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ABSTRACT

Objective To examine B cell-activating factor (BAFF) and type I interferon (IFN) activity at the transcriptional and protein levels in blood and placental tissue in SLE compared with healthy pregnancies to assess their relationship and to determine whether BAFF levels are associated with pregnancy outcomes in SLE.

Methods In the SLE-Placenta study, we followed women with SLE (n=83) and healthy controls (n=67) throughout pregnancy. Blood samples were collected in all trimesters and at delivery from peripheral blood, placental intervillous blood and cord blood. Postpartum blood samples were obtained from a subset of women with SLE. Bulk messenger RNA (mRNA) sequencing was performed on peripheral blood mononuclear cells (PBMCs) and placental tissue from a subgroup of women with SLE and healthy controls. BAFF concentrations were measured by ELISA and IFNα protein levels by single-molecule array (Simoa).

Results Women with SLE had upregulated BAFF (*TNFSF13B*) and IFN-stimulated gene expression in PBMCs and placenta compared with controls. BAFF blood levels were consistently and significantly higher in SLE throughout pregnancy and inversely correlated with circulating B cell numbers. SLE pregnancies with IF-ANA or anti-dsDNA positivity displayed higher BAFF levels than antibody-negative pregnancies but BAFF showed no association with disease activity. Both BAFF and IFNα concentrations were higher in placental than peripheral blood in SLE, whereas only BAFF showed additional accumulation in cord blood. Finally, elevated BAFF levels were associated with shorter pregnancy duration in SLE but not in healthy pregnancy.

Conclusions Pregnant women with SLE exhibited persistently elevated BAFF levels, which were associated with lower B cell numbers, SLE-related autoantibody positivity and shorter pregnancy duration. Together with a disease-specific placental enrichment of IFNα, these findings support the presence of an inflammatory and potentially pathogenic IFN-BAFF signature in SLE pregnancy. Further studies are needed to determine the functional consequences of these immunological alterations on maternal-fetal health in SLE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Type I interferons (IFNs) and B cell-activating factor (BAFF) are central drivers of SLE and established therapeutic targets. Although SLE is associated with adverse pregnancy outcomes, the regulation and interaction of IFN and BAFF pathways during pregnancy remain poorly defined. In particular, longitudinal data on BAFF levels in SLE pregnancy compared with healthy pregnancies are lacking.

WHAT THIS STUDY ADDS

⇒ This study demonstrates persistently elevated BAFF levels throughout pregnancy in women with SLE, associated with lower B cell numbers, autoantibody positivity and shorter pregnancy duration. It also identifies an SLE-specific enrichment of IFNα in placental blood, together with coordinated upregulation of BAFF and interferon-stimulated genes in blood and placenta. These findings support the presence of a distinct IFN-BAFF inflammatory signature in SLE pregnancy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results highlight the involvement of BAFF and IFNα in systemic and placental inflammation and the potential role of BAFF in the regulation of pregnancy duration in SLE. Since pregnant women are traditionally excluded from clinical trials, mapping the IFN-BAFF axis could increase our understanding of the functional consequences of targeting this pathway in SLE pregnancy.

INTRODUCTION

SLE is a chronic autoimmune disease that predominantly affects women and often manifests during the reproductive years. During pregnancy, SLE often flares, and women with SLE are at increased risk of pregnancy complications, including pre-eclampsia, delivery

of small for gestational age (SGA) infants and preterm birth.[1] The specific underlying pathophysiological mechanisms of these adverse outcomes are unknown, since we lack information about immunological and biological factors that may be affected by the disease as well as by pregnancy.

The interferon (IFN) signature is a common feature in patients with SLE, characterised by the upregulation of type I IFNs, including IFNα, and their downstream IFN-stimulated genes (ISGs).[2 3] There is currently no accepted gold standard for quantifying ISG activity, and several methodological approaches and gene sets have been described in the literature (reviewed in 4). One strategy has been to identify transcriptional IFN modules, groups of ISG transcripts that consistently co-cluster across diverse inflammatory conditions, using modular analysis framework.[5] Within the second-generation modular repertoire, the M1.2 module has been characterised as a type I IFN-dominated signature.[6 7] Blocking type I IFN signalling through the IFN receptor (IFNAR) with anifrolumab is an effective treatment for many patients with SLE,[8 9] although there are only case reports of its use during pregnancy.[10] In SLE pregnancy, IFNα protein levels in peripheral blood are increased compared with healthy controls and are associated with giving birth to SGA infants,[11 12] suggesting that IFNα might exert a pathological effect on the placenta. However, it remains unknown whether IFNα protein accumulates in placental intervillous blood and is transferred to the foetal circulation.

Type I IFNs induce B cell-activating factor (BAFF) expression in various cells, including monocytes, neutrophils, T cells and airway epithelial cells, at both the gene and protein levels.[13–15] In line with this, we previously reported that placental stromal cells from healthy pregnancies respond to IFNα with BAFF production.[16] The BAFF-encoding gene itself has also been suggested to be an ISG directly regulated by IFN regulatory factors.[14] Still, in SLE pregnancy, the relationship between ISGs and BAFF expression has not been studied. In particular, it is unknown whether ISGs and BAFF show correlated gene expression patterns in placental tissue and blood cells and whether such expressions differ between women with SLE and healthy controls.

Elevated circulating BAFF levels are observed in several autoimmune diseases, including most patients with SLE.[17] In SLE pregnancy, it was recently shown that elevated BAFF levels are associated with anti-dsDNA positivity and pre-eclampsia.[18] BAFF plays a central role in B cell activation, differentiation and survival, and excessive BAFF may promote the maturation of autoreactive B cells.[19–21] Therapeutic BAFF blockade with belimumab reduces circulating B cell subsets and anti-dsDNA titres,[22] and this treatment is approved for non-pregnant patients with SLE. In addition, several observational studies report beneficial effects of belimumab during SLE pregnancy.[23–25] However, whether BAFF levels are affected by pregnancy in SLE or differ longitudinally in SLE relative to healthy pregnancies has not been investigated.

In healthy women, BAFF levels decline in pregnancy and circulating B cell numbers are reduced throughout pregnancy.[26–28] In SLE pregnancy, in contrast, we have demonstrated that circulating B cell numbers remain unchanged as compared with non-pregnant women with SLE.[29] However, it remains unknown whether BAFF levels differ between SLE and healthy pregnancies, whether pregnancy modulates BAFF levels in SLE and how BAFF relates to autoantibodies, B cell numbers and clinical features during SLE pregnancy. Here, we investigated BAFF and type I IFN activity in blood and placenta in SLE and healthy pregnancies, assessed their relationship and determined whether BAFF levels are associated with pregnancy outcomes in SLE.

