

Original article

Evaluation of lupus anticoagulant, damage, and remission as predictors of pregnancy complications in systemic lupus erythematosus: the French GR2 study

Maddalena Larosa^{1,2}, Véronique Le Guern¹, Gaëlle Guettrot-Imbert¹, Nathalie Morel¹, Noémie Abisror³, Chafika Morati-Hafsaoui⁴, Pauline Orquevaux⁵, Elisabeth Diot⁶, Andrea Doria ², Françoise Sarrot-Reynaud⁷, Nicolas Limal⁸, Viviane Queyrel⁹, Odile Souchaud-Debouverie¹⁰, Laurent Sailler¹¹, Maëlle Le Besnerais¹², Tiphaine Goulenok ¹³, Anna Molto ^{14,15}, Emmanuelle Pannier-Metzger¹⁶, Loic Sentilhes¹⁷, Luc Mouthon^{1,18}, Estibaliz Lazaro¹⁹ and Nathalie Costedoat-Chalumeau^{1,15}, the GR2 Group*

Abstract

Objectives. The specific roles of remission status, lupus low disease activity state (LLDAS), and damage accrual on the prognosis of pregnancies in women with SLE are unknown. We analysed their impact on maternal flares and adverse pregnancy outcomes (APOs).

Methods. We evaluated all women (≥ 18 years) with SLE enrolled in the prospective GR2 study with an ongoing singleton pregnancy at 12 weeks (one pregnancy/woman). Several sets of criteria were used to define remission, disease activity and damage. APOs included: foetal/neonatal death, placental insufficiency with preterm delivery and small-for-gestational-age birth weight. First trimester maternal and disease features were tested as predictors of maternal flares and APOs.

Results. The study included 238 women (98.3% on hydroxychloroquine (HCQ)) with 230 live births. Thirty-five (14.7%) patients had at least one flare during the second/third trimester. At least one APOs occurred in 34 (14.3%) women. Hypocomplementemia in the first trimester was the only factor associated with maternal flares later in pregnancy ($P=0.02$), while several factors were associated with APOs. In the logistic regression models, damage by SLICC-Damage Index [odds ratio (OR) 1.8, 95% CI: 1.1, 2.9 for model 1 and OR 1.7, 95% CI: 1.1, 2.8 for model 2] and lupus anticoagulant (LA, OR 4.2, 95% CI: 1.8, 9.7 for model 1; OR 3.7, 95% CI: 1.6, 8.7 for model 2) were significantly associated with APOs.

Conclusion. LA and damage at conception were predictors of APOs, and hypocomplementemia in the first trimester was associated with maternal flares later in pregnancy in this cohort of pregnant patients mostly with well-controlled SLE treated with HCQ.

Trial registration. ClinicalTrials.gov, <https://clinicaltrials.gov>, NCT02450396.

¹Service de Médecine Interne, Centre de Référence Maladies Autoimmunes et Systémiques Rares Île de France, APHP Hôpital Cochin, Paris, France, ²Rheumatology Unit, Department of Medicine-DIMED, University of Padova, Padova, Italy, ³Service de Médecine Interne, Hôpital Saint Antoine, Paris, ⁴Service d'Infectiologie et Médecine Interne, CH Annecy Genevois—Site d'Annecy, Annecy, ⁵Service de Médecine Interne, Hôpital Robert Debré, CHU de Reims, Reims, ⁶Service de Médecine Interne, CHRU de Tours—Hôpital Bretonneau, Tours, ⁷Service de Médecine Interne, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, ⁸Service de Médecine Interne, CHU Henri Mondor, Créteil, ⁹Service de Rhumatologie, CHU L'Archet, Nice, ¹⁰Service de Médecine Interne, CHU Poitiers, Poitiers, ¹¹Service de Médecine Interne, CHU Toulouse, Toulouse, ¹²Service de Médecine Interne, CHU Rouen, Rouen, ¹³Service de Médecine Interne, Hôpital Bichat Claude Bernard, ¹⁴AP-HP, Hôpital Cochin, Service de Rhumatologie, ¹⁵Université de Paris, Centre de Recherche Épidémiologie et Bio Statistiques de Sorbonne Paris Cité, ¹⁶Service de Maternité Gynécologie Obstétrique Port-Royal, Hôpital Cochin, Paris,

