Title

Placental lesions in systemic lupus erythematosus pregnancies associated with small for gestational age infants.

Journal

Rheumatology, 63(11)

Authors

Dhital, Rashmi

Jacobs, Marni

Smith, Chelsey

et al.

Publication Date

2024-11-01

DOI

10.1093/rheumatology/keae454

Peer reviewed

Rheumatology, 2024, **63**, 3006–3014
https://doi.org/10.1093/rheumatology/keae454
Advance access publication 28 August 2024
Original Article

British Society for Rheumatology RHEUMATOLOGY OXFORD

Clinical science

Placental lesions in systemic lupus erythematosus pregnancies associated with small for gestational age infants

Rashmi Dhital [1,2,*], Marni Jacobs[3], Chelsey J. F. Smith[2], Mana M. Parast[4,5]

[1]Department of Medicine, Division of Rheumatology & Immunology, Vanderbilt University Medical Center, Nashville, TN, USA
[2]Department of Medicine, Division of Rheumatology, Autoimmunity and Inflammation, School of Medicine, University of California San Diego, La Jolla, CA, USA
[3]Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California San Diego School of Medicine, UC San Diego Health, La Jolla, CA, USA
[4]Department of Pathology, University of California San Diego, La Jolla, CA, USA
[5]Sanford Consortium for Regenerative Medicine, La Jolla, CA, USA

*Correspondence to: Rashmi Dhital, Division of Rheumatology & Immunology, Vanderbilt University Medical Center, 1161 21st Avenue South, T-3107 MCN, Nashville, TN 37232, USA. E-mail: rashmidhital.md@outlook.com

Abstract

Objectives: Up to a quarter of pregnant individuals with SLE have small for gestational age (SGA) infants. We aimed to characterize placental pathology associated with SGA infants in SLE.

Methods: We retrospectively analysed SLE deliveries with placental analysis at UCSD from November 2018 to October 2023, comparing SLE pregnancies resulting in SGA to those that did not, and additionally, to matched pregnancies with SGA but without SLE.

Results: Placental analysis was available only for 28/70 (40%) SLE deliveries, which had high rates of adverse outcomes (75%). All exhibited at least one histopathologic abnormality. Key findings distinguishing 12 SLE placentas resulting in SGA infants (*vs.*16 without) included small placental disc for gestational age (100% *vs* 56%, $P=0.01$), placental disc infarct (50% *vs* 6%, $P=0.02$) and increased perivillous fibrin deposition (PVFD, 58% *vs* 0%, $P=0.001$). All seven SLE placentas with increased PVFD resulted in SGA infants. Compared with matched non-SLE pregnancies with SGA ($n=36$), the only distinguishing placental lesion was a higher prevalence of increased PVFD in SLE-associated SGA (58% *vs* 22%, $P=0.03$).

Conclusion: The higher prevalence of increased PVFD in placentas of SLE-associated SGA may indicate a specific mechanism of placental injury leading to SGA in this context. Thus, its presence, particularly in context of SGA, should prompt providers to screen for an underlying autoimmune disease, including SLE. Systematic placental examination in context of SLE and associated autoimmune diseases could help evaluate responses to existing therapies, comparative studies of novel therapies and correlation to adverse outcomes.

Keywords: SLE, pregnancy, small for gestational age, placental pathology

Rheumatology key messages

- Increased perivillous fibrin deposition (PVFD) was significantly more common in placentas from SLE deliveries with small for gestational age (SGA) infants.
- Increased PVFD in the setting of SGA might warrant evaluation for potential underlying autoimmune disease.
- Analysing placentas from all SLE deliveries can clarify the incidence and recurrence of increased PVFD.

Introduction

The placenta is a transient organ at the interface between the maternal uterus and the foetus. While it is often referred to as a 'diary of intrauterine life', placental patterns of injury are rarely specific to either a particular maternal disease or neonatal outcome [1–3]. Placental patterns of injury commonly associated with adverse pregnancy outcomes include acute chorioamnionitis [4], chronic inflammation/villitis of unknown aetiology (VUE) [5, 6], maternal vascular malperfusion (MVM) [7–9], foetal vascular malperfusion (FVM) [9, 10] and increased/massive perivillous fibrin deposition (PVFD) [11–15]. Except for acute chorioamnionitis, all of these patterns of injury have been associated with intrauterine growth restriction (IUGR)/small for gestational age (SGA) infants [16].

Prior published research indicates a significant association between autoimmune diseases and increased PVFD, a rare thrombo-inflammatory lesion characterized by fibrin deposition in the intervillous space and/or within and around the

Received: 24 May 2024. **Accepted:** 16 August 2024

basal plate, impairing perfusion and gas/nutrient exchange, and leading to serious obstetric complications such as IUGR/SGA infants, recurrent miscarriages and intrauterine foetal death (IUFD) [11–15, 17, 18]. For example, in a study by Ackerman *et al.* all nine placentas from women with connective tissue diseases, complicated by adverse neonatal outcomes (stillbirth or neonatal death), demonstrated extensive intervillous fibrin [18]. Increased/massive PVFD is also associated with high recurrence, with reported rates ranging from 12% to 80% in subsequent pregnancies [11].

Pregnant women with SLE face an elevated risk of adverse pregnancy outcomes, including miscarriages, preeclampsia, preterm birth (PTB) and having IUGR/SGA infants [19, 20]. Available placental studies in SLE patients have primarily focused on those with antiphospholipid antibody (aPL) positivity, and have noted features of MVM, including extensive infarction, and decidual vasculopathy/thrombosis, as well as increased PVFD [21, 22]. Studies of SLE-associated placentas in the context of PTB also suggest higher prevalence of uteroplacental vascular and coagulation-related lesions [23]. Such lesions may be partly predicted by increased infiltration of neutrophil and neutrophil extracellular traps (NETs) in the intervillous spaces [24]. However, there is an overall lack of data on placental findings in SLE in general, but particularly those correlating with SGA infants, which is a common adverse outcome, affecting up to a quarter of SLE pregnancies [25, 26]. In this study, we sought to compare the histopathologic features of placentas from SLE-associated pregnancies resulting in SGA infants, to those without SGA infants. Additionally, to identify specific underlying mechanisms leading to SGA within the context of SLE, we compared placental findings between SLE-associated SGA to SGA not associated with SLE. We hypothesized that SGA in the context of SLE would be associated with increased PVFD in the placenta.