MATERIALS AND METHODS

Patients and healthy controls

This study included 83 SLE and 67 healthy pregnancies from the prospective Swedish multicentre SLE-Placenta study, with comparable age and parity distributions between groups.[11 12 29] Participants with SLE met the 1997 American College of Rheumatology and/or 2012 Systemic Lupus International Collaborating Clinics classification criteria[30 31] and were recruited from rheumatology clinics in Gothenburg (Sahlgrenska University Hospital, n=27), Stockholm (Karolinska University Hospital, n=38), Uppsala (Uppsala University Hospital, n=3), Linköping (Linköping University Hospital, n=6) and Lund (Skåne University Hospital, n=9). Healthy pregnant women were recruited at one antenatal clinic in Gothenburg (Regionhälsan, Gothenburg). Pregnant women with SLE and healthy pregnant controls were enrolled between October 2018 and September 2023. Only live singleton births were included, and seven women with SLE participated in the study twice. Exclusion criteria included the inability to understand study-related patient information and consent forms, the presence of other serious diseases (eg, active malignancy or other rheumatic autoimmune diseases) or treatment with anti-BAFF or anti-Cluster of Differentiation 20 (CD20) antibodies within 12 months prior to inclusion. None were treated with anifrolumab before or during their pregnancy. Clinical and obstetric data, including disease duration, medication, gestational age at birth and pregnancy outcome, were retrieved from medical records. Assessment of disease activity followed local clinical routines and was performed at least once during pregnancy using the Systemic Lupus Disease Activity Index 2000 (SLEDAI-2K).[32] If more than one assessment was available, the highest SLEDAI-2K score was recorded. As previously shown for this cohort, SLEDAI-2K values remained stable throughout pregnancy.[29] Autoantibody status during pregnancy, that is, indirect immunofluorescence (IF) of ANA (IF-ANA), ANA fine specificities including antibodies to double stranded DNA (dsDNA), Smith (Sm), ribonucleoprotein (RNP), Sjögren's syndrome related antigen A (SSA), Sjögren's syndrome related antigen B (SSB), chromatin

and ribosomal P protein and anti-phospholipid antibodies including anti-cardiolipin (CL) and anti-beta-2-glycoprotein I (β_2GPI), was determined as previously described in detail.[29] The cut-off for IF-ANA was 1:200. TruCount was used to assess the total number of B cells as previously described in detail.[11 29] All participants gave their written informed consent. For cord blood, both parents gave their informed consent. The ethics board in Gothenburg (Dnr 404–18) and the Swedish Ethical Review Authority (amendments Dnr 2020–05101, Dnr 2022–01158-02 and Dnr 2023–00985-02) approved the study, and the study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Adverse pregnancy outcomes

Adverse pregnancy outcomes included SGA, preterm birth and pre-eclampsia. SGA was defined as birth weight below the 10th percentile of expected according to Marsál *et al* and/or Gardosi *et al*,[33 34] and preterm birth as delivery before 37 weeks of gestation. Pre-eclampsia was defined as a multiorgan disease occurring after 20 weeks of gestation, characterised by hypertension and new-onset clinical symptoms or involvement of one or more organ systems (renal, hepatic, neurologic, haematologic, circulatory or utero-placental).[35] Only five women with SLE had gestational hypertension defined as a systolic blood pressure ≥140 mm Hg and a diastolic blood pressure ≥90 mm Hg in the absence of pre-eclampsia. The outcome groups, including SGA, preterm birth and pre-eclampsia, and their demographical features in this cohort were previously described by Torell *et al*.[36] Overlapping outcomes were observed in four women with SLE: one with both SGA and pre-eclampsia, two with SGA and preterm birth and one with pre-eclampsia and preterm birth. In outcome-dependent analyses, data from these individuals were included in both relevant outcome groups.

Sample collection

Peripheral blood samples were collected in heparinised tubes from pregnant women with SLE and healthy pregnant women in the first (SLE n=45, controls n=50), second (SLE n=71, controls n=49) and third trimesters (SLE n=74, controls n=61), as well as at delivery (SLE n=26, controls n=20). From placentas collected following delivery, maternal-derived intervillous blood was obtained by manual compression (SLE n=26, controls n=20), and tissue samples were dissected from the maternal-derived decidua basalis (SLE n=16, controls n=8). Additionally, blood samples were obtained from the umbilical cord at delivery (SLE n=19, controls n=18). For a subset of women with SLE, late postpartum samples were collected at least 6 months after delivery to serve as non-pregnant controls (n=19). Density gradient centrifugation of whole blood was performed to isolate plasma and peripheral blood mononuclear cells (PBMC). Plasma was stored at −80°C, and PBMC samples were frozen at −150°C in fetal bovine serum (FBS, #11550356, Fisher Scientific) with 7.5% dimethyl sulfoxide (#D2650, Sigma Aldrich). Decidual tissue samples were stored at −80°C in RNAlater (#AM7020, Fisher Scientific) until further analysis. The number of collected plasma samples is summarised in online supplemental table 1.

RNA extraction of PBMC and placental tissue

RNA extraction was performed on PBMC samples and maternal-derived decidua basalis tissue from a subset of pregnant women with SLE (n=16) and healthy controls (n=6) (figure 1A). Samples were selected based on the availability of decidual tissue, and eight of the women with SLE gave birth to SGA infants. PBMC samples were primarily collected in the second trimester, with third-trimester samples included when the second-trimester sample was unavailable (online supplemental table 1). In brief, frozen PBMC samples were thawed in a water bath (37°C) until only a small portion of ice remained. Heated Gibco Dulbecco's modified Eagle medium GlutaMAX (#11584516, Fisher Scientific) supplemented with 10% FBS and 0.1% gentamicin (#15750037, Thermo Fisher) (37°C) was slowly added, and the PBMCs were pelleted by centrifugation (400 g, 5 min). Decidual tissue was thawed at 4°C overnight. RNA extraction of PBMCs and decidual tissue was performed using the RNeasy MiniKit (#74104, Qiagen) on the same day, according to the manufacturer's instructions. Decidual tissue samples were homogenised with Lysing Matrix A (#116910050, Nordic Biolabs) using a FastPrep-24 5G instrument (MP Biomedicals). RNA quality was assessed using a NanoDrop One spectrophotometer (Thermo Fisher), yielding A260/280 ratios ranging from 1.97 to 2.12. Extracted RNA was stored at −80°C until sequencing.

