







## Clinical science

# Plasma interferon-alpha protein levels during pregnancy are associated with lower birth weight in systemic lupus erythematosus

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## Abstract

**Objectives:** Adverse pregnancy outcomes are more common in women with SLE compared with healthy women, but we lack prognostic biomarkers. Plasma IFN- $\alpha$  protein levels are elevated in a subgroup of pregnant women with SLE, but whether this is associated with pregnancy outcomes is unknown. We investigated the relationship between IFN- $\alpha$ , adverse pregnancy outcomes and the presence of autoantibodies in SLE pregnancy.

**Methods:** We followed 76 women with SLE prospectively. Protein levels of IFN- $\alpha$  were quantified in plasma collected in the second and third trimester with single-molecule array. Positivity for ANA and aPL antibodies was assessed during late pregnancy with multiplexed bead assay. Clinical outcomes included the adverse pregnancy outcomes small for gestational age (SGA), preterm birth and preeclampsia.

**Results:** During SLE pregnancy, women with SGA infants compared with those without had higher levels of plasma IFN- $\alpha$  protein, and IFN- $\alpha$  positivity was associated with lower birth weight of the infant. Preterm birth was associated with autoantibodies against chromatin. IFN- $\alpha$  protein levels associated positively with autoantibodies against chromatin, Smith/RNP (SmRNP) and RNP, but negatively with aPL antibodies.

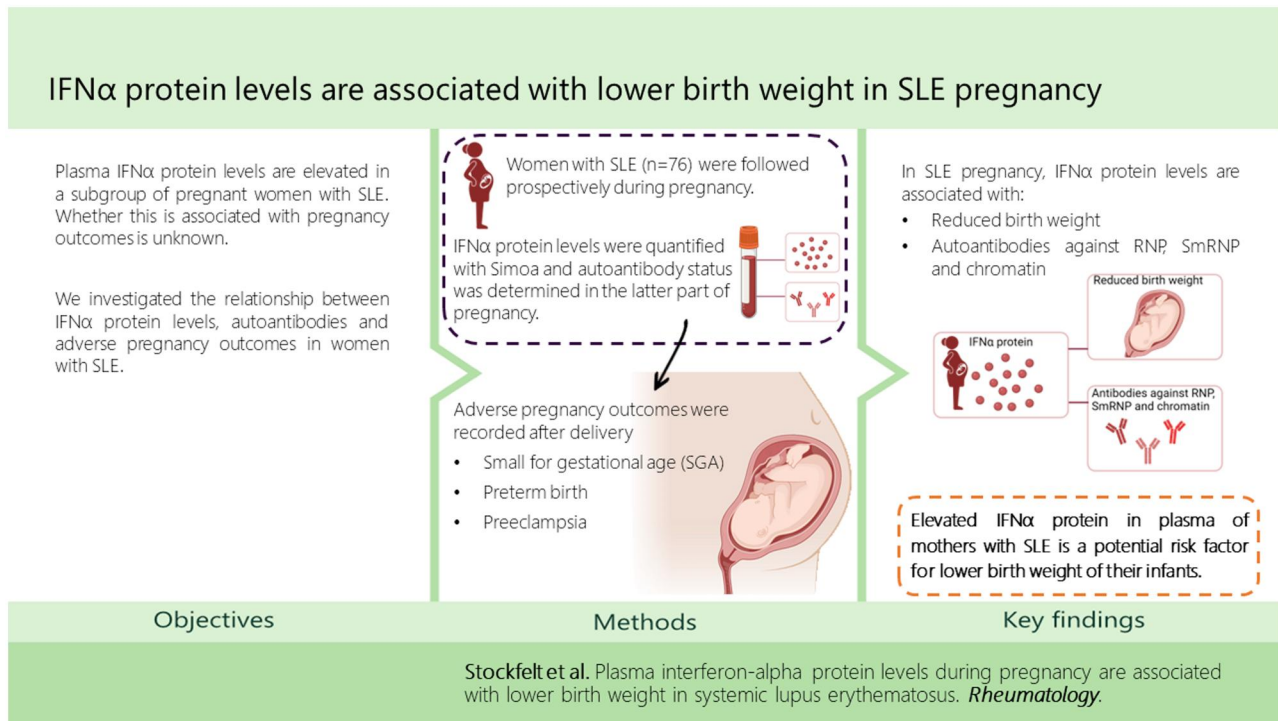
**Conclusion:** Elevated IFN- $\alpha$  protein in plasma of women with SLE is a potential risk factor for lower birth weight of their infants. The association between IFN- $\alpha$  and lower birth weight warrants further investigation regarding the pathophysiological role of IFN- $\alpha$  during SLE pregnancy.

