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ORIGINAL RESEARCH

Tumor Necrosis Factor Inhibitor Use Increases Birthweight in Pregnant Women With Rheumatoid Arthritis Independently of the Soluble Fms-Like Tyrosine Kinase-1/ Placental Growth Factor Ratio

Cornelia H. Quaak, MD; Anna C. M. Kluivers, MD; Sara J. Baart, PhD; Hieronymus T. W. Smeele, MD; Rugina I. Neuman, MD, PhD; Langeza Saleh, MD, PhD; Willy Visser, MD, PhD; A. H. Jan Danser, PhD; Radboud J. E. M. Dolhain, MD, PhD

BACKGROUND: To study whether the use of TNF (tumor necrosis factor) inhibitors (TNFi) by pregnant women with rheumatoid arthritis affects sFlt-1 (soluble Fms-like tyrosine kinase-1), PlGF (placental growth factor), or their impact on birthweight.

METHODS AND RESULTS: sFlt-1 and PlGF were measured in all trimesters of pregnancy in the Preconception Counseling in Active Rheumatoid Arthritis study and were compared according to the use of TNFi. The association of sFlt-1 and PlGF with birthweight in relation to TNFi was determined. The study included 158 women, of whom 52.5% used TNFi during pregnancy. Both sFlt-1 and PlGF increased during pregnancy, whereas their ratio declined. Taking into consideration the trimester-related variation in levels of sFlt-1 and PlGF, after correction for relevant confounders, the sFlt-1/PlGF ratio was not significantly different between patients who did or did not use TNFi (sFlt-1/PlGF ratio in the second trimester compared with the first trimester: estimated change 8.17 [95% CI, 2.54–26.29], P=0.79; sFlt-1/PlGF ratio in the third trimester compared with the first trimester: estimated change 6.25 [95% CI, 1.73–22.50], P=0.25). In women who did not use TNFi, birthweight was significantly lower (3180 versus 3302 g; P=0.03), and sFlt-1 displayed a negative correlation with birthweight (r=−0.462, P<0.001) and birthweight percentile (r=−0.332, P=0.008). In TNFi users, these correlations were absent.

CONCLUSIONS: TNF inhibitor use increases birthweight in pregnant women with rheumatoid arthritis independently of the sFlt-1/ PlGF ratio.

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Key Words: birthweight ■ pregnancy ■ rheumatoid arthritis ■ sFlt-1/PlGF ratio ■ TNF inhibitors

Rheumatoid arthritis (RA) is a common autoimmune disorder with a relatively high prevalence in women of childbearing age.[1] Research suggests that women with RA have greater difficulty conceiving. When pregnant, the overall risk of adverse obstetric outcomes increases, including hypertensive disorders, lower birthweight/fetal growth restriction (FGR), and prematurity.[2] These findings could be related to impaired placentation or impaired placental function in women with RA.

Correspondence to: Cornelia H. Quaak, MD, Erasmus Medical Center room Na-523, Postbus 2040, 3000 CA Rotterdam, the Netherlands, Email: c.witte-quaak@erasmusmc.nl

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CLINICAL PERSPECTIVE

What Is New?

- TNF (tumor necrosis factor) inhibitor use in pregnant women with rheumatoid arthritis does not exert a direct influence on the levels of sFlt-1 (soluble Fms-like tyrosine kinase-1) and PlGF (placental growth factor), or their ratio, although it does increase birthweight.
- In case of using a TNF inhibitor during pregnancy, the well-known negative correlation of sFlt-1 and birthweight disappeared.
- When subdividing the patients of our rheumatoid arthritis cohort into those with sFlt-1 levels above and below the median, only patients with high sFlt-1 levels displayed an increase in PlGF after TNF inhibitor use.

What Are the Clinical Implications?

- TNF inhibitors increase birthweight in pregnant women with rheumatoid arthritis independently of the sFlt-1/PlGF ratio.
- TNF inhibitors could be explored as a therapeutic intervention in women with clinical conditions characterized by increased sFlt-1 levels, such as preeclampsia.