Bulk RNA-sequencing of PBMCs and decidual tissue

The quantity and quality of isolated RNA were assessed using an Agilent 4200 TapeStation Automated Electrophoresis System (Agilent Technologies). All samples had an RNA integrity number greater than 5.1. Sequencing libraries were prepared with the Illumina Stranded mRNA Prep Kit (Illumina, USA) according to the manufacturer's instructions. Library construction was performed following the Illumina Stranded messenger RNA (mRNA) Prep Guide 1000000124518 v02 (Illumina, San Diego, California, USA), using 500 ng of total RNA as input. Sequencing was performed on the NovaSeq 6000 platform to generate 150 bp paired-end reads at Clinical Genomics (Gothenburg, Sweden).

RNA sequencing data analysis

Raw gene counts from RNA sequencing were aligned to and annotated with the reference genome *NCBI Homo sapiens* Annotation Release 109 (GRCh38.p12).[37] Preprocessing was performed using the edgeR and limma/voom R packages (R in RStudio, R Foundation for Statistical Computing, Vienna, Austria). In brief, genes with more than 10 counts in at least six samples were kept for further analysis. To account for highly expressed genes during normalisation and to ensure comparability

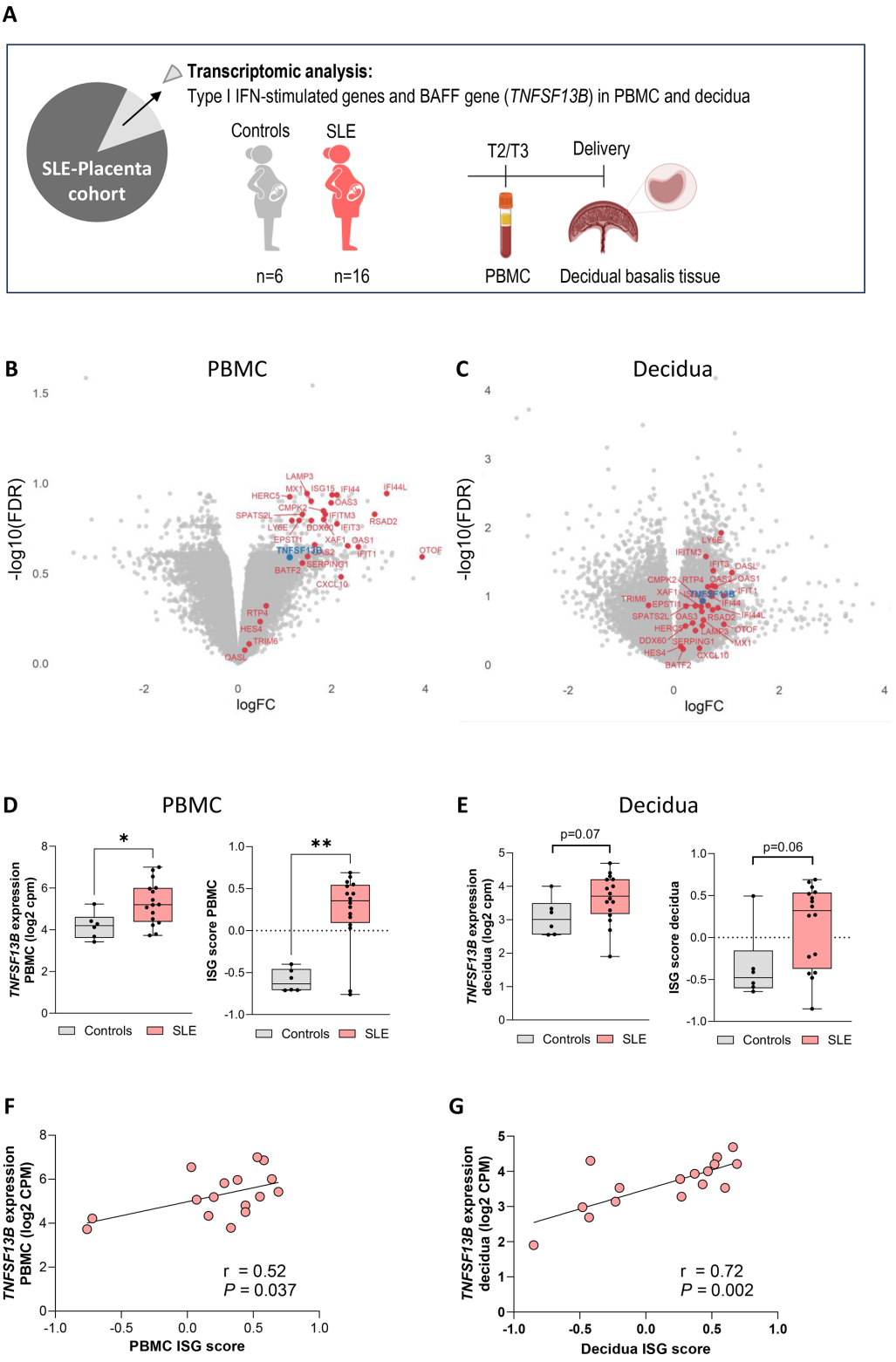

Figure 1 Upregulation of the interferon signature and the BAFF gene *TNFSF13B* in blood and placenta in pregnant women with SLE compared with controls. (A) Illustration of the subgroup of pregnant women with SLE (SLE) and healthy pregnant women (controls) who were selected from the full SLE-placenta study for mRNA sequencing. Eight of the women with SLE delivered SGA infants. Volcano plot depicting up and downregulated genes in SLE compared to controls in (B) PBMC and (C) decidua, with ISG genes within the M1.2 module (red dots) and *TNFSF13B* (blue dot) highlighted. Comparison of gene expression of *TNFSF13B* and ISG score in (D) PBMC and (E) decidua between SLE and controls. Correlation analysis of *TNFSF13B* expression and ISG score in (F) PBMC and (G) decidua in SLE. Differentially expressed genes were defined as genes with an FDR ≤0.05. *p<0.05, **p<0.01. (D–E) Mann-Whitney U test and (F–G) Spearman rank correlation test. BAFF, B cell-activating factor; FDR, false discovery rate; IFN, interferon; ISG, IFN-stimulated gene; mRNA, messenger (RNA); PBMC, peripheral blood mononuclear cell.

of gene expression across samples, raw counts were first normalised using the trimmed mean of M-values method and subsequently $\log_2$-transformed for downstream analyses. Differential expression analysis comparing SLE to controls was performed using empirical Bayes moderated *t*-statistics, with p values corrected for multiple testing using the Benjamini-Hochberg false discovery rate (FDR). Genes with an FDR ≤0.05 were considered differentially expressed. IFN activity was assessed by calculating a gene signature score based on 27 ISGs from gene module M1.2 of the second-generation blood transcriptional modules (online supplemental table 2), obtained from a previous study.[6] Genes in M1.2 were selected to primarily reflect type I IFN activity.[7] Gene set variation analysis (GSVA) was used to calculate ISG scores using the GSVA R package. GSVA computes sample-specific enrichment scores using a non-parametric, rank-based approach that considers the relative expression of genes within and outside the gene set. To confirm the robustness and method-independence of ISG scores, alternative scoring approaches were compared with GSVA, including *z*-score, single-sample gene set enrichment analysis and single-sample scoring (singscore) using the hacksig R package (online supplemental figure S1).