¹⁷Service de Gynécologie Obstétrique, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, ¹⁸INSERM U1016, CNRS UMR8104, Université de Paris, Paris and ¹⁹Service de Médecine Interne et Maladies Infectieuses (Sud), Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France
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Correspondence to: Nathalie Costedoat-Chalumeau, Service de Médecine Interne, Centre de Référence Maladies Auto-immunes et Systémiques Rares, Hôpital Cochin, Centre for Clinical Epidemiology, Hôpital Hôtel-Dieu, Université de Paris, Centre of Research in Epidemiology and Statistics, Paris, France.
E-mail: nathalie.costedoat@aphp.fr

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Key words: systemic lupus erythematosus, pregnancy, adverse pregnancy outcome, damage, remission

Rheumatology key messages

- First trimester positive LA predicts adverse pregnancy outcome (APOs).
- Chronic irreversible damage in the first trimester also predicts APOs.
- Damage should be considered in preconception counseling and in early pregnancy.

Introduction

SLE mainly affects women of childbearing age, and optimal management of lupus pregnancies is essential [1, 2]. Historically, we have moved from pregnancy being contraindicated in SLE to considering it not as a contraindication but as an indicator of high risk for flares and adverse pregnancy outcomes (APOs), to a progressive decline in these risks, which nonetheless continue to be higher than in the general population [3]. Guidelines issued by both the EULAR in 2016 [1] and ACR in 2020 [2] currently recommend treating women with HCQ during pregnancy and planning pregnancy when their SLE is in either remission or a lupus low disease activity state (LLDAS). The level of the risk reduction when these recommendations are applied remains unknown. Moreover, the lack of available data prevents defining precisely which of these states should be achieved before attempting pregnancy [2]. While several definitions of remission and LLDAS [4] have been validated, those proposed by the DORIA/Zen [5] and DORIS [6] groups for remission and by Franklyn for LLDAS [7] have not been tested in pregnant women [8].

Optimizing the management of pregnancy in SLE requires the analysis of large prospective cohorts of pregnancies. The American “PROMISSE” (Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus) study [9] was a major advance, showing that severe flares were uncommon in pregnant women with inactive or stable mild or moderate SLE [9] and that lupus anticoagulant (LA), antihypertensive drug use, a physician global assessment (PGA) score >1 and a low platelet count were the main baseline predictors of APOs, while non-Hispanic White ethnicity/race was protective against them [9]. However, these findings may not be applicable to other settings, especially because HCQ was given to only 64.7% of cases and severe SLE patients were excluded from the PROMISSE study [9].

In 2014, we set up a French prospective study of pregnancies in women affected with rare diseases including SLE (the GR2 study, clinicaltrial.gov NCT02450396). Here, we aim to report pregnancy outcomes (maternal flares and APOs) in this large cohort of pregnant women with SLE. We tested remission definitions and LLDAS as well as cumulative damage (SLICC-Damage Index) in the first trimester as

predictors of poor outcome (flares and APOs) later in pregnancy.

Patients and methods

We report data from the GR2 (‘Groupe de recherche sur la Grossesse et les Maladies Rares’) study, a French multi-centre prospective observational study of pregnant women with rare and/or rheumatological diseases, including SLE and antiphospholipid syndrome (APS), conducted since October 2014 in 63 active centres (not all recruiting patients with SLE as the cohort is intended to study several rare and rheumatological diseases). Pregnant women are included by their clinicians (internists, rheumatologists and nephrologists) and are followed up to 12 months postpartum. The treating physicians made all treatment decisions.

The GR2 study is part of the European network of pregnancy registers in Rheumatology (EuNeP) supported by FOREUM (Foundation for Research in Rheumatology) [10] and follows EULAR recommendations regarding core data sets for pregnancy registers in rheumatology [11].

Inclusion criteria

Criteria for the current analysis required inclusion in the GR2 before 13 weeks, SLE classified according to the SLICC 2012 criteria [12] and conception before 15 July 2019 (to have complete data at delivery), with an ongoing singleton pregnancy that reached 12 weeks. Only the first singleton pregnancy per woman was analysed.