Nonstandard Abbreviations and Acronyms

FGR	fetal growth restriction
sFlt-1	soluble Fms-like tyrosine kinase-1
TNFi	tumor necrosis factor inhibitors

A tight balance between proinflammatory (eg, TNFα [tumor necrosis factor α]) and IL-6 (interleukin-6) and anti-inflammatory (eg, IL-10) cytokines is required for adequate placentation, with the anti-inflammatory cytokines predominating. In RA, proinflammatory cytokines, such as TNFα and IL-6, are increased. High levels of IL-6 are associated with a reduced birthweight.[3] This high inflammatory state could be related to poor pregnancy outcome in terms of a lower birthweight as a result from disturbed placentation.

sFlt-1 (soluble Fms-like tyrosine kinase-1, an antiangiogenic factor), PlGF (placental growth factor, an angiogenic factor), and their ratio, are currently considered biomarkers of placentation and placental function.[4] A high sFlt-1/PlGF ratio predicts adverse pregnancy outcomes such as lower birthweight, preeclampsia, and FGR.[5] Furthermore, high sFlt-1 levels are associated with reduced birthweight. For daily practice, a low sFlt-1/PlGF ratio is a clinically valuable tool to rule out preeclampsia within 7 days.[6] Also, in patients with RA, it was shown that a low sFlt-1/PlGF ratio could be used to rule out preeclampsia.[7] Surprisingly, baseline levels of PlGF were lower in pregnant women with RA, especially when they were using prednisone.[8]

Smeele et al. recently found that treatment with TNF inhibitors (TNFi) improves pregnancy outcomes, reflected by a significantly higher birthweight of 173 grams at term, compared with the neonates of women not using these drugs.[9] Also, fewer children were born small for gestational age in pregnant patients with RA after correction for disease activity. This suggests that the positive association between treatment with TNFi during pregnancy and higher birthweight may result from better placentation, for instance because of a reduction in IL-6 due to the use of TNFi.[3] In patients with preeclampsia, it was previously established that besides an increased sFlt-1, levels of IL-6 were also increased.[10]

In the current study, we hypothesize that TNFi treatment during pregnancy exerts its positive effect on birthweight directly by reducing sFlt-1 or increasing PlGF or indirectly by influencing the negative effect of sFlt-1 on birthweight. We therefore measured sFlt-1 and PlGF in samples collected in the same prospective cohort study of pregnancy in RA in which the observation between TNFi use and a higher birthweight was made. We particularly investigated differences between TNFi users and those who did not use TNFi during pregnancy.

METHODS

Data Sharing

Data are not publicly available due to protected health information. Data request proposals can be submitted to the corresponding author with appropriate regulatory approval and signed data use agreement.

Patient Population and PreCARA Treatment Protocol

The Preconception Counseling in Active RA (PreCARA) study is a prospective cohort study on pregnancy and inflammatory arthritis. The present study is embedded within the PreCARA study. The PreCARA study protocol was reviewed and approved by the Medical Ethics Committee of the Erasmus MC University Medical Center Rotterdam according to the Dutch Medical Research with Human Subjects Law (MEC-2011-032). All participants gave informed consent before participation.

The PreCARA study is performed in the Erasmus Medical Center, a tertiary referral hospital in Rotterdam, the Netherlands. The PreCARA protocol has been

described previously.[11] In short, women with inflammatory arthritis were eligible for participation if they were planning to conceive or were already pregnant. For the current analysis, we excluded twin pregnancies and pregnancies in women with diseases other than RA. Patients were treated according to a modified treat-to-target approach aimed at remission. If needed, treatment was intensified at every study visit. The first step at intensifying is starting sulfasalazine or hydroxychloroquine, followed by adding prednisone or a TNFi. Patients remained on the same TNFi they used at study enrolment, while trying to conceive. TNFi was stopped during pregnancy at the gestational age recommended by the European Alliance of Associations for Rheumatology.[12] Adalimumab and infliximab were stopped at 20 weeks of gestation, etanercept at 28 to 32 weeks of gestation, and certolizumab-pegol at 38 weeks of gestation. After stopping adalimumab, infliximab, or etanercept, a switch to certolizumab-pegol or prednisone was considered. For this article, we used data up to May 2021.

Data Collection

Preferably, patients entered the PreCARA study before pregnancy. Before conception, patients visited the hospital every 3 months. During pregnancy, visits were scheduled in the first, second, and third trimester. Postpartum visits were at weeks 6, 12, and 26. Patients were seen by their rheumatologist and rheumatology nurse. Clinical data and venous blood samples were collected during each visit. Data on frequencies and dosages of conventional synthetic disease-modifying antirheumatic drugs, biologic disease modifying antirheumatic drugs, and other medication were collected using electronic questionnaires. Data on pregnancy outcomes included gestational age at delivery, birthweight, fetal sex, and parity.

Pregnancy complications were defined as preterm delivery (delivery at <37 weeks of gestational age), gestational diabetes, and hypertensive disorders (gestational hypertension and preeclampsia). Gestational hypertension is defined as the new onset of a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg. Preeclampsia is the combination of gestational hypertension or deteriorated preexistent hypertension and proteinuria.