Quantification of IFNα and BAFF

Concentrations of IFNα protein in plasma from peripheral blood at delivery, placental intervillous blood (IVB) and cord blood were quantified in both women with SLE and healthy controls using single molecule array (Simoa) digital ELISA (Quanterix, Billerica, Massachusetts, USA), as previously described.[29] Values below the minimum limit of quantification (70 fg/mL) were set to 35 fg/mL, and concentrations ≥136 fg/mL were considered IFNα-positive.[38] In this cohort, we have previously reported higher levels of IFNα protein among women with SLE compared with controls during pregnancy and in the non-pregnant state.[11] In addition, we have previously published data on IFNα protein levels in IVB and peripheral blood in a smaller subgroup (SLE n=10, controls n=7).[39] Now, we add data for additional samples (SLE n=16, controls n=13) to a total of 26 SLE and 20 control samples. Concentrations of BAFF in plasma were quantified in peripheral blood from SLE (n=83) and control (n=68) pregnancies, at all timepoints and in all available plasma samples within the full SLE-Placenta cohort (online supplemental table 1) using the Human BAFF/BlyS/TNFSF13B DuoSet ELISA (#DY124-05, R&D Systems) according to the manufacturer's protocol.

Statistical analysis

Univariate statistical tests, including the Kruskal-Wallis test followed by Dunn's multiple comparison test, the Mann-Whitney U test, Wilcoxon matched-pairs signed rank test and the Spearman rank correlation test (GraphPad Prism software, La Jolla, California, USA), were performed to assess ISG scores, expression of *TNFSF13B* (here referred to as the BAFF gene) and protein concentrations, as described in the respective figure legends. The strength of the correlations was classified according to Spearman's rank correlation coefficient (r): r=0.20–0.39, weak; r=0.40–0.59, moderate; r=0.60–0.79, strong; r≥0.80, very strong correlation. P values <0.05 were considered statistically significant.

Multivariate data analysis was performed using the SIMCA-P software (Sartorius Stedem Biotech, Göttingen, Germany). Orthogonal partial least squares (OPLS) analysis was performed to investigate BAFF concentration at different trimesters (Y-variables) in relation to the presence of ANA and including antibodies to dsDNA, Sm, SmRNP, RNP, SSA, SSB, chromatin, β_2GPI and CL (X-variables) in pregnant women with SLE. In the OPLS models, default settings were used; data were centred and scaled to unit-variance to give all variables equal weight. Model quality was based on R2 and Q2 parameters that are presented in each figure.

RESULTS

Upregulated BAFF and ISG expression in PBMCs and decidua from SLE pregnancies

To investigate the expression of the BAFF gene and ISGs (online supplemental table 2), RNA sequencing was performed on PBMCs and decidual tissue in a subgroup of pregnant women with SLE and healthy controls (figure 1A and online supplemental table 3). The BAFF gene and all but one ISG (*TRIM6* in decidua) showed higher expression in SLE than in controls in both PBMCs and decidua (figure 1B,C) and were among the most upregulated genes, particularly within the PBMC fraction. When all genes from the differential expression analysis in the PBMC fraction were ranked by p value, 16 of the 27 ISGs were positioned among the top 100 genes (online supplemental table 2). The BAFF gene ranked 1197 in PBMC and 2335 in decidua. The type I IFNARs, IFNAR1 and IFNAR2, were expressed in both PBMCs and decidua, whereas the IFNα-encoding gene *IFNA1* was filtered out due to low read counts. Univariate analysis revealed increased expression of both the BAFF gene and the ISG score in SLE relative to controls in the PBMC fraction, with a similar trend observed in decidua (figure 1D,E). Moreover, there was a moderate to strong correlation between the BAFF gene expression and ISG score in PBMCs and decidual tissue from women with SLE (figure 1F,G). Neither the BAFF gene expression nor the ISG score in PBMCs or decidua was associated with SGA outcome (online supplemental figure S2A–D). Taken together, SLE pregnancies display elevated BAFF gene expression and enhanced IFN signature in both PBMC and decidua, and these measures correlate with each other.

BAFF levels inversely correlate with B cell numbers in SLE pregnancy

We next measured BAFF protein levels in plasma at all time points in the full SLE-Placenta cohort (figure 2A