Methods

To identify the individuals with SLE who delivered at UCSD in the past 5 years (November 2018 to October 2023), we queried electronic health records (EHR) to identify individuals with the ICD10 code M32.X in the inpatient setting, cross-referencing with charge capture procedures for vaginal or caesarean deliveries. Each case was individually confirmed for the presence of SLE by chart review. Patient demographics, clinical comorbidities, SLE disease characteristics, aPL positivity, antiphospholipid syndrome (APS), prior obstetric history and adverse pregnancy outcomes (APOs: preeclampsia, PTB, SGA), as well as neonatal intensive care unit (NICU) admission, were extracted from the medical charts. Of the 88 patients (99 pregnancies) with ICD codes for SLE in the medical record, only 59 patients (70 pregnancies) had a confirmed SLE diagnosis by a rheumatologist or nephrologist.

At our institution, placentas are sent for examination when there is a clinical indication for examination, as per published guidelines, which includes underlying maternal autoimmune disease [27]. However, these criteria are not consistently applied, with the final decision being at the delivering obstetrician's discretion. Based on our review of the characteristics of SLE deliveries with placental pathology data, this decision appeared primarily influenced by the presence of adverse pregnancy outcomes (Supplementary Table S1, available at *Rheumatology* online).

Where available, placental pathology data were extracted from the medical record and coded as previously reported [28]. All placental examinations were reviewed, and final reports generated, by the same perinatal pathologist (M.M.P.). The data extracted encompassed macroscopic features such as trimmed placental disc weight, placental weight for gestational age (categorized as small, normal or large for ≤10th, 11–89th and ≥90th percentile for gestational age, respectively) [29], umbilical cord (UC) insertion, UC abnormalities (e.g. hypertwisted, true knot, long cord), as well as histologic findings, diagnosed per the Amsterdam Workshop Consensus guidelines [30]. The histologic findings were grouped into the four major patterns of placental injury per Redline *et al.* [3]: maternal vascular malperfusion (small placental disc, plus, at least one of the following four findings-accelerated villous maturation, placental disc infarction, decidual vasculopathy and retroplacental/marginal haematoma), foetal vascular malperfusion (any of the following findings: foetal vascular thrombosis, avascular villi, villous stromal karyorrhexis), VUE (any of the following findings: focal, patchy or extensive chronic villitis, chronic intervillositis or chronic chorioamnionitis), ACA (subchorionitis/chorionitis/chorioamnionitis with or without a foetal response, defined by umbilical cord or chorionic plate vasculitis), as defined and reported in previous studies [3, 28]. Additional lesions were categorized as evidence of foetal stress (normoblastemia or meconium staining), and other placental pathology (increased/massive PVFD, chorangiosis, intervillous thrombosis and villous oedema). In our study, increased perivillous fibrin was defined as the presence of perivillous fibrin involving at least 20% of the placental disc.

In the pregnancies with available placental pathology data ($n = 28$, from 25 patients), we examined clinical and placental features for all SLE-affected pregnancies and made comparisons between those that resulted in SGA ($n = 12$, from 11 patients) and those that did not ($n = 16$, from 14 patients). A diagnosis of SGA was made when the birthweight fell below the 10th percentile for the gestational age at the time of birth, based on the growth percentile charts provided by Hadlock *et al.* [31] Additionally, we randomly selected a control group of pregnancies without SLE that resulted in SGA infants from the UC San Diego Center for Perinatal Discovery's ongoing Obstetric Registry (IRB approval # 181917), which includes pathological analysis conducted *via* the same pathway as the SLE cases, matching them based on maternal age at delivery (starting with ±1 year, extending to ±5 years if necessary) and gravidity status (primigravida *vs* non-primigravida) at a 3:1 ratio to cases of SLE-associated SGA.

Categorical variables were expressed as numbers (percentages) and continuous variables as median (interquartile range, IQR). Fisher's exact test was used to determine association between categorical variables and the Mann–Whitney *U* test (Wilcoxon rank-sum test) for continuous variables. Given the exploratory nature of this study, no adjustments were made for multiple comparisons. All statistical tests were two sided, with *P*-value of <0.05 considered statistically significant. The analysis was performed using STATA version 13.

The study was approved by the University of California San Diego (UCSD) Institutional Review Board (IRB approval

#181845). Individual patient consent was not required given the retrospective chart review nature of the study.

Results

Clinical characteristics of SLE patients with and without placental evaluation

Of the 59 patients (70 pregnancies) with a confirmed SLE diagnosis, placental analysis was available for 28/70 (40%) pregnancies. For comparison, clinical data for all lupus pregnancies, including those who did not have placental pathology, are also presented. As expected, those who underwent placental examination were retrospectively identified to have a higher prevalence of lupus nephritis (32% *vs* 7%) as well as APO's (75% *vs* 12%), compared with those without placental examination (Supplementary Table S1, available at *Rheumatology* online).

Clinical and placental characteristics of SLE, with and without associated SGA infants

The clinical characteristics of the 28 SLE pregnancies with placental pathology, as well as the SLE pregnancies with ($n = 12$) and without ($n = 16$) SGA infants are presented in Table 1. Of all patients with SLE, about 40% had chronic hypertension, 32% had lupus nephritis, 21% had elevated aPL antibodies, 85% were prescribed hydroxychloroquine, 32% were on steroids for SLE and nearly all (93%) were prescribed low-dose aspirin. Seventy-five percent experienced at least one APO (preeclampsia: 54%, PTB: 54%, SGA: infant 43%). Maternal and SLE disease characteristics were similar

Table 1. Clinical characteristics of individuals with SLE with and without small for gestational age (SGA) infants (November 2018 to October 2023), $n = 28$