Measurements of sFlt-1 and PlGF

Venous blood collected during all trimesters is used to analyze sFlt-1 and PlGF. Blood samples were stored at −80°C until analysis. Measurement of sFlt-1 and PlGF was performed using an automated Elecsys immunoassay analyzer (Cobas 6000, E-module; Roche Diagnostics, Ltd., Rotkreuz, Switzerland), as described previously.[13] Levels were displayed in pg/mL.

Statistical Analysis

The corresponding author had full access to all the data in the study and takes responsibility for its integrity and the data analysis. Disease activity was calculated using the Disease Activity Score in 28 joints based on swollen and tender joints and CRP (C-reactive protein) (3),[14] which has been validated for use during pregnancy.[15] Birthweight percentiles are reported as a correction of the given gestational age and sex of the newborn on birthweight.[16] The definition of small for gestational age is a birthweight <p10, and large for gestational age is a birthweight >p90 based on Dutch growth charts.[17] The definition of FGR is failing to attain the fetal growth potential as determined by the genetic makeup.[18]

Normality of continuous data was evaluated by graphical plotting the distribution of data in histograms and using the Shapiro–Wilk W test. Descriptive data are reported as numbers (n) and percentages (%). Continuous variables are given as mean (+SD) or median (+ interquartile range) as appropriate. The Mann–Whitney *U* test was performed to investigate differences in continuous variables between 2 groups, and differences in categorical variables were investigated with chi-square test.

To evaluate the differences in birthweight between women who used TNFi and those who did not, we investigated the same variables in the uni- and multivariable regression analysis as Smeele et al. did, namely disease activity in third trimester of pregnancy, diabetes, parity, maternal age, and gestational age at delivery.[9] Correlations were studied with Spearman's rank correlation coefficient.

To study the association of levels of sFlt-1 in relation to TNFi use, patients were stratified based upon the median sFlt-1 level for each trimester separately.

The association of TNFi and the sFlt-1/PlGF ratio during pregnancy was studied using a linear mixed model with unstructured covariance. All values were analyzed on a log-scale and reported as back log-transformed values.

First, we performed a linear mixed model with unstructured covariance to correlate TNFi use during pregnancy with sFlt-1, PlGF, and the sFlt-1/PlGF ratio in all trimesters (fixed effects), considering the individual patients and trimester as random effects. The dependent variable is the sFlt-1 or PlGF or the sFlt-1:PlGF ratio.

Second, we performed a linear mixed model with unstructured covariance to study the association of TNFi use during pregnancy on the sFlt-1/PlGF ratio, considering explanatory variables for the variation of the sFlt-1/PlGF ratio between women who did not use TNFi and did use TNFi during pregnancy. The dependent variable is the sFlt-1/PlGF ratio. Based on literature and expert opinion, the following variables were

Table 1. Baseline Characteristics

Parameter	TNFi –	TNFi +	*P* value
N	75	83	
Age, y	32.1 (28.8–35.0)	33.1 (30.5–35.6)	0.01†
Race, White, n (%)	66 (88.0%)	67 (80.7%)	0.21‡
Body mass index	23.6 (21.1–27.0)	23.1 (20.9–27.2)	0.55†
Rheumatologic characteristics			
Duration of rheumatoid arthritis, y	5.9 (2.3–10.3)	7.7 (4.2–12.0)	0.08†
Rheumatoid factor positive	48 (64.0%)	58 (69.9%)	0.31‡
Anticyclic citrullinated peptide positive	43 (57.3%)	62 (74.7%)	0.02‡
Bone erosions	58 (77.3%)	32 (38.6%)	0.03‡
DAS28CRP (3) trimester 1	2.00 (1.65–2.57)	1.94 (1.59–2.67)	0.85†
DAS28CRP (3) trimester 2	1.96 (1.69–2.51)	2.17 (1.78–2.88)	0.08†
DAS28CRP (3) trimester 3	1.84 (1.65–2.35)	2.09 (1.69–2.88)	0.11†
Obstetric characteristics			
Nulliparity, n (%)	46 (61.3%)	39 (47.0%)	0.07‡
Artificial reproductive technologies, n (%)	13 (17.3%)	11 (13.3%)	0.45‡
Smoking during pregnancy, n (%)	2 (2.7%)	3 (3.6%)	0.73‡
Treatment during pregnancy, n (%)			
No medication	9 (12.0%)	-	
Prednisone	30 (40.0%)	39 (47.0%)	0.38‡
Sulfasalazine	47 (62.7%)	51 (61.4%)	0.88‡
Hydroxychloroquine	48 (64.0%)	42 (51.8%)	0.12‡
Maternal-fetal outcomes			
Gestational age at delivery	39^{+1} (37^{+4}–40^{+3})	39^{+0} (38^{+0}–40^{+0})	0.33†
Gestational age at delivery <34 wks, n (%)	3 (4.0)	1 (1.2)	0.27‡
Gestational age at delivery <37 wks, n (%)	11 (14.7)	7 (8.4)	0.16‡
Fetal sex male, n (%)	34 (45.3)	47 (56.6)	0.16‡
Birthweight in grams (SD)	3180 (61)	3302 (47)	0.03*
Birthweight in percentiles	53.5 (36.7–79.6)	55.9 (28.7–78.7)	0.03*
Small for GA (birthweight *P*≤10), n (%)	8 (10.7%)	3 (3.6%)	0.05‡
Large for GA (birthweight *P*≥90), n (%)	14 (18.6%)	11 (13.3%)	0.66‡
Gestational hypertension, n (%)	6 (8.0)	4 (4.8)	0.31‡
Preeclampsia, n (%)	1 (1.3)	2 (2.4)	0.54‡
Gestational diabetes, n (%)	2 (2.7)	5 (6.0)	0.27‡
Diabetes type 1, n (%)	2 (2.7)	2 (2.4)	0.65‡