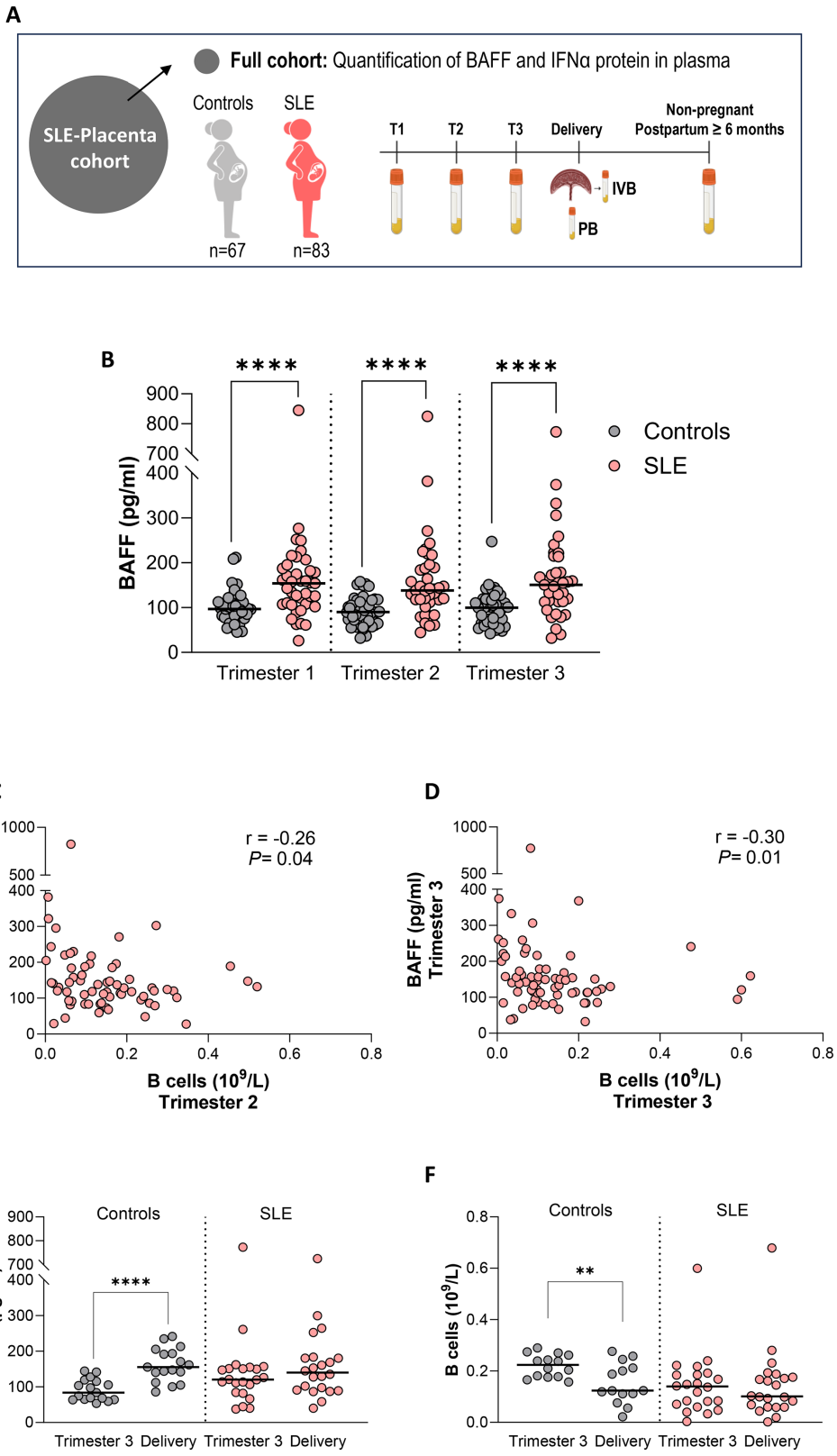

Figure 2 Comparison of BAFF protein levels in blood from SLE and healthy pregnancies. (A) Illustration of the full SLE-Placenta cohort consisting of healthy pregnant women (control group) and pregnant women with SLE (SLE group). (B) BAFF protein levels in the first, second and third trimester in SLE patients (n=39) compared with controls (n=43) from whom samples were available for all three trimesters. Correlation analysis of BAFF and B cell numbers in the (C) second and (D) third trimester in women with SLE. Comparison of (E) BAFF levels and (F) B cell counts in peripheral blood between paired third trimester and delivery blood samples in women with SLE and controls. **p<0.01, ****p<0.0001. (B and E) Mann-Whitney U test, (C–D) Spearman rank correlation test and (F) Wilcoxon matched-pairs signed rank test. BAFF, B cell-activating factor; IFN, interferon; IVB, intervillous blood; PB, peripheral blood.

and online supplemental table 4). BAFF concentrations were consistently elevated in women with SLE compared with controls across all trimesters when restricting the analysis to patients and controls with samples available from all three trimesters (figure 2B). BAFF levels remained stable throughout pregnancy in both groups, and in SLE, BAFF levels were similar to those in the non-pregnant state (median; first trimester 156 pg/mL vs non-pregnant 147 pg/mL). Similar results were observed when including all available samples in the full cohort (online supplemental figure S3A). We next examined whether BAFF levels and circulating B cell numbers were related during pregnancy. In SLE, BAFF levels showed a weak inverse correlation with B cell counts in both the second and third trimesters (figure 2C,D) but not in the first (r=−0.08, p=0.62). In controls, BAFF levels and B cell counts did not correlate (online supplemental figure S3B,C).

At delivery, however, peripheral BAFF levels increased significantly compared with paired third trimester samples among controls but not in women with SLE, resulting in similar levels between the groups at term (figure 2E). In parallel, B cell numbers in peripheral blood were significantly lower at delivery compared with paired samples in the third trimester among controls, whereas B cell counts were unchanged in SLE (figure 2F). Thus, during pregnancy, women with SLE display consistently elevated BAFF levels that inversely correlate with circulating B cell numbers. In healthy women, B cells declined at delivery alongside increased BAFF levels, a change that did not occur in SLE pregnancies.

Placental blood enrichment of BAFF and IFNα in SLE

From samples obtained at delivery, we analysed BAFF and IFNα protein levels in placental maternal-derived IVB and cord blood. BAFF was enriched in IVB compared with peripheral blood in both SLE and control pregnancies (figure 3A), but BAFF concentrations did not differ between the groups in either compartment. To further assess maternal-fetal dynamics, we compared BAFF levels between IVB and cord blood. In SLE, BAFF concentrations were approximately twofold higher in cord blood compared with IVB, whereas a similar but not significant trend was observed among controls (figure 3A). However, BAFF concentrations in IVB did not correlate with those in cord blood in either group (SLE, r=−0.35, p=0.14; Controls, r=0.21, p=0.41).

We previously showed that IFNα protein levels are elevated in SLE compared with control pregnancies, but unaffected by and stable throughout SLE pregnancy,[29] and in a small subgroup of the SLE-Placenta cohort, we have reported an indication of higher IFNα levels in IVB.[39] Here, IFNα concentrations were additionally measured in cord blood, peripheral blood at delivery and IVB in the full cohort. In SLE, IFNα levels were higher in IVB compared with peripheral blood, and IFNα levels in IVB were also higher in SLE compared with controls (figure 3B). Unlike BAFF, IFNα was nearly undetectable