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## Graphical abstract



**Keywords:** systemic lupus erythematosus, adverse pregnancy outcomes, IFN $\alpha$  protein, autoantibodies.

### Rheumatology key messages

- During SLE pregnancy, IFN- $\alpha$  protein levels are higher in mothers with small for gestational age infants.
- The association between IFN- $\alpha$  protein levels and adverse pregnancy outcomes is not dependent on disease activity or treatment.
- IFN- $\alpha$  associated positively with anti-chromatin, -SmRNP and -RNP, but negatively with aPL antibodies.

## Introduction

The chronic inflammatory disease SLE preferentially affects women during their fertile ages. During pregnancy, the risk of adverse pregnancy outcomes such as giving birth to a small for gestational age (SGA) infant, preterm birth and preeclampsia is elevated 2–3 times in women with SLE compared with healthy women [1]. Serological activity with elevated dsDNA and positivity for aPL are associated with adverse pregnancy outcomes [2, 3]. Apart from this, we have limited understanding of the immunological events that precede adverse pregnancy outcomes in SLE, and we lack biomarkers to predict them.

Sustained systemic activation of IFN-stimulated gene (ISG) expression is evident in a majority of SLE patients and associates with distinct clinical features [4]. The importance of this pathway is highlighted by the disease amelioration induced by the type I IFN receptor inhibitor anifrolumab [5]. The ISG signature is elevated in pregnant women with SLE compared with healthy women [6, 7] but the role of this pathway for the development of adverse pregnancy outcomes during SLE pregnancy has not been clarified.

IFN- $\alpha$  is a prominent member of the type I IFN family and a potential common denominator in several rheumatic diseases including SLE, Sjögren's disease and RA. Since IFN- $\alpha$  is produced at low levels, a method sensitive enough to evaluate attomolar levels is needed. Using digital ELISA, elevated IFN- $\alpha$  protein levels were found in SLE compared with healthy controls and were associated with disease activity [8]. We recently reported elevated IFN- $\alpha$  protein levels during pregnancy and postpartum in a subgroup of women with SLE [9], but it is unknown whether IFN- $\alpha$  protein levels are associated with adverse pregnancy outcomes in SLE. In this study, we investigated the relationship between plasma IFN- $\alpha$  protein levels, adverse pregnancy outcomes and ANA and aPL antibodies in women with SLE.

## Methods

### Study population

The study population consisted of 76 pregnant women with SLE (83 pregnancies), included at five Swedish sites:

Stockholm, Gothenburg, Malmö/Lund, Linköping and Uppsala. All women fulfilled the 1997 ACR and/or the 2012 SLICC classification criteria and only live singleton births were analysed. Exclusion criteria were inability to understand patient information, presence of other serious diseases, including active cancer and other rheumatic autoimmune diseases, and treatment with anti-CD20 or anti-B cell activating factor (BAFF) antibodies within 12 months before inclusion. All participants signed a written informed consent, and the study was conducted in compliance with the Helsinki Declaration and approved by the ethics committees in Sweden (d.nr. 404-18 and amendments 2020-05101, 2022-01158-02 and 2023-00985-02).