Values are median (interquartile range) unless stated otherwise.

DAS28CRP (3) indicates Disease Activity Score in 28 joints based on swollen and tender joints and C-reactive protein; GA, gestational age; and TNFi, tumor necrosis factor α inhibitor; †, mwu-test; ‡, chi-square test; *After correction for confounders (see methods).

included in our linear mixed model: age; duration of RA; disease activity score based on swollen and tender joints and CRP (3); rheumatoid factor; anticitrullinated protein antibodies positivity; bone erosions; use of prednisone, hydroxychloroquine, and sulfasalazine; sex of the newborn; and parity.[19] Other relevant confounders such as smoking or gestational hypertension were excluded because of the low number of patients per group. Besides those confounders, all trimesters were included in the model as fixed effects. Individual patients and trimesters were considered as random effects.

A 2-sided $P<0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 28.0 and Stata version 17.0.

RESULTS

Differences Between TNFi Users and Non-TNFi Users

The baseline characteristics of all included women (N=158) are presented in Table 1. The patients who were not included in this study, but were included in

Table 2. sFlt-1, PlGF, and sFlt-1/PlGF Ratio Values per Trimester for All Patients Who Did Not Use TNFi During Pregnancy and Patients Who Ever Used TNFi During Pregnancy and Used TNFi During All Trimesters of Pregnancy

	TNFi –	TNFi +	TNFi All Trimesters
Angiogenic marker values	N=75	N=83	N=46
Trimester 1			
sFlt-1	1188 (816–1542)	1110 (574–1379)	1063.0 (618–1289)
PlGF	31.4 (19.8–50.4)	27.8 (16.2–46.6)	27.9 (16.7–46.1)
sFlt-1/PlGF	33.4 (17.0–51.2)	33.0 (17.8–45.9)	31.0 (18.9–40.0)
Trimester 2			
sFlt-1	1321 (1051–1761)	1557 (1039–2211)	1440.5 (922–2115)
PlGF	346 (240–462)	360 (247–597)	351 (196–541)
sFlt-1/PlGF	4.1 (2.3–5.9)	4.9 (2.3–7.1)	5.7 (2.0–8.2)
Trimester 3			
sFflt-1	1933 (1380–2682)	2011 (1453–2821)	1771 (1278–2541)
PlGF	497 (300–765)	644 (407–979)	562 (365–869)
sFlt-1/PlGF	3.8 (1.8–7.3)	3.2 (1.8–5.5)	3.1 (1.7–5.6)

Values are median (interquartile range) in pg/mL. PlGF indicates placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; and TNFi, tumor necrosis factor α inhibitor. Differences between the values presented were not statistically significantly different between ever TNFi use, never TNFi use, and use of TNFi during all trimesters.

the birthweight analysis of Smeele et al., were patients for whom we did not have any available venous blood samples.[9] Patients were divided into 2 groups based on the use of TNFi during pregnancy. Eighty-three (52.5%) women ever used a TNFi during their pregnancy and in 46 women (29.1%), this concerned use in all trimesters of pregnancy. Seventy-five women were not treated with TNFi. Disease activity was comparable in all trimesters.

After correction for confounders (gestational age at delivery, maternal age, diabetes including gestational diabetes, and Disease Activity Score based on swollen and tender joints and CRP (3) in third trimester of pregnancy[9]), birthweight was significantly higher in the offspring of TNFi users (P=0.03) (data not shown).

Ten women developed gestational hypertension, and 3 women developed preeclampsia during pregnancy. No difference in preeclampsia rate nor gestational hypertension was observed in patients who used TNFi compared with patients who did not use TNFi.