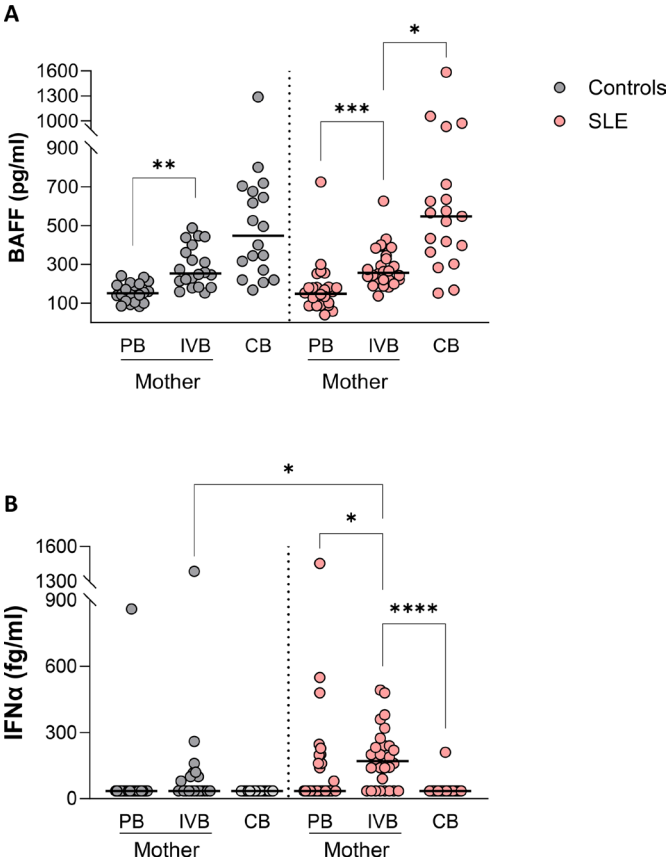

Figure 3 Placental enrichment of BAFF and IFNα in women with SLE. Protein levels of (A) BAFF and (B) IFNα in PB, IVB and CB at delivery in SLE and controls. *p<0.05, **p<0.01 ***p<0.001, ****p<0.0001. Kruskal-Wallis followed by Dunn's multiple comparison test. BAFF, B cell-activating factor; CB, cord blood; IFN, interferon; IVB, intervillous blood; PB, peripheral blood.

in cord blood, with only a single SLE sample showing a modest elevation (figure 3B). We found no relation between BAFF and IFNα levels in neither peripheral, placental or cord blood, except for a weak correlation in the first trimester (r=0.33, p=0.03). In conclusion, both BAFF and IFNα are enriched in placental blood in SLE, but only BAFF shows additional accumulation in cord blood. The lack of correlation between protein levels in placental and cord blood suggests limited placental transfer of either protein.

Higher BAFF levels in IF-ANA and anti-dsDNA-positive women during SLE pregnancy

The anti-BAFF treatment belimumab is known to reduce anti-dsDNA titres in SLE.[22] Therefore, we investigated whether BAFF levels were related to anti-dsDNA and other autoantibodies in SLE pregnancy using a multivariate OPLS analysis. Results were similar in the second and third trimesters and indicated a positive association between BAFF concentrations and anti-dsDNA (by either multiplex or chritidiae), anti-chromatin and IF-ANA positivity, and an inverse association with anti-SSA and anti-SSB positivity (figure 4A,B). Univariate analysis

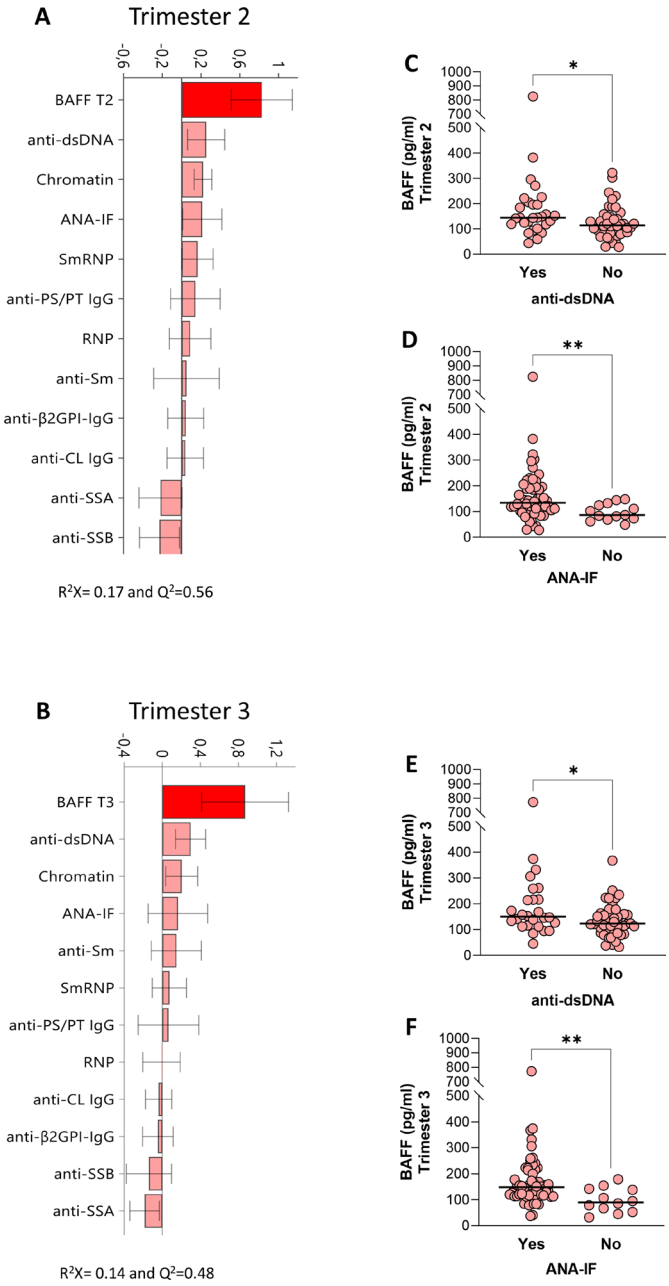

Figure 4 Elevated BAFF in pregnant women with SLE positive to ANA and anti-dsDNA. OPLS loading column plots depicting cross-sectionally measured autoantibodies positively or negatively associated with BAFF levels in the (A) second and (B) third trimester. BAFF concentrations in anti-dsDNA positive compared to anti-dsDNA negative women with SLE in the (C) second and (E) third trimester. BAFF concentrations in ANA-positive compared to ANA-negative women with SLE in the (D) second and (F) third trimester. *p<0.05, **p<0.01. Mann-Whitney U test. β2GPI, beta-2-glycoprotein I; BAFF, B cell-activating factor; CL, cardiolipin; dsDNA, double-stranded DNA; IF, immunofluorescence; Ig, immunoglobulin; OPLS, Orthogonal partial least squares; PS/PT, phosphatidylserine/prothrombin; SmRNP, Smith/ribonucleoprotein; SSA, Sjögren's syndrome related antigen A; SSB, Sjögren's syndrome related antigen B.

confirmed higher BAFF levels in anti-dsDNA-positive women in the second and third trimesters (figure 4C,E) but not in the first (median; positive=160 pg/mL vs negative=154 pg/mL, p=0.76). Moreover, BAFF levels were elevated in IF-ANA positive women (figure 4D,F), but again not in the first trimester (IF-ANA positivity median; positive=160 pg/mL vs negative=124 pg/mL, p=0.13). BAFF levels were unrelated to antibodies against chromatin, SSA, SSB and to the number of ANA specificities. In summary, SLE pregnancies with IF-ANA or anti-dsDNA positivity display higher BAFF levels compared with those lacking these antibodies.