	Overall SLE pregnancies ($n = 28$)	SLE pregnancies w/o SGA infants ($n = 16$)	SLE pregnancies w SGA infants ($n = 12$)	*P*-value (No SGA vs SGA)
Patient demographics				
Race/ethnicity, *n* (%)				
Non-Hispanic White	2 (7.14)	2 (12.50)	0 (0.00)	0.2
Non-Hispanic Black	3 (10.71)	0 (0.00)	3 (25.00)	
Hispanic	15 (53.57)	9 (56.25)	6 (50.00)	
Asian	7 (25.00)	4 (25.00)	3 (25.00)	
Preexisting comorbidities				
Chronic hypertension, *n* (%)	11 (39.29)	6 (37.50)	5 (41.67)	1.00
BMI: median (IQR)	27.17 (24.68–30.31)	27.7 (25.01–30.73)	27.16 (24.28–28.60)	0.52
SLE characteristics, n (%)				
Age at diagnosis: median (IQR)	21 (18–25)	23 (18–28)	20 (18–24)	0.45
Lupus nephritis	9 (32.14)	5 (31.25)	4 (33.33)	1.00
HCQ at the time of first prenatal visit	17 (60.71)	10 (62.50)	7 (58.33)	1.00
HCQ during delivery admission	24 (85.71)	12 (75.00)	12 (100)	0.11
Aspirin during pregnancy	26 (92.86)	14 (87.50)	12 (100)	0.5
Anticoagulation during pregnancy	6 (21.43)	3 (18.75)	3 (25)	1.00
Any steroid use during pregnancy	12 (42.86)	6 (37.50)	6 (50)	0.7
SLE flare	7 (25.00)	3 (18.75)	4 (33.33)	0.42
Low C3/C4 during delivery admission	9 (32.14)	4 (25)	5 (41.67)	0.66
Abnormal dsDNA during delivery admission	7 (25.00)	2 (12.50)	5 (41.67)	0.15
UPCR > 0.5 during delivery admission	11 (39.29)	5 (31.25)	6 (50.00)	0.52
Moderate–high titre SSA/SSB positive[a]	12 (42.86)	5 (31.25)	7 (58.33)	0.25
APLA-positive[b]	6 (21.43)	3 (18.75)	3 (25.00)	1.00
APS	4 (14.29)	2 (12.50)	2 (16.67)	1.00
Obstetric history				
Age at delivery: median (IQR)	30 (26–37.5)	30.5 (25.5–39)	28.5 (26–35.5)	0.43
Primigravida	8 (28.57)	3 (18.75)	5 (41.67)	0.23
Mode of delivery, *n* (%)				
Vaginal delivery	12 (42.86)	10 (62.50)	2 (16.67)	**0.02**[c]
C/S	16 (57.14)	6 (37.50)	10 (83.33)	
Neonatal characteristics				
Neonatal weight (g) median	2395 (1905-3208)	3143 (2413–3365)	1980 (1343–2355)	**0.001**[c]
Outcomes of current pregnancy, n (%)				
Preeclampsia	15 (53.57)	6 (37.50)	9 (75.00)	0.07
Preterm birth (<37 WOG)	15 (53.57)	8 (50.00)	7 (58.33)	0.72
Early to moderate preterm birth (<34 weeks)	3 (10.71)	0 (0.00)	3 (25.00)	0.07
NICU admission	15 (53.57)	8 (50)	7 (58.33)	0.72
Length of delivery hospitalization, days: median (IQR)	4 (3–6.5)	3 (3–5)	6.5 (3–9)	**0.03**[c]

[a] Anti-Ro/La (anti-SSA/SSB antibody) positivity defined as having moderate to high titre positivity (≥ 50 U/ml).
[b] APLA-positivity defined as having positive lupus anticoagulant assay or anti-cardiolipin or anti-Beta 2 glycoprotein antibody at titre of ≥ 40 U/ml.
[c] Significant results are in bold.

APLA: antiphospholipid antibody; IQR: interquartile range; NICU: neonatal intensive care unit; SGA: small for gestational age; WOG: weeks of gestation.

Table 2. Placental characteristics of individuals with SLE with and without small for gestational age (SGA) infant (November 2018 to October 2023), $n = 28$

	Overall SLE pregnancies ($n = 28$)	SLE pregnancies w/o SGA dx ($n = 16$)	SLE pregnancies w/SGA dx ($n = 12$)	*P*-value (No SGA vs SGA)
Morphologic characteristics				
Placental weight (g) – median (IQR)	312 (256–379)	364 (300–436)	250 (202–319)	0.18
Small placental (<10th percentile for GA), *n* (%)	**21 (75.00)**	**9 (56.25)**	**12 (100)**	**0.01**[a]
UC insertion, *n* (%)				
Central/eccentric	26 (92.86)	15 (93.75)	11 (91.67)	1.00
Marginal	2 (7.14)	1 (6.25)	1 (6.25)	
UC abnormalities (hypertwisted, true knot, long cord), *n* (%)	2 (7.14)	1 (6.25)	1 (8.33)	1.00
Histologic characteristics				
Maternal vascular malperfusion (MVM), *n* (%)	18 (64.29)	8 (50)	10 (83.33)	0.11
Accelerated villous maturation (↑ syncytial knots)	12 (42.86)	7 (43.75)	5 (41.67)	1.00
Placental disc infarct	**7 (25)**	**1 (6.25)**	**6 (50.00)**	**0.02**[a]
Decidual vasculopathy	15 (53.57)	11 (68.75)	4 (33.33)	0.13
Haematoma (retroplacental/marginal)	3 (10.71)	1 (6.25)	2 (16.67)	0.56
Foetal vascular malperfusion (FVM), *n* (%)				
Any FVM	8 (28.57)	4 (25.0)	4 (33.33)	0.69
Pure FVM	1 (3.57)	1 (6.25)	0 (0.00)	1.00
Villitis of unknown aetiology (VUE), *n* (%)	5 (17.86)	2 (12.50)	3 (25.00)	0.62
Acute chorioamnionitis (ACA), *n* (%)	8 (28.57)	4 (25.00)	4 (33.33)	0.69
Chorioamnionitis/subchorionitis/chorionitis	8 (28.57)	4 (25.00)	4 (33.33)	0.69
Fetal vasculitis	3 (10.71)	2 (12.50)	1 (8.33)	1.00
Evidence of foetal stress, *n* (%)	20 (71.43)	11 (68.75)	9 (75.00)	0.66
Normoblastemia	19 (67.86)	11 (68.75)	8 (66.67)	1.00
Meconium staining	2 (7.14)	1 (6.25)	1 (8.33)	1.00
Other placental processes, *n* (%)	21 (75.00)	12 (57.14)	9 (75.00)	1.00
Increased perivillous fibrin	**7 (25.00)**	**0 (0.00)**	**7 (58.33)**	**0.001**[a]
Chorangiosis	4 (14.29)	4 (25)	0 (0.00)	0.11
Intervillous thrombosis	6 (21.43)	5 (31.25)	1 (8.33)	0.20
Villous oedema	1 (3.57)	1 (6.25)	0 (0.00)	1.00