Determinants of sFlt-1, PlGF, and the sFlt-1/PlGF Ratio

Table 2 and Figure 1 show sFlt-1, PlGF, and the sFlt-1/PlGF ratio values for all patients divided into groups of no TNFi, TNFi use anytime during pregnancy, and TNFi use in all trimesters of pregnancy. There was no significant difference in sFlt-1 and PlGF or their ratio between ever TNFi users and nonusers in any trimester. Also, women who used TNFi in all trimesters of pregnancy showed no differences in their levels of sFlt-1, PlGF, or their ratio compared with women who did not use TNFi.

In our simple linear mixed model, the use of TNFi was not significantly associated with a lower sFlt-1/PlGF ratio nor lower sFlt-1 levels (Table S1).

Subsequently, a linear mixed model was performed to assess whether TNFi use influences the sFlt-1/PlGF ratio after correcting for potential explanatory variables (Table S2). This model showed again that TNFi use during pregnancy did not significantly influence the estimate when comparing the first trimester sFlt-1/PlGF ratio to the ratio of either the second or the third trimester (P=0.791 and P=0.252 respectively). Even for sFlt-1 and PlGF separately, no significant changes in aforenamed markers were found (data not shown).

TNFi Use Mitigates the Negative Association Between Birthweight and sFlt-1

In women not using TNFi, sFlt-1 displays a negative association with birthweight in all trimesters, in full agreement with previous observations.[20] However, significance was reached only in the second and third trimester (r=– 0.27, P=0.03 and r=–0.46, P≤0.01). In women using TNFi, no association of sFlt-1 with birthweight was found in any trimester (r=–0.01, P=0.91; and r=0.08, P=0.53; and r=0.08, P=0.52) (Figure 2). Findings were comparable when replacing sFlt-1 with the sFlt-1/PlGF ratio (Figure S1). Calculated birthweight percentiles were used to determine whether the birthweight was in line with the birthweight expected based on the gestational age. This approach did not alter the findings for both sFlt-1 and the sFlt-1/PlGF ratio (data not shown).

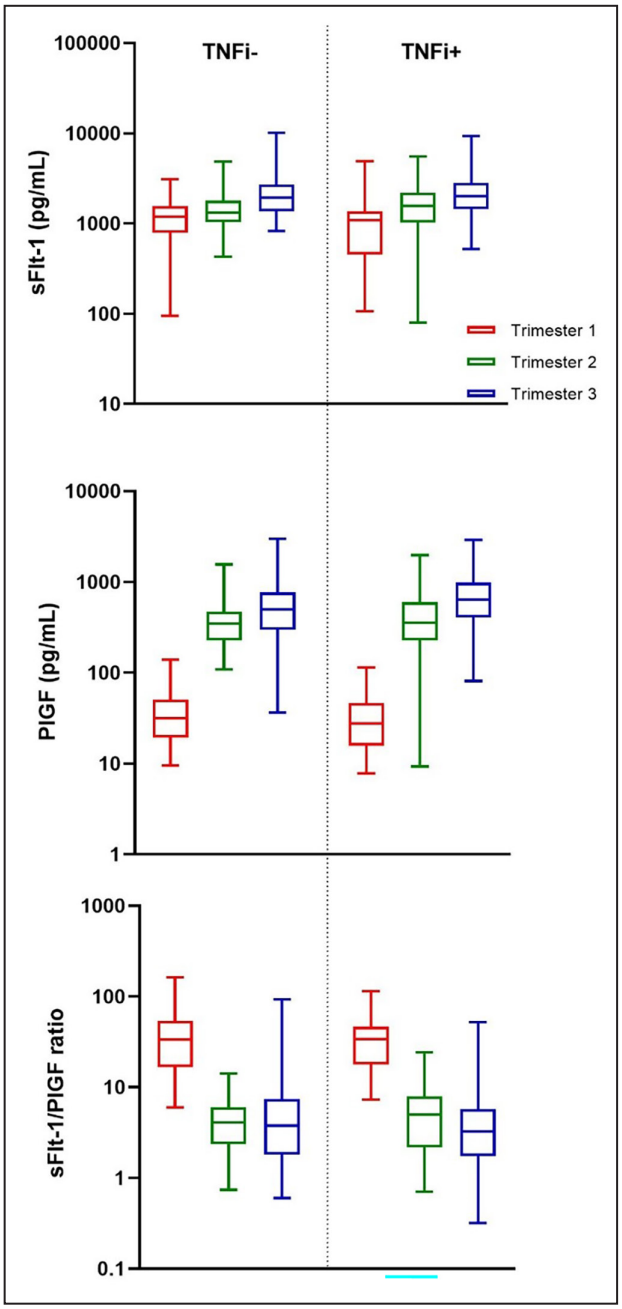

Figure 1. Longitudinal plots presenting the levels of sFlt-1, PlGF, and the sFlt-1/PlGF ratio on a log scale per trimester for all patients without and with ever-use of TNFi during pregnancy.
PlGF indicates placental growth factor; sFlt-1, soluble Fms-like tyrosine kinase-1; and TNFi, Tumor necrosis factor inhibitors.