Increased BAFF levels are associated with shorter pregnancy duration only in SLE

In healthy pregnancy, cord blood BAFF levels correlate positively with gestational age at birth.[28] In SLE pregnancy, we instead found a weak but consistent negative correlation between BAFF levels in all trimesters and gestational age, and a non-significant negative trend between cord blood BAFF levels and gestational age (figure 5A–D). In controls, BAFF levels during pregnancy were unrelated to gestational age, although cord blood BAFF showed a non-significant positive trend (figure 5E–H). Moreover, BAFF levels were not associated with disease activity as assessed by SLEDAI-2K with overlapping levels observed between patients with SLEDAI-2K <4 and ≥ 4 (online supplemental figure S4A–C). BAFF levels were also unrelated to adverse pregnancy outcomes, including SGA, pre-eclampsia and preterm birth (online supplemental figure S4D–F). Women receiving prednisone treatment had slightly higher BAFF levels in the third trimester compared with those without, but no other treatment was related to BAFF (online supplemental figure S5A–C). Hydroxychloroquine and acetylsalicylic acid were not analysed, as most women with SLE received these treatments. Taken together, elevated BAFF levels are associated with shorter pregnancy duration in SLE.

DISCUSSION

The interconnected type I IFN, BAFF and B cell pathways are central to the immunopathogenesis of SLE. Indeed, the only approved biological therapies for SLE target these pathways.[40] Although a limited number of observational studies have contributed to more generous recommendations, especially regarding belimumab,[41] the use of these therapies during pregnancy is still restricted.[42] Pregnancy affects the immune system, and the lack of mechanistic studies prevents a firm understanding of their roles in SLE pregnancy. Moreover, pregnant women are traditionally excluded from clinical trials. In SLE, the interplay between type I IFN and BAFF pathways during pregnancy remains incompletely understood, and longitudinal data on BAFF protein levels relative to healthy pregnant controls are lacking. Against this background, we investigated the dynamics of BAFF and type I IFNs in blood and placenta among women with SLE and healthy controls.

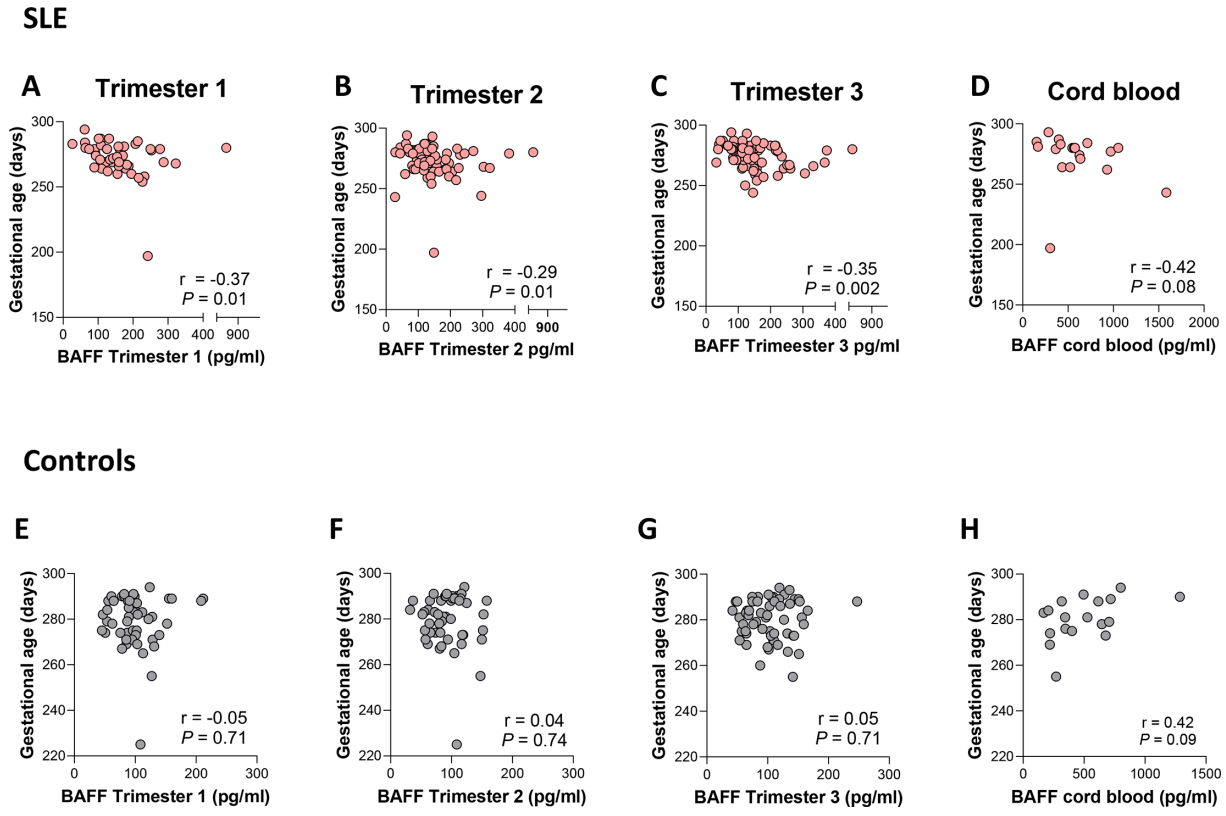

Figure 5 Circulating BAFF is associated with pregnancy duration in women with SLE. Correlation analysis of gestational age at delivery and BAFF protein levels in the (A) first, (B) second and (C) third trimesters and in (D) cord blood in the SLE group. BAFF protein levels in the (E) first, (F) second and (G) third trimesters and in (H) cord blood in the control group. Spearman rank correlation test. BAFF, B cell-activating factor.

Here, we demonstrate for the first time that women with SLE have higher BAFF protein levels compared with healthy pregnant women across all trimesters. BAFF concentrations in SLE remained stable throughout pregnancy and were similar to those found in the non-pregnant women with SLE. This contrasts with a healthy pregnancy, where BAFF levels increase compared with those of non-pregnant women.[43] Our findings suggest that the physiological pregnancy-associated modulation of BAFF levels does not occur in SLE. Instead, we observe sustained BAFF production that is unaltered by the immunological adaptations of pregnancy.