### Fetal and maternal outcomes

Outcomes were the development of the following adverse pregnancy outcomes: SGA, defined as a birth weight less than the 10th percentile of expected [10]; preterm delivery, before 37 weeks of gestation; and/or preeclampsia, defined as a multi-organ disease occurring after 20 weeks of gestation including hypertension and new onset of clinical symptoms or involvement of one or multiple organ systems (renal, hepatic, haematologic, neurologic, circulatory or utero-placental) and/or fetal effects. Three of the women with preeclampsia developed the condition within 1 week postpartum. Disease activity was evaluated at least once during pregnancy with SLEDAI 2000 (SLEDAI-2K) according to local clinical routine. When several measurements were available, the highest SLEDAI-2K value was used. For women with SLEDAI-2K  $\geq 4$ , we confirmed that the observed disease activity was attributed to SLE and not to pregnancy. The weight and length of the infant was recorded, and gestational age at birth was determined from a US assessment at  $\sim 12$  weeks of gestation, or, if unavailable, calculated from the last menstrual period.

### Autoantibody status

Positivity for ANA fine specificities including dsDNA, SSA 52 and 60, SSB, Smith antigen (Sm), U1 RNP, Sm/RNP and chromatin; and aPL including CL and  $\beta 2$ -glycoprotein-I ( $\beta 2$ GPI) were determined in plasma as previously described [11]. Positivity for anti-phosphatidyl-serine/prothrombin (PS/PT) was assessed with QUANTA Lite<sup>®</sup> aPS/PT (Werfen, Barcelona, Spain).

### Quantification of IFN- $\alpha$ in plasma

IFN- $\alpha$  protein concentration was measured in plasma samples diluted 1:1 in PBS and obtained in the second ( $n = 70$ ) and third trimester ( $n = 72$ ) by single molecule array (Simoa) technology on an HD-X Analyzer using the Interferon-alpha Advantage kit (cat no. 100860, Quanterix, Billerica, MA, USA). Values below the detection limit (70 fg/ml) were set at 35 fg/ml. IFN- $\alpha$  protein positivity was defined as a level  $\geq 136$  fg/ml based on 3 s.d. above mean level for healthy blood donors [8].

### Statistical analysis

Multivariate factor analysis was performed using SIMCA<sup>®</sup> software version 17 (Sartorius Stedim Biotech, Goettingen, Germany). Orthogonal partial least squares analysis (OPLS) was used to analyse adverse pregnancy outcomes (SGA, preterm birth or preeclampsia) in relation to autoantibody status and IFN- $\alpha$  protein level in women with SLE. OPLS was also used to analyse IFN- $\alpha$  protein level in relation to

autoantibody status. Default settings for the OPLS models were utilized, and data were centred and scaled to unit variance for equal weight. Model quality was based on R2 and Q2 parameters, presented in each figure. Univariate analyses were performed for variables that showed the strongest associations in the OPLS models using Mann–Whitney *U* test, Fisher's exact test or Spearman rank correlation test as described in the figure legends (GraphPad Prism software v9.02, La Jolla, CA, USA). A *P*-value of  $< 0.05$  was considered statistically significant ( $*P < 0.05$  and  $***P < 0.001$ ).

## Results

### Study population

Demographic and clinical characteristics of the pregnant women with SLE are shown in [Supplementary Table S1](#), available at *Rheumatology* online. All but one woman with SLE were ever ANA-positive, and the ANA-negative woman had a class IV LN and fulfilled the 1997 ACR classification criteria. During pregnancy, 36% were positive for anti-dsDNA antibodies. Most women with SLE were treated with HCQ/chloroquine phosphate (92%) and ASA (87%). Disease activity during pregnancy was generally low, with a median score of 2 according to SLEDAI-2K.