The Impact of TNFi on Birthweight in Relation to Levels of sFlt-1

To get more insight into the absolute effect of the use of TNFi on birthweight, patients were stratified based upon the median level of sFlt-1 in third trimester (1996 pg/mL). This cutoff was chosen to compare women with "high" sFlt-1 levels with women with "low" sFlt-1 levels, thereby mimicking the fact that women with preeclampsia display relatively high sFlt-1 levels. In women with sFlt-1 ≥1996 pg/mL, the use of TNFi was associated with an increase in birthweight of 352 g (Table 3, *P*=0.01). Also for birthweight percentiles, statistically significant differences were observed in this group. Besides that, the mean PlGF level in these women was higher when they used TNFi (*P*=0.02), resulting in a significantly lower sFlt-1/PlGF ratio (*P*=0.03). No such differences in relation to the use of TNFi were found in women with sFlt-1 levels <1996 pg/mL (Table 3). Furthermore, stratifying patients in the first and second trimester based upon the median sFlt-1 level (Tables S3 and S4) did not yield this outcome. This is in agreement with Figure 2, displaying the highest degree of correlation between sFlt-1 and birthweight in the third trimester.

DISCUSSION

In the current study, we describe the association between sFlt-1, PlGF and their ratio and birthweight in pregnant women with RA related to TNFi treatment. In our primary analysis and after correction for potential confounders, TNFi use during pregnancy did not reveal different patterns in sFlt-1, PlGF, and the sFlt-1/PlGF ratio. However, in women with relatively high levels of sFlt-1 in the third trimester of pregnancy and the use of TNFi any time during pregnancy, an increase in PlGF and a concomitant decrease of the sFlt-1:PlGF ratio was found, whereas sFlt-1 was unchanged. These changes were associated with increased birthweight and birthweight percentile.

Furthermore, in patients who did not receive TNFi, sFlt-1 showed its well-known negative correlation with birthweight, although this negative correlation was absent in the patients receiving TNFi treatment during pregnancy. Based on these data, a possible explanation for improved birthweight in patients who use TNFi may be based on an selective increase of PlGF.

Due to the earlier described positive impact of TNFi use on birthweight in RA,[1] we hypothesized that the use of TNFi could be associated with lower levels of sFlt-1 or higher levels PlGF mediated by a sFlt-1 lowering effect of TNFi. This hypothesis is based on human in vitro studies in which TNFα was able to induce the production of sFlt-1 in placental explants[21]. Also, in the reduced uterine perfusion pressure rat (animal model for preeclampsia and FGR), both TNFα and sFlt-1 are elevated. Administration of etanercept (a TNFi) decreased sFlt-1 and normalized fetal and placental weight.[22,23] On the contrary, we did not find any direct effect of TNFi on the levels of sFlt-1 in this study. By this, we expect that in humans, in vivo modulation of the levels of sFlt-1 by TNFi is not a relevant mechanism.