ACA: chorioamnionitis, subchorionitis, chorionitis; FVM: foetal thrombotic vasculopathy, foetal vascular thrombosis, avascular or near-avascular villi, villous stromal karyorrhexis, obliterative vasculopathy, mural thrombosis in any foetal vessel, cushion in foetal vessel; Pure FVM: FVM without evidence of VUE and not meeting the criteria for MVM; MVM: any small placenta PLUS at least 1 of the following four findings: hypermaturity, placental disc infarction, decidual vasculopathy, and retroplacental/marginal haematoma; VUE: at least one focus of chronic villitis; chorangiosis includes chorangiosis, chorangiomatosis or chorangioma.

[a] Significant results are in bold.

FVM: foetal vascular malperfusion; IQR: interquartile range; MVM: maternal vascular malperfusion; VUE: villitis of unknown aetiology.

between SLE pregnancies with and without SGA infants. In SLE pregnancies resulting in SGA infants, there was a higher rate of delivery by caesarean section (83% *vs* 38%, $P = 0.02$) and a tendency towards a higher rate of preeclampsia (75% *vs* 38%, $P = 0.07$) (Table 1).

Placental findings in the setting of SLE, including a comparison of findings between those with and without SGA infants are presented in Table 2. All 28 SLE pregnancies with placental pathology exhibited at least one histopathologic abnormality. About 54% had decidual vasculopathy, 43% had accelerated villous maturation, 71% had evidence of foetal stress (normoblastemia, meconium staining), 29% had foetal vascular malperfusion, 25% had acute chorioamnionitis, with no differences in these findings between SLE pregnancies with or without an SGA infant. Placental abnormalities that differed between SLE pregnancies with and without SGA infants included small placental disc for gestational age (100% *vs* 56%, $P = 0.01$), placental disc infarct (50% *vs* 6%, $P = 0.02$) and increased PVFD (58% *vs* 0%, $P = 0.001$), respectively (Table 2, Fig. 1). Notably, 7/28 (25%) of SLE pregnancies with available placental pathology exhibited increased PVFD, and all seven resulted in SGA infants. Of the seven with increased PVFD, only one (14.29%) had elevated aPL antibodies. Six out of seven placentas that exhibited placental disc infarct were associated with SGA (Table 2).

Clinical and placental characteristics of SLE-associated SGA *vs* non-SLE SGA

There were no statistically significant differences in clinical features of individuals with SGA, with and without SLE (Table 3). When we compared patterns of placental injury between the 12 SLE-associated pregnancies with SGA infants and 36 maternal age-matched non-SLE pregnancies with SGA infants, the only lesion that distinguished the two groups was higher prevalence of increased PVFD in SLE-associated SGA cases (58% *vs* 22%, $P = 0.03$). The rate of placental disc infarct was similar in both groups (50%) (Table 3).

Discussion

Placental pathology is commonly used to evaluate the underlying cause of an adverse pregnancy outcome. In our study, all 28 SLE pregnancies with available placental pathology exhibited at least one histopathologic abnormality. Placental abnormalities that were observed at significantly higher rates in SLE pregnancies with SGA infants (compared with those

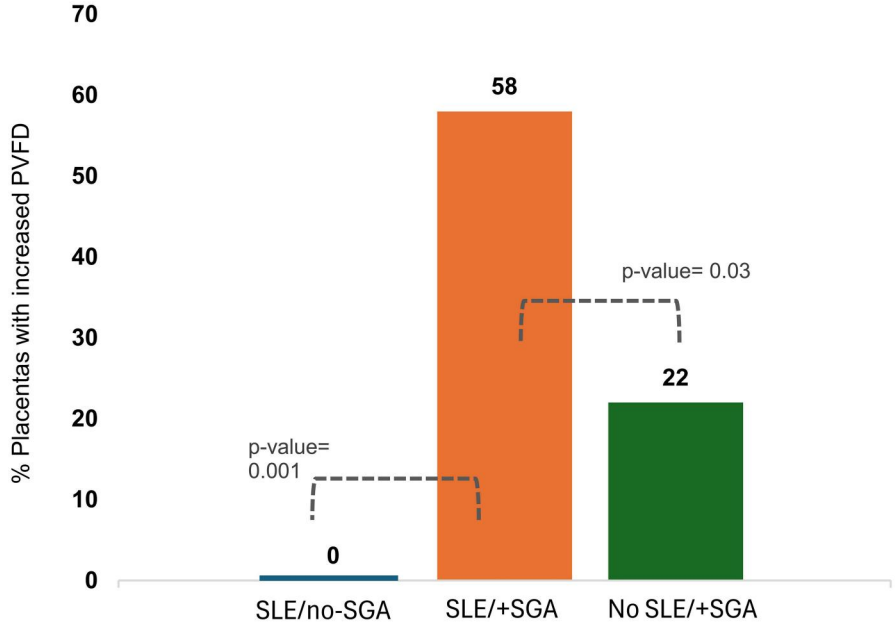

Figure 1. Comparison of increased perivillous fibrin deposition (PVFD) across groups

without SGA) included small placenta for gestational age, placental disc infarct and increased PVFD. Remarkably, all seven placentas from SLE patients that showed PVFD resulted in SGA infants. Other placental findings commonly observed in SLE in our study included normoblastemia in over two-thirds, decidual vasculopathy and accelerated villous maturation in about one-half, and ACA and placental disc infarct in about one-fourth of the studied placentas, but the rates of these lesions did not differ based on SGA infant status. While our study did not include placentas from healthy mothers without adverse pregnancy outcomes, a previous longitudinal analysis of 439 pregnancies, of which 64 resulted in SGA infants, found 51.6% and 6.3% of the latter group to have MVM and FVM, respectively, in their placentas [8]. In our population of SGA infants, MVM was observed in 83% and 64%, and FVM in 33% and 39% of pregnancies with and without SLE, respectively. However, these placental lesions did not distinguish between SLE-associated SGA and matched non-SLE pregnancies that resulted in SGA; instead, only increased PVFD appeared at higher prevalence in the SLE group.