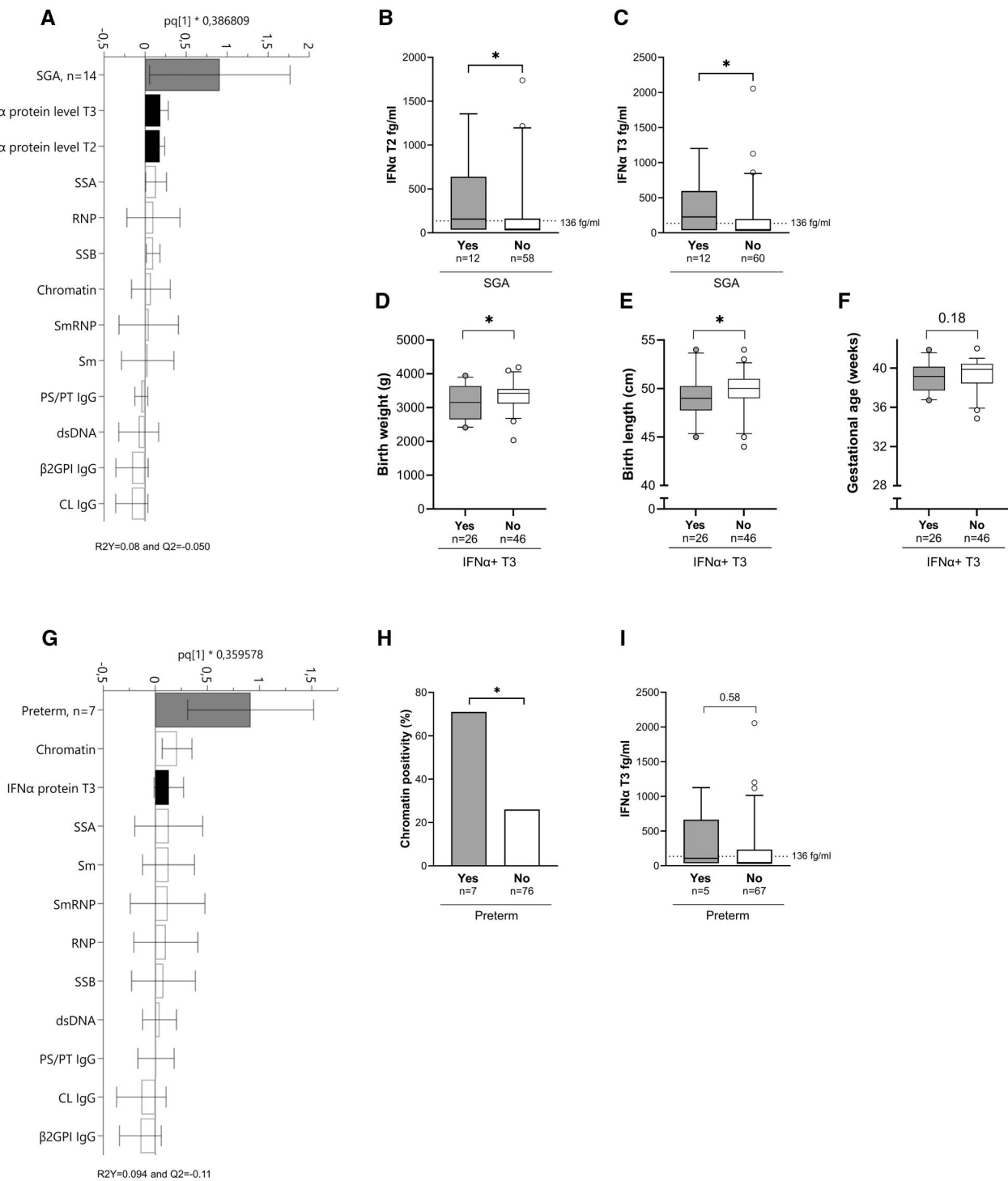
### Reduced birth weight is associated with plasma IFN- $\alpha$ protein in SLE pregnancy