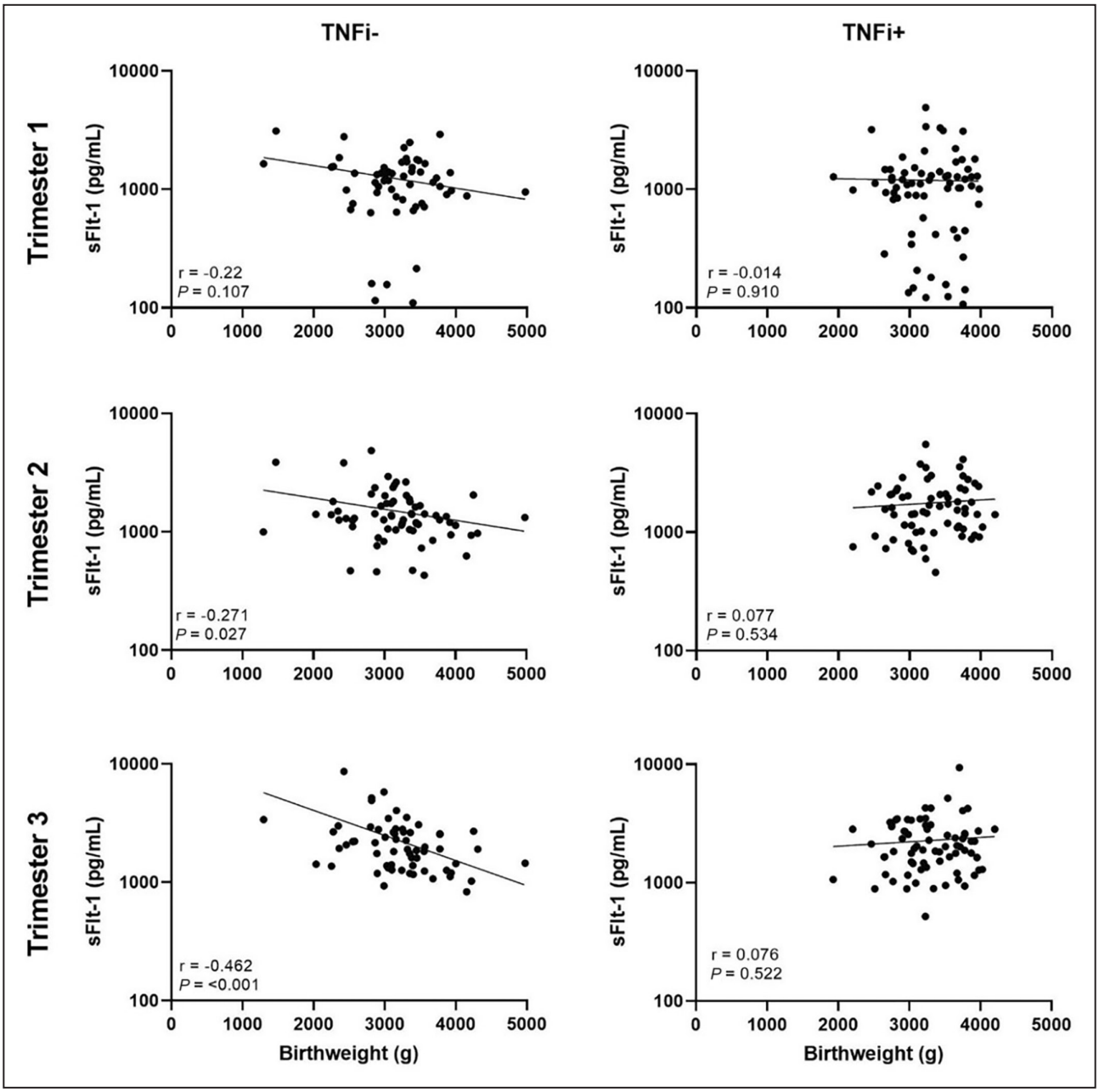

Figure 2. Correlation between the levels sFlt-1 and birthweight (grams) per trimester for all patients without and with ever-use of TNFi during pregnancy.
sFlt-1 indicates soluble Fms-like tyrosine kinase-1; and TNFi, tumor necrosis factor inhibitors.

The absence of the negative correlation of sFlt-1 and birthweight in women using TNFi, is in line with the previously cited literature. This suggests that the positive effect of TNFi on birthweight may be the result of a downstream blockade of the impact of sFlt-1 by inhibiting TNFα. One may speculate that TNFi mainly exerts its effect on birthweight by lowering disease activity because in pregnant women with RA, active disease is associated with lower birthweight.[14] However, in our study almost all patients had very low disease activity as they were treated according to a treat-to-target approach aimed at remission and hence no difference in disease activity between women using TNFi or not were observed. In addition, disease activity was corrected for in our statistical model.[9]

Besides birthweight, also birthweight percentile (ie, corrected for gestational age and sex of the newborn) was used as outcome measure to determine whether sFlt-1 has a direct effect on birthweight. Because using birthweight percentiles did not alter our findings, it can be concluded that sFlt-1 has a direct effect on birthweight and not an indirect effect by lowering gestational age.

Table 3. Differences in Angiogenic Factors and Birthweight Between Not Using TNFi and Using TNFi in Relation to sFlt-1 Levels in Third Trimester When Patients Were Stratified Based Upon the Median sFlt-1 Level

sFlt-1 ≥1996	TNFi –		TNFi +		
Parameter	N=32	95% CI	N=37	95% CI	*P* value
Birthweight, g	2950 (60)	2734–3166	3302 (46)	3147–3456	0.02
Birthweight percentile	30.5 (26.0)	21.1–39.9	45.9 (29.8)	35.9–55.8	0.03
sFlt-1	3373 (1813)	2719–4026	3136 (1276)	2710–3562	0.89
PlGF	497 (557)	296–698	681 (492)	516–845	0.02
sFlt-1/PlGF	16.6 (24.1)	7.9–25.3	9.1 (11.5)	5.3–13.0	0.03
sFlt-1 <1996	**TNFi –**		**TNFi +**		
Parameter	N=33	95% CI	N=36	95% CI	*P* value
Birthweight (grams)	3414 (60)	3201–3627	3280 (49)	3114–3446	0.32
Birthweight percentile	49.3 (31.4)	38.2–60.4	45.5 (29.0)	35.7–55.3	0.73
sFlt-1	1446 (3244)	1332–1561	1380 (3710)	1255–1505	0.49
PlGF	783 (472)	615–950	824 (546)	639–1009	0.90
sFlt-1/PlGF	3.0 (3.2)	1.9–4.2	2.5 (2.4)	1.7–3.3	0.74