Data collected

At first-trimester consultations, we assessed demographic, clinical, serological and treatment features. Anti-phospholipid (aPL) status included anti-cardiolipin (aCL), anti-Beta2 glycoprotein type I antibodies (anti-β2GPI) and LA. In France, all laboratories are regularly audited and certified by a central agency. More details on the variety and types of assays are reported in [Supplementary Data S1](#), available at *Rheumatology* online. Triple positive aPL status was defined by positive aCL, anti-β2GPI and LA.

All data were prospectively collected in electronic case report forms at each consultation. Because all women received standard treatment, written informed consent was not required by French law. The women

were, however, informed of their right to oppose the use of their data for the study and orally stated their lack of objection. This project adheres to the principles of the Declaration of Helsinki and was approved by the Local Ethics Committee (CPP Ile de France VI, Groupe Hospitalier Pitié-Salpêtrière, 29 August 2012).

Definitions of remission, LLDAS, disease activity and damage

Disease activity was scored by the SLE Disease Activity Index-2000 (SLEDAI-2K) [13] adapted to pregnancy (SLEPDAI) [14] and we considered the first SLEPDAI available during the first trimester. Remission status was assessed by the DORIA/Zen [5] and DORIS [6] criteria and by clinical SLEPDAI=0 [8]. Damage was scored by the SLICC-Damage Index [15] (see definitions in [Supplementary Data S2](#), available at *Rheumatology* online).

Definition of outcomes

Maternal flares were defined according to the SELENA-SLEDAI Flare Index (SFI) [16]. This score divides flares into mild/moderate and severe flares and notably captures any increase in the PGA or in the steroid dose, any introduction of an immunosuppressive drug and any hospitalization.

To make our results comparable to those of the PROMISSE study [9], we defined APOs by a composite binary variable (the occurrence of at least one of the following events vs the non-occurrence of any of them): an otherwise unexplained intrauterine foetal death (IUFD) ≥ 12 weeks, a neonatal death (within 28 days after birth), placental insufficiency (i.e. foetal growth restriction (FGR), preeclampsia/eclampsia, Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome, and/or placental abruption, see [Supplementary Data S3](#), available at *Rheumatology* online) leading to preterm delivery < 37 weeks, small-for-gestational-age (SGA: birth weight below the third percentile according to the French AUDIPOG curve) [17].

Statistical analyses

Continuous variables normally and not-normally distributed were expressed, respectively, by their means with S.D. and medians with interquartile ranges (IQR). Incidence and 95% CIs were assessed for both maternal flares and APOs. To identify their predictors, we tested the following variables during the first trimester: (i) continuous: maternal age, disease duration, SLEPDAI, PGA, SLICC-Damage Index scores; and (ii) categorical: family geographical origins (European descent, African descent and Asian descent, see [Supplementary Table S1](#), available at *Rheumatology* online), overweight (BMI ≥ 25 kg/m²), tobacco and alcohol consumption (at least 10 units per week), associated APS, nulliparity, previous thrombosis, IUFD, or renal involvement, low platelet count (platelets $< 100 \times 10^9/l$), positive anti-double-stranded (ds) DNA, hypocomplementemia, positive aPL,

24-hours (h) proteinuria, concomitant treatment, remission and LLDAS.

Pearson's χ^2 test (or Fisher's exact test when appropriate) was used to evaluate univariate associations between categorical variables. Student's *t* test and Wilcoxon's rank-sum test were used to compare the parametric and non-parametric continuous variables, respectively. The choice of independent variables added to the logistic regression model in the multivariate analysis was based on current knowledge and the variables significant at the univariate analysis ($P < 0.1$). Significance for the logistic regression analyses was set at 5%. When the univariate analysis found significant associations between variables with high collinearity, separate multivariate models were tested for complete cases only.

All analyses were conducted with STATA v.16.1.

Results

Patient characteristics at enrolment

This study includes 238 women with SLE from 34 centres (see [Supplementary Tables S2](#) and [S3](#) and [Fig. S1](#), available at *Rheumatology* online). Their mean age was 31.6 (S.D. 4.5 years), 88 (37.0%) were nulliparous and 34 (14.3%) had an associated APS.