Increased PVFD includes massive PVFD (MPVFD) and maternal floor infarction (MFI), in which fibrin deposition in the intervillous space and/or within and around the basal plate (typically defined as involving at least 20–25% of the placental disc), impairing perfusion and gas/nutrient exchange function of the chorionic villi [11, 14, 15, 17]. It is a rare condition with varying prevalence rates based on gestational age at delivery and clinical context, ranging from 0.03% of all placentas analysed to up to 2.7% in those with recurrent early miscarriages, 5.4% in spontaneous abortions with a normal karyotype and up to 11.8% in pregnancies associated with foetal growth restriction [11, 15, 32–34]. Increased PVFD can lead to significant perinatal morbidity including IUGR/SGA, PTB and IUFD [11]. The observed prevalence of various APOs in placentas with increased PVFD is high, varying from 15% to 80% for foetal death, except for a lower reported rate of 2.4% in one study [11, 12, 34, 35], 16.7% to 60% for PTB [11, 34, 36] and 9% to 92% for IUGR/SGA (most commonly in the range of 40–70%) [11, 37, 38]. Reported recurrence rates of increased PVFD range from 12% to 67% [13, 36]. Such wide variability in reported prevalence, recurrence and associated adverse outcomes are likely related to differences in definitions of increased PVFD, sample sizes, study designs, as well as study populations.

We observed a significantly higher prevalence of increased PVFD in placentas from SLE mothers with SGA (58%), compared both to those without SGA (0%) as well as to SGA cases not related to SLE (22%), suggesting that increased PVFD may be a specific mechanism of SGA in the context of SLE. Increased PVFD is considered idiopathic, although association of increased PVFD/MFI with thrombophilia and autoimmune diseases (such as lupus, primary and secondary APS, and polymyositis) have been noted [12, 14, 18, 39–41]. In one study, all nine placentas from women with connective tissue disease (five SLE, two mixed connective tissue disease, one rheumatoid arthritis, one without prior known connective tissue disease but subsequently diagnosed as SLE), with prior pregnancy loss and adverse outcomes of foetal or neonatal death in the studied pregnancy, demonstrated increased intervillous and PVFD, with all five SLE placentas also showing extensive infarction. Of the nine studied pregnancies, seven had anti-cardiolipin antibody and six tested positive for lupus anticoagulant. Notably, a diagnosis of SLE was established for one woman with two previous pregnancy losses, only after the placental examination showed the above features indicative of a connective tissue disease process [18]. In another study comparing 39 placentas with MPVFD (>50% placental disc involved) to 142 cases without increased PVFD, the prevalence of autoimmune diseases was notably higher in the former (12.8% *vs* 2.1%, $P = 0.012$) [12]. Another study defined low, moderate and severe PVFD as extent of fibrin deposition of 20–32%, 33–50% and >50%, respectively, and found an autoimmune disease prevalence of 11.5% in 52 cases with severe PVFD, compared with 0% in

Table 3. Comparison of clinical and placental characteristics between SLE-associated small for gestational age (SGA) infants compared with SGA infants from matched individuals without SLE (November 2018 to October 2023)

	SLE pregnancies vs SGA ($n = 12$)	Non-SLE pregnancies vs SGA ($n = 36$)	*P*-value (SLE vs non-SLE SGA)
Maternal and pregnancy characteristics			
Age at delivery: median (IQR)	28.5 (26.0–35.5)	28.5 (25.0–35.0)	0.97
Mode of delivery, *n* (%)			
Vaginal delivery	2 (16.67)	15 (41.67)	0.17
Caesarean section	10 (83.33)	21 (58.33)	
Diabetes mellitus			
No DM	12 (100.00)	26 (72.22)	0.35
Type 1 or 2 DM	0 (0.00)	5 (13.89)	
Gestational	0 (0.00)	5 (13.89)	
Chronic hypertension	5 (41.67)	8 (22.22)	0.26
Pregnancy outcomes, n (%)			
Preeclampsia, *n* (%)	9 (75.00)	27 (75.00)	1.00
PTB (<37 WOG), *n* (%)	7 (58.33)	28 (77.78)	0.26
Early PTB (<32 WOG)	3 (25.00)	15 (41.67)	0.48
NICU admission, *n* (%)	7 (58.33)	28 (77.78)	0.26
Infant weight in grams: median (IQR)	1980 (1343–2355)	1655 (985–2065)	0.38
Morphologic characteristics			
Placental weight (g) – median (IQR)	249.5 (202.0–318.5)	248.5 (198.0–315.0)	0.95
Small placental (<10th percentile for GA)	12 (100)	29 (80.56)	0.49
UC insertion			
Central/eccentric	11 (91.67)	24 (66.67)	0.34
Marginal, velamentous	1 (8.33)	8 (22.22)	
Avulsed, fragmented, disrupted	0 (0.00)	4 (11.11)	
Umbilical cord abnormalities (hypertwisted, true knot, long cord)	1 (8.33)	1 (2.78)	0.44
Histologic characteristics			
Maternal vascular malperfusion (MVM)	10 (83.33)	23 (63.89)	0.29
Accelerated villous maturation (↑syncytial knots)	5 (41.67)	35 (69.44)	0.10
Placental disc infarct	6 (50.00)	18 (50.00)	1.00
Decidual vasculopathy	4 (33.33)	19 (52.78)	0.32
Haematoma (retroplacental/marginal)	2 (16.67)	2 (5.56)	0.26
Foetal vascular malperfusion (FVM)			
Any FVM	4 (33.33)	14 (38.89)	1.00
Pure FVM	0 (0.00)	5 (13.89)	0.31
Villitis of unknown aetiology (VUE)	3 (25.00)	6 (16.67)	0.67
Acute chorioamnionitis (ACA)	4 (33.33)	13 (36.11)	1.00
Chorioamnionitis/subchorionitis/chorionitis	3 (25.00)	13 (36.11)	0.73
Fetal vasculitis	1 (8.33)	5 (13.89)	1.00
Evidence of foetal stress	9 (75)	26 (72.22)	1.00
Normoblastemia	8 (66.67)	25 (69.44)	1.00
Meconium staining	1 (8.33)	2 (5.56)	1.00
Other placental processes	8 (66.67)	14 (38.89)	0.11
Increased perivillous fibrin	7 (58.33)	8 (22.22)	**0.03**[a]
Chorangiosis	0 (0.00)	2 (5.56)	1.00
Intervillous thrombosis	1 (8.33)	4 (11.11)	1.00
Villous oedema	0 (0.00)	1 (2.78)	1.00