Values sFlt-1 and PlGF are mean (SD) in pg/mL, birthweight (SD) in grams.
PlGF indicates placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; TNFi, tumor necrosis factor α inhibitor.

Moreover, after adding high levels of exogenous sFlt-1 to placental explants, the release of TNFα is stimulated, raising TNFα levels by 500%.[21] It has also been reported that sFlt-1 sensitizes endothelial cells to proinflammatory factors such as TNFα, resulting in increased release of factors such as endothelin-1. This provides a possible explanation how placental stress may precipitate placental insufficiency, which may result in preeclampsia or FGR.[24] From this perspective, treatment with TNFi could have beneficial effects even without altering sFlt-1. In our cohort, we did not have any data regarding subclinical inflammation due to RA, and thus it remains unknown to what degree TNFi use exerts its beneficial effects (including those on PlGF) by interfering with inflammation. Although TNFi might exert its effect downstream of sFlt-1, it should be acknowledged that the impact of TNFi on birthweight may not solely be mediated through the sFlt-1 pathway. In addition, it is imperative to acknowledge that birthweight is intricately associated with a myriad of other known factors, including maternal comorbidities, maternal nutrition, assisted conception, and the fetal genetic composition.[24] Asserting that the use of TNFi singularly influences birthweight without accounting aforenamed explanations should be avoided.

Various placental complications, such as preeclampsia and FGR, are associated with an angiogenic imbalance, partially caused by high levels of sFlt-1.[4,5] Currently, there are no medical interventions available to alter this imbalance. Various drugs, including sulfasalazine, proton pump inhibitors, and statins have been evaluated as potential sFlt-1 lowering treatment, but the results are inconclusive.[7,25,26] Our study suggests that treatment with TNFi may have the potential to be such a medical intervention, as we found that the use of TNFi was associated with higher levels of PlGF in patients with relatively high sFlt-1 levels in the third trimester of pregnancy. Similar patterns were not seen in the first and second trimester of pregnancy. This could relate to the fact that sFlt-1 and PlGF alter continuously during pregnancy, often in an opposing manner, as confirmed in the present study. These observations are relevant in the quest for a preeclampsia and FGR treatment, as low PlGF levels may not only be due to sFlt-1 binding but also to diminished PlGF production.[20] Future studies should investigate whether the use of TNFi truly has impact on PlGF levels and at what time point this is most relevant, particularly in patients with an angiogenic imbalance.

Our study is the first to evaluate a potential correlation between TNFi use and sFlt-1, PlGF and the sFlt-1/PlGF ratio in relation to birthweight. This study comprises a large, well-defined, prospectively followed-up cohort of women with a homogeneous disease. Due to the nature of this cohort, we were able to correct for relevant confounding factors. However, we should acknowledge some limitations of the current study. Laboratory samples were not available for all included patients from all trimesters. Furthermore, women that used a TNFi in a certain trimester were also likely to use this in other trimesters, and thus it was not possible to study the effect of TNFi treatment per trimester.

CONCLUSIONS

In conclusion, our study shows that TNFi use during pregnancy in patients with RA does not affect the

levels of sFlt-1 and PlGF or their ratio. However, in patients with relatively high levels of sFlt-1, we observed an improved angiogenic balance. As an angiogenic imbalance has pathogenic significance in pregnancy complications such as preeclampsia and FGR, our results pave the way for medical intervention with TNFi in those conditions.

ARTICLE INFORMATION

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Affiliations

Department of Rheumatology, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands (C.H.Q., H.T.S., R.J.D.); Department of Internal Medicine, Division of Pharmacology and Vascular Medicine, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands (C.H.Q., A.C.K., R.I.N., W.V., A.H.D.); Department of Gynecology and Obstetrics, Erasmus Medical Center, Rotterdam, the Netherlands (A.C.K., L.S.); and Department of Biostatistics, Erasmus Medical Center, Rotterdam, the Netherlands (S.J.B.).

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Supplemental Material

Tables S1–S4
Figure S1

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