In the OPLS analysis, giving birth to an SGA infant associated most strongly to plasma IFN- $\alpha$  protein levels and we also found a potential association to positivity for autoantibodies against SSA ([Fig. 1A](#)). Univariate analyses confirmed that women who gave birth to SGA infants had significantly higher IFN- $\alpha$  protein levels during pregnancy compared with women who did not in both second and third trimester ([Fig. 1B](#) and [C](#)). We proceeded to analyse IFN- $\alpha$  protein data from the third trimester, in which we had the larger numbers of samples. Here, we found lower birth weight (median difference 273 g) and shorter birth length (median difference 1 cm) in IFN- $\alpha$ -positive compared with IFN- $\alpha$ -negative women with SLE ([Fig. 1D](#) and [E](#)). However, there was no significant association between IFN- $\alpha$  positivity and gestational age at delivery ([Fig. 1F](#)). Positivity for anti-SSA antibodies tended to be more common in women with SGA infants, but there were no statistically significant differences ([Supplementary Fig. S1A](#), available at *Rheumatology* online).

There were no significant differences in the proportion of patients with HCQ/chloroquine phosphate treatment between IFN- $\alpha$ -positive and IFN- $\alpha$ -negative women with SLE (85 vs 96%,  $P = 0.18$ ). In addition, IFN- $\alpha$  protein levels did not correlate with disease activity measured by SLEDAI-2K, and IFN- $\alpha$ -positive women did not have higher SLEDAI-2K scores compared with IFN- $\alpha$ -negative women ([Supplementary Fig. S1B](#) and [C](#), available at *Rheumatology* online). To conclude, in women with SLE, IFN- $\alpha$  protein was associated with giving birth to an SGA infant and with reduced birth weight, but this association was not mediated by increased disease activity or different treatments.

### Preterm birth is related to positivity for anti-chromatin antibodies

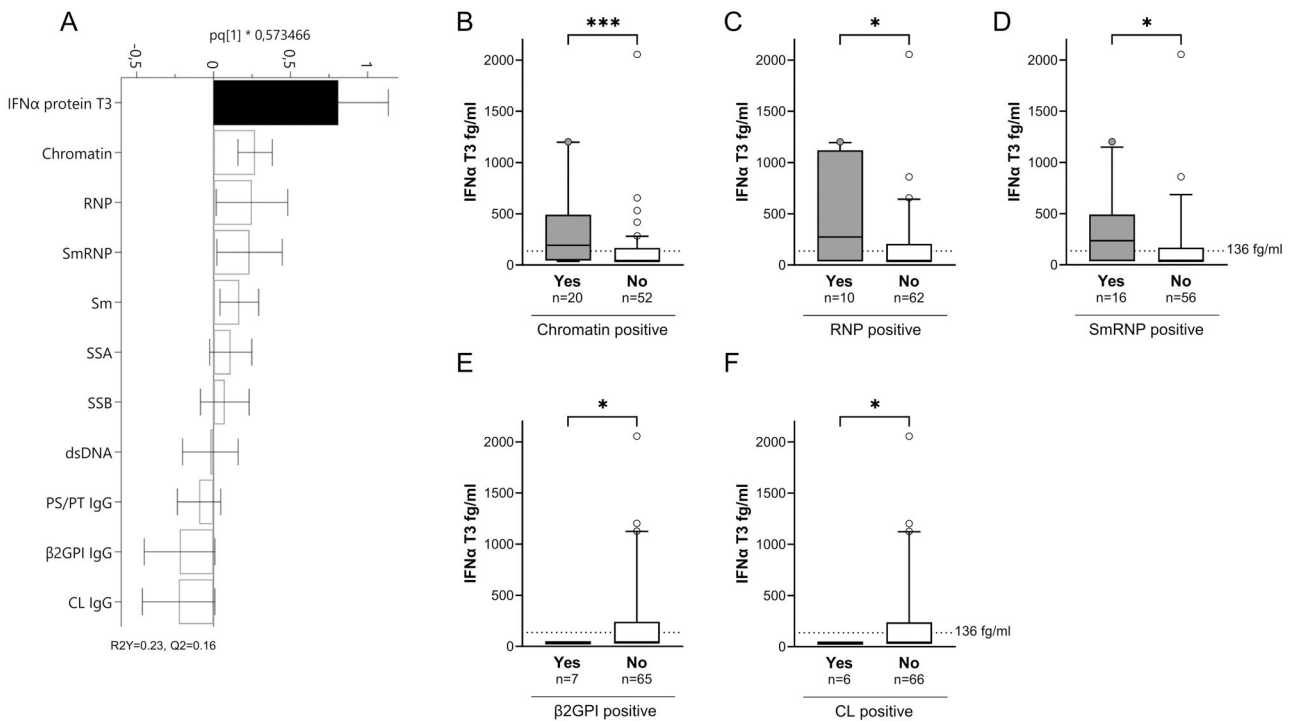
The OPLS analysis indicated an association between giving birth preterm and being positive for anti-chromatin antibodies, and univariate analysis confirmed that preterm birth was related to positivity for anti-chromatin antibodies ([Fig. 1G](#) and [H](#)).