ACA: chorioamnionitis, subchorionitis, chorionitis; FVM: foetal thrombotic vasculopathy, foetal vascular thrombosis, avascular or near-avascular villi, villous stromal karyorrhexis, obliterative vasculopathy, mural thrombosis in any foetal vessel, cushion in foetal vessel; Pure FVM: FVM without evidence of VUE and not meeting the criteria for MVM; MVM: any small placenta PLUS at least one of the following four findings: hypermaturity, placental disc infarction, decidual vasculopathy and retroplacental/marginal haematoma; VUE: at least one focus of chronic villitis; Chorangiosis includes chorangiosis, chorangiomatosis or chorangioma.

[a] Significant results are in bold.

FVM: fetal vascular malperfusion; IQR: interquartile range; MVM: maternal vascular malperfusion; VUE: villitis of unknown aetiology.

48 cases with low PVFD ($P = 0.03$) [14]. Although the prevalence of autoimmune diseases in those with increased placental PVFD is significantly higher than in the general pregnant population, the true incidence of increased PVFD in autoimmune diseases, including SLE, remains unknown due to the nature of available studies.

The exact mechanisms leading to increased PVFD are poorly understood, but immune dysregulation involving complement system activation may play a role, as indicated by strongly positive C4d deposition observed in placentas affected by increased PVFD [32, 35]. Studies have also linked increased placental C4d deposition in conditions such as SLE, pregnancy-induced hypertension and positive aPL, to low placental weight, low birth weight and lower gestational age at delivery, indicating that C4d may be a biomarker of adverse outcomes [42, 43]. Increased placental deposition of beta 2-glycoprotein I (β2GP1), the main antigen for APS-associated pregnancy morbidity, has also been noted in patients with recurrent foetal loss and elevated aPL titres. It has been suggested that aPL may bind to a β2GP1 phospholipid complex in the placenta, causing complement activation and diffuse trophoblastic damage [44–46]. Indeed, *in vivo*, complement activation is essential for aPL-associated foetal morbidity, which could be reduced by inhibiting complement

cascade [47]. However, not all APS pregnancies exhibit increased PVFD, nor is increased PVFD diagnostic of APS; thus, further research into specific antibodies and other pathogenic mechanisms is needed to better understand this placental pattern of injury. One such mechanism implicated in increased PVFD is maternal antibody-mediated anti-foetal rejection. This is supported by the observation that mothers who had severe massive PVFD had significantly increased frequency of anti-HLA class I seropositivity (80% *vs* 36%, $P = 0.01$). Further, the maternal antibodies were noted to be specific to foetal HLA antigens. This, along with increased prevalence of plasma cell deciduitis in such placentas and strongly positive C4d deposition in the umbilical vein endothelium, support the concept of anti-foetal rejection as a mechanism in a subset of increased PVFD [35].

Although there is no known treatment for this lesion, one study has demonstrated efficacy of a combination regimen of aspirin, dipyridamole and heparin for women with a prior history of massive PVFD and SGA infant. Specifically, there was no recurrence of increased PVFD and a decreased recurrence of SGA in the treated group, with only 12.5% (1/8) of treated patients experiencing SGA, compared with 66.6% (4/6) of untreated patients [13]. In one case report, Chang *et al.* showed that adding IVIG to a regimen of aspirin and heparin, in the setting of an APS-associated increased PVFD with recurrent pregnancy loss, resulted in two successful pregnancies, despite extensive PVFD still noted in the placentas [48]. These cases suggest that obstetric APS with increased PVFD in prior pregnancies may indicate the need for triple therapy; however, it should be noted that IVIG has not been found to be beneficial in preventing recurrent abortions, and hence causal pathways need to be more clearly determined [49, 50]. Chaiworapongsa *et al.* have demonstrated elevation in maternal plasma concentrations of the anti-angiogenic factors, soluble vascular endothelial growth factor receptor (sVEGFR)-1 and soluble endoglin (sEng) in the setting of massive PVFD, for which statins may have a preventative role [51, 52]. In our study of 28 SLE pregnancies, we did not note any difference in placental pathology between those with ($n = 4$) and without ($n = 24$) APS; however, the sample size is likely too small to allow for a meaningful comparison. Determining the true incidence of increased PVFD in SLE, and its association with other maternal conditions (such as APS), adverse pregnancy outcomes (such as SGA or recurrent pregnancy loss) and relationship to treatments (such as hydroxychloroquine, aspirin, anticoagulation and immunomodulatory therapy) in a large cohort of SLE patients would bridge an important knowledge gap and help unravel the link between this placental pattern of injury and disease outcomes.

A significant limitation of our study is the selection bias from having placental analysis available for only 28 of 70 SLE deliveries in the study period. This bias, primarily influenced by the presence of pregnancy complications, resulted in a study group with notably higher APOs compared with the broader SLE population, thus limiting representativeness of our findings. Additionally, caesarean delivery rates were higher among pregnancies resulting in SGA, with or without SLE, compared with pregnancies that did not result in SGA. However, this is not unexpected as SGA is an indication for caesarean delivery. It should also be noted that while some placental pathology correlates with mode of delivery, the latter is not causative of any pathology, including increased PVFD. Other limitations include small sample size restricting statistical power and limiting our ability to detect other potentially significant differences. Despite its limitations, this study uses a well-characterized group of SLE pregnancies to add to our understanding of placental abnormalities in SLE, particularly highlighting the significant association of increased PVFD with SGA within the context of SLE, as compared with SLE without SGA and non-SLE-related SGA. Future studies, with placental examination across all SLE deliveries, will offer clearer insights into whether/how increased PVFD and other placental patterns of injury mediate SLE-related APOs, and their likelihood for recurrence in subsequent deliveries.