BAFF plays a central role in B cell maturation and survival. During a healthy pregnancy, B cells are proposed to contribute to maternal-fetal tolerance, including the production of protective antibodies against paternal antigens,[44 45] a process supported by physiological BAFF levels. The persistently elevated BAFF levels that we observe in SLE pregnancy may promote the maturation and survival of autoreactive B cells and autoantibody-secreting plasma cells.[19 20] This reasoning is supported by studies in non-pregnant and pregnant SLE patients, where excessive BAFF production associates with anti-dsDNA.[18 46 47] Our data suggest similar patterns, with higher BAFF levels in anti-dsDNA-positive compared with anti-dsDNA-negative women.

Given the central role of BAFF in B cell biology, we examined how BAFF levels relate to circulating B cell numbers during pregnancy. We found a weak inverse correlation between BAFF levels and B cell counts during the second half of pregnancy, an association observed only in SLE. A similar inverse relationship is found in individuals with primary antibody deficiencies.[48] The presence of an inverse relationship in SLE, but not in healthy pregnancy, could be explained by differences in BAFF availability. In SLE, a higher BAFF to B cell ratio means that changes in BAFF receptor-expressing B cells influence how much BAFF is bound. During a healthy pregnancy, BAFF levels are physiologically lower and mostly bound to B cells, meaning that fluctuations in B cell numbers have little impact on soluble BAFF. However, as B cell numbers decline towards the end of a healthy pregnancy, this is accompanied by increased BAFF concentrations.

We also had the opportunity to examine BAFF dynamics at delivery in maternal peripheral blood, placental IVB and cord blood. In both SLE and healthy pregnancies, BAFF concentrations were enriched in the placenta compared with paired maternal peripheral samples. BAFF levels were even higher in cord blood, again in both groups, consistent with previous reports showing higher BAFF concentrations in cord blood than in maternal third-trimester samples.[28] Despite the stepwise increase from peripheral to placental to cord blood, BAFF

concentrations in placental blood did not correlate with those in cord blood, suggesting that BAFF is not transferred across the maternal-fetal interface. Thus, despite the increased BAFF levels during SLE pregnancy, BAFF concentrations at delivery were similar between SLE and healthy pregnancies, indicating that the SLE-associated BAFF elevation does not persist at term.

We previously reported that pregnant women with SLE have consistently higher circulating IFNα protein levels than healthy controls throughout pregnancy,[11] which is associated with giving birth to an SGA infant.[12] We now demonstrate that IFNα concentrations are also locally increased in placental blood in SLE. These findings are in line with our earlier observations from a smaller number of patients and controls[39] and support a placenta-specific accumulation of IFNα in SLE. In contrast to BAFF, however, IFNα was almost undetectable in cord blood and showed no evidence of maternal-foetal transfer. This suggests that the fetus is isolated from the maternal elevated type I IFN levels. Whether locally increased IFNα contributes to impaired placental development or to adverse pregnancy outcomes warrants further investigation.

At the transcriptional level, we observed a pattern similar to that seen for IFNα protein. Here, we show for the first time that women with SLE have increased ISG expression not only in PBMCs but also in the placental decidua, consistent with reports of a stronger peripheral IFN signature in SLE pregnancy.[49–51] We previously identified an association between increased IFNα protein levels and SGA in SLE.[12] However, when examining ISG scores in PBMCs or decidua in relation to SGA in SLE, we found no such association. Although this may be due to the lower sample size, it may also suggest a more specific link between IFNα and fetal growth, since ISGs are also affected by IFNs other than IFNα. Given the close connection between type I IFN and BAFF, we also examined the expression of the BAFF gene. To our knowledge, this is the first study to demonstrate elevated BAFF gene expression in PBMCs during SLE pregnancy, with a similar trend in placenta. BAFF gene expression correlated strongly with ISG scores in placenta and moderately in PBMCs, supporting coordinated activation of the IFN-BAFF axis in both maternal blood and placenta. These findings align with evidence that placental stromal cells respond to IFNα with BAFF production[16] and that type I IFNs directly induce BAFF transcription.[14] Together, these data indicate a heightened IFN-BAFF-driven inflammatory milieu systemically and locally in SLE pregnancy.

Regarding BAFF and pregnancy outcome, a recent American study reported an association between elevated first-trimester BAFF levels and pre-eclampsia in women with SLE,[18] a relation not observed in our cohort. This discrepancy may be explained by differences in demographic characteristics between the cohorts, as well as other cohort-specific factors, including an almost threefold higher proportion of pre-eclampsia compared with our cohort, with a majority of pre-eclampsia cases occurring preterm. Instead, in our study, higher maternal BAFF concentrations were associated with shorter gestational age. A similar trend was observed in cord blood. These patterns contrast with those of a healthy pregnancy, in which we found no such association except for a weak positive trend between cord blood BAFF and gestational age, consistent with previous findings.[28] Further studies are needed to establish causality and to clarify the mechanisms linking BAFF to shortened pregnancy duration in SLE.

A major strength of this study is the well-characterised patients and healthy controls from whom paired maternal, placental, and foetal blood samples were prospectively collected during pregnancy and in the non-pregnant state. Additional strengths include the integration of both transcriptional and protein analyses, together with detailed clinical and immunological data. A limitation is that the study was affected by missing data, mainly due to unavailable blood samples in the first trimester and at delivery among women with SLE. The cohort primarily reflects a well-controlled pregnant SLE population with low disease activity. This may have contributed to the relatively low number of adverse pregnancy outcomes, which limits the power to detect associations between placental IFNα and BAFF protein concentration and specific pregnancy outcomes.

In conclusion, pregnant women with SLE exhibit persistently elevated BAFF protein levels throughout pregnancy, which are associated with lower circulating B cell numbers and shorter pregnancy duration. SLE pregnancy is also characterised by locally increased placental IFNα. Together, these findings indicate that both BAFF and type I IFN contribute to a heightened inflammatory environment in maternal blood and placenta during SLE pregnancy, with potential implications for pregnancy outcomes.

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Competing interests CS has been an employee of Bristol Myers Squibb since April 2024. AR is a member of the advisory board for Astra Zeneca regarding SLE treatment. LR reports a relationship with Astra Zeneca, Biogen, Bayer, BMS and UCB which includes: consulting or advisory, funding grants and speaking and lecture fees. HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche and WebMD, is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, and is a shareholder of CERimmune Therapeutics (outside submitted work).

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the regional ethics committee of Gothenburg. Participants gave informed consent to participate in the study before taking part.

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