**Figure 1.** IFN- $\alpha$  protein level during pregnancy is associated with reduced birth weight in infants born to mothers with SLE. **(A)** OPLS plot depicting SGA in relation to IFN- $\alpha$  protein level and autoantibody positivity. IFN- $\alpha$  protein level in **(B)** second and **(C)** third trimester in women with SLE who give birth to an SGA infant compared with women with SLE who do not. **(D)** Birth weight, **(E)** birth length and **(F)** gestational age in women with SLE who are IFN- $\alpha$ -positive (IFN- $\alpha$  protein  $\geq 136$  fg/ml) compared with IFN- $\alpha$ -negative in the third trimester. **(G)** OPLS plot depicting preterm birth in relation to IFN- $\alpha$  protein level and autoantibody positivity. **(H)** Positivity for chromatin and **(I)** IFN- $\alpha$  protein level in women with SLE who give birth preterm compared with not preterm. Box-and-whiskers, 5–95 percentile, Mann–Whitney  $U$  test (B–F and I), Fisher’s exact test (H). OPLS: orthogonal partial least squares analysis

Women with SLE who gave birth preterm did not differ in their IFN- $\alpha$  protein levels compared with those who did not, however there were only five preterm cases for which we had IFN- $\alpha$  protein levels (Fig. 1H). Preeclampsia was unrelated to IFN- $\alpha$  and

to positivity for ANA and aPL antibodies, although there was a non-significant tendency for higher PS/PT positivity among women with preeclampsia (Supplementary Fig. S1D and E, available at *Rheumatology* online).



**Figure 2.** IFN- $\alpha$  protein level is associated with autoantibodies against chromatin, RNP and SmRNP. **(A)** OPLS plot depicting IFN- $\alpha$  protein level in the third trimester in relation to autoantibody positivity. IFN- $\alpha$  protein level in women with SLE who are positive for autoantibodies against **(B)** chromatin, **(C)** RNP, **(D)** SmRNP, **(E)**  $\beta$ 2GPI and **(F)** CL. Box-and-whiskers, 5–95 percentile, Mann–Whitney *U* test (B–F). SmRNP: Smith/RNP; OPLS: orthogonal partial least squares analysis;  $\beta$ 2GPI:  $\beta$ 2-glycoprotein-I. OPLS: orthogonal partial least squares analysis

### IFN- $\alpha$ protein level is associated with autoantibodies against chromatin, RNP and SmRNP

Positive associations between IFN- $\alpha$  protein and autoantibodies have been demonstrated in non-pregnant individuals with SLE [12]. We therefore examined which serological factors that were associated with IFN- $\alpha$  protein in the third trimester in pregnant women with SLE. In the OPLS analysis, IFN- $\alpha$  protein level associated positively with autoantibodies against chromatin, RNP and SmRNP, but negatively with autoantibodies against  $\beta$ 2GPI and CL (Fig. 2A). This was confirmed in the univariate analyses, where IFN- $\alpha$  protein levels were higher among women with SLE who were positive for autoantibodies against chromatin, RNP and SmRNP (Fig. 2B–D), but lower in women with SLE who were positive for autoantibodies against  $\beta$ 2GPI or CL (Fig. 2E and F).