In conclusion, the finding of increased PVFD in SLE-associated SGA (58%), a rate notably higher than SLE pregnancies without SGA infants (0%) and SGA cases unrelated to SLE (22%), may indicate a specific mechanism of placental injury leading to SGA in SLE. We propose that the presence of this lesion in the placenta, particularly in the setting of SGA, should warrant a closer look for potential underlying maternal autoimmune disease, such as SLE. The poor overall outcome associated with this finding, and the high risk of recurrence, should alert the clinicians of high risk of APOs in subsequent pregnancies, which may potentially be mitigated with use of certain therapies. Future prospective studies incorporating clinical and placental pathology data may help to better probe the mechanisms underlying APO's related to maternal autoimmune disease. Future research on detection of this pathology prior to the occurrence of adverse outcomes, through discovery of biomarkers in maternal circulation diagnostic placental imaging, could enhance proactive intervention strategies to mitigate APOs in SLE, other autoimmune diseases, and in the general pregnant population.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Patient-level data are not available for sharing to protect patient privacy. All pertinent aggregate level data are presented in the article.

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Acknowledgements

R.D.'s training received support from research training grant from NIH/NIAMS (T32AR064194) and the Gary S. Gilkeson Career Development Award from the Lupus Foundation of America.

References

1. Griffiths SK, Campbell JP. Placental structure, function and drug transfer. Contin Educ Anaesth Crit Care Pain 2015;15:84–9.
2. Meserve EE, Parast MM, Boyd TK. Chapter 33 – gestational diseases and the placenta. In: Crum CP, Nucci MR, Howitt BE, Granter SR, Parast MM, Boyd TK, eds. Diagnostic gynecologic and obstetric

pathology. 3rd edn. Philadelphia: Elsevier, 2018:1219–49. https://www.sciencedirect.com/science/article/pii/B9780323447324000339.
3. Redline RW, Ravishankar S, Bagby CM, Saab ST, Zarei S. Four major patterns of placental injury: a stepwise guide for understanding and implementing the 2016 Amsterdam consensus. Mod Pathol Off J U S Can Acad Pathol Inc 2021;34:1074–92.
4. Budal EB, Ebbing C, Kessler J *et al.* Placental histology predicted adverse outcomes in extremely premature neonates in Norway—population-based study. Acta Paediatr 2022;111:546–53.
5. Salafia CM, Vintzileos AM, Silberman L, Bantham KF, Vogel CA. Placental pathology of idiopathic intrauterine growth retardation at term. Am J Perinatol 1992;9:179–84.
6. Nowak C, Joubert M, Jossic F *et al.* Perinatal prognosis of pregnancies complicated by placental chronic villitis or intervillositis of unknown etiology and combined lesions: about a series of 178 cases. Placenta 2016;44:104–8.
7. Mestan KK, Check J, Minturn L *et al.* Placental pathologic changes of maternal vascular underperfusion in bronchopulmonary dysplasia and pulmonary hypertension. Placenta 2014;35:570–4.
8. Loverro MT, Di Naro E, Nicolardi V *et al.* Pregnancy complications, correlation with placental pathology and neonatal outcomes. Front Clin Diabetes Healthc 2021;2:807192.
9. Gardella B, Dominoni M, Caporali C *et al.* Placental features of fetal vascular malperfusion and infant neurodevelopmental outcomes at 2 years of age in severe fetal growth restriction. Am J Obstet Gynecol 2021;225:413.e1–11.
10. Vinnars MT, Papadogiannakis N, Nasiell J, Holmström G, Westgren M. Placental pathology in relation to stillbirth and neonatal outcome in an extremely preterm population: a prospective cohort study. Acta Obstet Gynecol Scand 2015;94:584–90.
11. Cheloufi M, Coulomb A, Abisror N *et al.* Massive perivillous fibrin deposition: diagnosis, obstetrical features, and treatment. Eur J Obstet Gynecol Reprod Biol 2024;292:125–32.
12. Devisme L, Chauvière C, Franquet-Ansart H *et al.* Perinatal outcome of placental massive perivillous fibrin deposition: a case-control study. Prenat Diagn 2017;37:323–8.
13. Fuke Y, Aono T, Imai S *et al.* Clinical significance and treatment of massive intervillous fibrin deposition associated with recurrent fetal growth retardation. Gynecol Obstet Invest 1994;38:5–9.
14. Lampi K, Papadogiannakis N, Sirotkina M, Pettersson K, Ajne G. Massive perivillous fibrin deposition of the placenta and pregnancy outcome: a retrospective observational study. Placenta 2022;117:213–8.
15. Bane AL, Gillan JE. Massive perivillous fibrinoid causing recurrent placental failure. BJOG Int J Obstet Gynaecol 2003;110:292–5.
16. Park SY, Kim MY, Kim YJ *et al.* Placental pathology in intrauterine growth retardation. Korean J Pathol 2002;36:30–7.
17. Faye-Petersen OM, Ernst LM. Maternal floor infarction and massive perivillous fibrin deposition. Surg Pathol Clin 2013;6:101–14.
18. Ackerman J, Gonzalez EF, Gilbert-Barness E. Immunological studies of the placenta in maternal connective tissue disease. Pediatr Dev Pathol Off J Soc Pediatr Pathol Paediatr Pathol Soc 1999;2:19–24.
19. Jakobsen I, Helmig R, Stengaard-Pedersen K. Maternal and foetal outcomes in pregnant systemic lupus erythematosus patients: an incident cohort from a stable referral population followed during 1990–2010. Scand J Rheumatol 2015;44:377–84.
20. Bundhun PK, Soogund MZS, Huang F. Arterial/venous thrombosis, fetal loss and stillbirth in pregnant women with systemic lupus erythematosus versus primary and secondary antiphospholipid syndrome: a systematic review and meta-analysis. BMC Pregnancy Childbirth 2018;18:212.
21. Magid MS, Kaplan C, Sammaritano LR *et al.* Placental pathology in systemic lupus erythematosus: a prospective study. Am J Obstet Gynecol 1998;179:226–34.
22. Ogishima D, Matsumoto T, Nakamura Y, Yoshida K, Kuwabara Y. Placental pathology in systemic lupus erythematosus with antiphospholipid antibodies. Pathol Int 2000;50:224–9.
23. Locatelli A, Patane L, Ghidini A *et al.* Pathology findings in preterm placentas of women with autoantibodies: a case-control study. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet 2002;11:339–44.
24. Marder W, Knight JS, Kaplan MJ *et al.* Placental histology and neutrophil extracellular traps in lupus and pre-eclampsia pregnancies. Lupus Sci Med 2016;3:e000134.
25. Barnabe C, Faris PD, Quan H. Canadian pregnancy outcomes in rheumatoid arthritis and systemic lupus erythematosus. Int J Rheumatol 2011;2011:345727.
26. Chen CY, Chen YH, Lin HC, Chen SF, Lin HC. Increased risk of adverse pregnancy outcomes for hospitalisation of women with lupus during pregnancy: a nationwide population-based study. Clin Exp Rheumatol 2010;28:49–55.
27. Roberts DJ, Baergen RN, Boyd TK *et al.* Criteria for placental examination for obstetrical and neonatal providers. Am J Obstet Gynecol 2023;228:497–508.e4.
28. Horii M, To C, Morey R *et al.* Histopathologic and transcriptomic profiling identifies novel trophoblast defects in patients with preeclampsia and maternal vascular malperfusion. Mod Pathol Off J U S Can Acad Pathol Inc 2023;36:100035.
29. Pinar H, Sung CJ, Oyer CE, Singer DB. Reference values for singleton and twin placental weights. Pediatr Pathol Lab Med J Soc Pediatr Pathol Affil Int Paediatr Pathol Assoc 1996;16:901–7.
30. Khong TY, Mooney EE, Ariel I *et al.* Sampling and definitions of placental lesions: Amsterdam Placental Workshop Group consensus statement. Arch Pathol Lab Med 2016;140:698–713.
31. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology 1991;181:129–33.
32. Kim EN, Lee JY, Shim J-Y *et al.* Clinicopathological characteristics of miscarriages featuring placental massive perivillous fibrin deposition. Placenta 2019;86:45–51.
33. Redline RW, Zaragoza M, Hassold T. Prevalence of developmental and inflammatory lesions in nonmolar first-trimester spontaneous abortions. Hum Pathol 1999;30:93–100.
34. Spinillo A, Gardella B, Muscettola G *et al.* The impact of placental massive perivillous fibrin deposition on neonatal outcome in pregnancies complicated by fetal growth restriction. Placenta 2019;87:46–52.
35. Romero R, Whitten A, Korzeniewski SJ *et al.* Maternal floor infarction/massive perivillous fibrin deposition: a manifestation of maternal antifetal rejection. Am J Reprod Immunol N Y N 1989 2013;70:285–98.
36. Andres RL, Kuyper W, Resnik R, Piacquadio KM, Benirschke K. The association of maternal floor infarction of the placenta with adverse perinatal outcome. Am J Obstet Gynecol 1990;163:935–8.
37. Naeye RL. Maternal floor infarction. Hum Pathol 1985;16:823–8.
38. Mandsager NT, Bendon R, Mostello D *et al.* Maternal floor infarction of the placenta: prenatal diagnosis and clinical significance. Obstet Gynecol 1994;83:750–4.
39. Al-Adnani M, Kiho L, Scheimberg I. Recurrent placental massive perivillous fibrin deposition associated with polymyositis: a case report and review of the literature. Pediatr Dev Pathol Off J Soc Pediatr Pathol Paediatr Pathol Soc 2008;11:226–9.
40. Sebire NJ, Backos M, Goldin RD, Regan L. Placental massive perivillous fibrin deposition associated with antiphospholipid antibody syndrome. BJOG Int J Obstet Gynaecol 2002;109:570–3.
41. Sebire NJ, Backos M, El Gaddal S, Goldin RD, Regan L. Placental pathology, antiphospholipid antibodies, and pregnancy outcome in recurrent miscarriage patients. Obstet Gynecol 2003;101:258–63.
42. Minamiguchi S, Mikami Y, Nakajima N *et al.* Complement split product C4d deposition in placenta in systemic lupus erythematosus and pregnancy-induced hypertension. Pathol Int 2013;63:150–7.

