |
| 0 | 1.65 | <0.0001 |
| 1 | 1.54 | <0.0001 |
| 2 | 1.44 | <0.0001 |
| 3 | 1.36 | <0.0001 |
| 4 | 1.29 | 0.0007 |
| 5 | 1.23 | 0.007 |
| 6 | 1.17 | 0.03 |
| 7 | 1.13 | 0.12 |
| 8 | 1.09 | 0.27 |
| 9 | 1.05 | 0.50 |
| 10 | 1.02 | 0.76 |
| 11 | −1.00 | 0.97 |
| 12 | −1.02 | 0.75 |
| 13 | −1.04 | 0.58 |
| 14 | −1.06 | 0.45 |
| 15 | −1.07 | 0.38 |
| 16 | −1.07 | 0.33 |
| 17 | −1.08 | 0.31 |
| 18 | −1.08 | 0.31 |
| 19 | −1.08 | 0.33 |
| 20 | −1.07 | 0.37 |