### Discussion

We found that women with SLE who gave birth to SGA infants had higher IFN- $\alpha$  protein levels during the second and third trimester compared with those without. Moreover, in SLE, IFN- $\alpha$ -positive women with SLE gave birth to infants with lower birth weight compared with IFN- $\alpha$ -negative women. IFN- $\alpha$  protein levels were unrelated to SLE disease activity captured by the SLEDAI-2K index and to treatment, as shown here and previously [9]. Whether there is a causal relationship between IFN- $\alpha$  protein levels and reduced birth weight is not answered by the present data, but we have previously demonstrated that IFN- $\alpha$  upregulates gene expression of neutrophil-recruiting chemokines in placental decidual stromal cells [13], which could lead to placental inflammation and reduced fetal growth. In addition, IFN- $\alpha$  inhibits

growth in human umbilical vein endothelial cells [14], and if placental endothelial cells are affected, that could also mechanistically contribute to the development of SGA.

Positivity for antibodies against chromatin was associated with preterm birth. Antibodies against chromatin can deposit in the kidneys as immune complexes and are related to LN [15], but these results show that their role in lupus pregnancy should be further explored. In contrast to previous studies, positivity for dsDNA was unrelated to pregnancy outcome [2]. This may be explained by the low disease activity in this cohort, since the association between dsDNA positivity and adverse pregnancy outcomes may partly be mediated by increased disease activity in dsDNA-positive patients [2].

Positivity for autoantibodies against chromatin, RNP and SmRNP was associated with IFN- $\alpha$  production. ISG expression and IFN- $\alpha$  protein levels are closely correlated [16] and anti-chromatin antibody positivity has been shown to increase the odds of being ISG-positive as well [17]. Immune complexes containing endogenous RNA may also stimulate ISG expression [18], and in a large database, anti-RNP emerged as the strongest predictor for elevated ISG expression [19]. In contrast, antibodies against  $\beta$ 2GPI and CL were negatively associated with IFN- $\alpha$  protein, and previous studies also failed to show an association between aPL and ISG expression [20]. This may reflect the different pathophysiological effects of aPL and ANA, since aPL antibodies do not bind nucleic acids and will not trigger IFN- $\alpha$  production.

The strengths of this study include its prospective design with well-characterized SLE patients. In addition, we measure IFN- $\alpha$  protein in plasma with a sensitive digital ELISA during pregnancy. A limitation is that we only examine pregnancies resulting in a live birth, so the association between

IFN- $\alpha$  and fetal loss is not evaluated. Higher IFN- $\alpha$  protein levels have been shown in patients with SLEDAI  $>4$  [8], but here, IFN- $\alpha$  protein levels were unrelated to SLEDAI-2K score. We cannot exclude that a more sensitive measure of disease activity would capture small fluctuations in disease activity that might be related to IFN- $\alpha$ .

In conclusion, women with higher IFN- $\alpha$  protein during pregnancy have higher risk of giving birth to infants who are small for their gestational age. IFN- $\alpha$  protein is also associated with autoantibodies against chromatin, SmRNP and RNP. Our findings suggest that the role of IFN- $\alpha$  for infant growth development in mothers with SLE should be investigated further.

## Supplementary material

Supplementary material is available at *Rheumatology* online.

## Data availability

Data are available upon reasonable request to the corresponding author but will not be shared publicly. For all types of access, a research proposal must be submitted for evaluation by the responsible researchers of the study sites.

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Images from BioRender were used in the preparation of the graphical abstract.

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