43. Viall CA, Chamley LW. Histopathology in the placentae of women with antiphospholipid antibodies: a systematic review of the literature. Autoimmun Rev 2015;14:446–71.
44. La Rosa L, Meroni PL, Tincani A *et al.* Beta 2 glycoprotein I and placental anticoagulant protein I in placentae from patients with antiphospholipid syndrome. J Rheumatol 1994; 21:1684–93.
45. Gropp K, Weber N, Reuter M *et al.* β2-glycoprotein I, the major target in antiphospholipid syndrome, is a special human complement regulator. Blood 2011;118:2774–83.
46. Pierik E, Prins JR, van Goor H *et al.* Dysregulation of complement activation and placental dysfunction: a potential target to treat preeclampsia? Front Immunol 2019;10:3098.
47. Holers VM, Girardi G, Mo L *et al.* Complement C3 activation is required for antiphospholipid antibody-induced fetal loss. J Exp Med 2002;195:211–20.
48. Chang P, Millar D, Tsang P *et al.* Intravenous immunoglobulin in antiphospholipid syndrome and maternal floor infarction when standard treatment fails: a case report. Am J Perinatol 2006; 23:125–9.
49. Stephenson MD, Kutteh WH, Purkiss S *et al.* Intravenous immunoglobulin and idiopathic secondary recurrent miscarriage: a multicentered randomized placebo-controlled trial. Hum Reprod 2010;25:2203–9.
50. Hutton B, Sharma R, Fergusson D *et al.* Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review. BJOG Int J Obstet Gynaecol 2007;114:134–42.
51. Whitten AE, Romero R, Korzeniewski SJ *et al.* Evidence of an imbalance of angiogenic/antiangiogenic factors in massive perivillous fibrin deposition (maternal floor infarction): a placental lesion associated with recurrent miscarriage and fetal death. Am J Obstet Gynecol 2013;208:310.e1–11.
52. Chaiworapongsa T, Romero R, Korzeniewski SJ *et al.* Pravastatin to prevent recurrent fetal death in massive perivillous fibrin deposition of the placenta (MPFD). J Matern Fetal Neonatal Med 2016; 29:855–62.

Rheumatology, 2024, 63, 3006–3014
https://doi.org/10.1093/rheumatology/keae454
Original Article