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# Letter to the Editor (Matters arising from published papers)

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## Comment on: The sFlt-1 to PlGF ratio in pregnant women with rheumatoid arthritis: impact of disease activity and sulfasalazine use. Reply

Dear Editor, We read with great interest the letter by Förger *et al.* regarding our publication [1]. In their comment letter, the authors showed that women with RA have lower free placental growth factor (PlGF) levels compared with healthy pregnant controls. This observation is a valuable addition to our data [2], since we were unable to evaluate angiogenic marker levels in women with RA in comparison with a healthy control group. Indeed, since both Förger *et al.* and our data show no significant correlation between free PlGF and DAS28-CRP, it is most likely that PlGF in women with RA is of fetoplacental origin. To truly evaluate whether these lower free PlGF levels are a reflection of placental dysfunction, we refer to our recent publication [3] showing that the levels of total PlGF can be determined easily using a mathematical formula describing drug–receptor interactions. Applying this calculation to the findings of Förger *et al.* results in median total PlGF levels of 781 and 1092 ng/ml in the RA *vs* control group, respectively.

As mentioned by Förger *et al.*, we agree that women with RA are more likely to give birth to a neonate with low birth weight. Here, an important question remains as to what could trigger placental dysfunction, and thus lower PlGF production in women with RA. Besides the disease itself, medication use during conception and (early) pregnancy could potentially be such a trigger. In our previous study involving 221 pregnant women with RA [2], we showed that levels of the angiogenic markers soluble Fms-like tyrosine kinase-1 (sFlt-1) and free PlGF did not differ between women who used SSZ and women who did not. However, additional analysis on the same group of patients revealed that prednisone use was associated with lower levels of free PlGF compared with women who did not use these drugs (387 *vs* 480 pg/ml; $P = 0.03$) (Table 1). This observation is in line with previously published animal studies which show that glucocorticoids can prevent the normal increase in angiogenic factors during pregnancy [4]. Previous literature shows that patients who use prednisone give birth at an earlier gestational age and can have neonates with lower birthweight [5, 6]. Therefore, it might be the case that glucocorticoid use affects placental dysfunction and indirectly PlGF production, thereby inducing a shorter gestational age at delivery and lower neonatal birthweight.

Table 1 Angiogenic markers stratified for any prednisone use during pregnancy in a cohort of 221 women with RA included in the PARA study

| | Prednisone (–) | Prednisone (+) | *P*-value |
|---|---|---|---|
| *N* | 136 | 85 | |
| sFlt-1, pg/ml [median (IQR)] | 1613 (1199–2220) | 1701 (1215–2363) | 0.51 |
| PlGF, pg/ml [median (IQR)] | 480 (312–750) | 387 (227–632) | 0.03 |
| sFlt-1/PlGF ratio [median (IQR)] | 3.2 (1.9–6.3) | 4.5 (2.3–11) | 0.03 |

IQR: interquartile range; PARA: Pregnancy-induced Amelioration of Rheumatoid Arthritis.

To study this hypothesis, we performed additional analysis on the same cohort of patients as our original publication [2]. Regression analysis on outcome free PlGF (after excluding preeclampsia and gestational hypertension cases) and prednisone as independent variables showed that prednisone had a negative effect on (log-transformed) free PlGF even when corrected for confounders (time of blood draw in the third trimester and maternal age) ($\beta$ −0.28, $P = 0.05$). Furthermore, linear regression analysis on the outcome free PlGF stratified for low free PlGF (1st quartile) and normal/high free PlGF (2nd–4th quartiles) showed that the effect of prednisone on gestational age at birth is larger when free PlGF is low: low free PlGF: prednisone $\beta$ −1.29, $P = 0.012$; and normal/high free PlGF: prednisone $\beta$ −0.77, $P = 0.008$. This could suggest effect modification of free PlGF on the observed effect of prednisone on gestational age at birth. Kaplan–Meier survival analysis showed that, in our cohort, patients with a low free PlGF gave birth earlier than patients with a normal/high free PlGF ($P = 0.02$) (supplementary Fig. S1, available at *Rheumatology* online). Similar regression analysis (corrected for gestational age at birth) for outcome neonatal birthweight (kg) showed, although non-significant, a similar trend (low free PlGF: prednisone $\beta$ −118.02, $P = 0.47$; and normal/high free PlGF: prednisone $\beta$ −28.98, $P = 0.72$). In the comment by Förger *et al.* more than half of women with RA used CS during pregnancy; stratified analysis of their data should reveal whether our observation is valid in their group of women with RA as well.

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Currently little is known about the effect of other frequently used DMARDs for rheumatic diseases on the placenta. Cornerstones in a modern treatment approach of RA during pregnancy, such as TNF inhibitors [7], could have the potential to impact angiogenesis, positively and/or negatively, during pregnancy [8]. Future research should reveal whether these biologics or any other DMARDs have the potential to alter angiogenic markers such as PlGF and sFlt-1. In addition, further research on the effect of prednisone and RA disease activity on the developing placenta is greatly needed.

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## Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

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