Previous lupus nephritis (LN) was reported in 67 women (28.2%) and was biopsy-proven in 62 (92.5%); one had class I, one had class II, twelve had class III, nineteen had class IV, sixteen had class V, one had class VI, five had class III+V and seven had class IV+V. Nine women had positive 24-h proteinuria (> 0.5 g/g or 0.5 g/day), attributed to active renal disease in only three.

All but four women (98.3%) took HCQ, 119 (50%) took prednisone, 56 (23.5%) took immunosuppressive drugs and 165 (69.3%) took low-dose aspirin. Finally, five women (2.1%) received antihypertensive drugs.

The median (IQR) SLEPDAI was 2 (0–3). Remission was achieved by 206 women (86.6%) with the clinical SLEPDAI=0, by 154 women (64.7%) with the DORIA/Zen definition and by 147 (61.8%) with the DORIS definition. LLDAS was achieved by 157 patients (71.7%).

Irreversible chronic damage was reported in 30 women (12.7%, missing data for two). All had been treated with prednisone, seven (23.3%) also had APS and 16 (53.3%) had a history of renal involvement. Details of SLICC-Damage Index domains are reported in [Supplementary Table S4](#), available at *Rheumatology* online.

Maternal flares

Thirty-five women (14.7%, 95% CI: 10.7, 19.8) had at least one flare during the second or third trimesters; most of them were articular ($n = 18$, 7.6%) and/or cutaneous ($n = 15$, 6.3%). Eight (3.4%) women had other types of flares: serositis in five (2.1%), renal in three (1.3%) and/or haematological in two (0.8%).

A severe flare occurred in only three women during the second trimester: two renal flares and one pericarditis associated with cutaneous rash. All three women required the addition of an immunosuppressive drug to the background treatment and had liveborn children, with an early delivery at 28 weeks for early preeclampsia in the woman with pericarditis and a rash.

At univariate analysis, only first-trimester hypocomplementemia was associated with flares ($P = 0.02$) (Table 1). Because hypocomplementemia is included in the SLEPDAI, no multivariate analysis could be performed for flares.

Finally, we found no association between maternal flare and APOs ($P > 0.99$). Neither the percentage of live births nor their median gestational age at delivery differed between patients with and without flares (97.1 vs 96.5% and 37.4 vs 37.7 weeks, respectively).

Obstetric and adverse pregnancy outcomes

Almost the entire cohort (230, 96.6%) had a live birth (median gestational age 37.7 ± 2.6 weeks). For the remaining eight women, one had a termination of pregnancy because of chromosomal abnormalities and seven had an IUID.

At least one APO occurred in 34 women (14.3%, 95%CI: 10.4, 19.4) (Table 2), including 22 (9.2%) preterm births due to placental insufficiency at a median gestational age of 33 weeks, seven (2.9%) IUIDs, five (2.1%, five missing data for the weight) SGA infants and one (0.4%) neonatal death. Among patients with placental insufficiency leading to preterm delivery, eight had FGR, six had HELLP syndrome, 14 had preeclampsia/eclampsia and/or one placental abruption.

At univariate analysis, women with at least one APOs were more likely to have LA ($P < 0.001$), at least one positive aPL ($P < 0.001$), an associated APS ($P = 0.01$) or prior thrombotic event ($P = 0.04$) (Table 2). They were also more likely to have positive anti-dsDNA ($P = 0.01$) and, accordingly, a higher SLEPDAI ($P = 0.01$). APOs were also associated with damage accrual (SLICC-Damage Index) ($P = 0.01$), immunosuppressive drug use ($P = 0.03$), low-dose aspirin ($P = 0.03$) and low molecular weight heparin ($P = 0.01$). Finally, APOs were not associated with antihypertensive drugs ($P = 0.15$), a low platelet count ($P > 0.99$) or geographical origin ($P = 0.40$) (Table 2).

To minimize collinearity, two different logistic regression models were tested for DORIA/Zen remission and LLDAS (Tables 3 and 4). Because prednisone, prednisone dosage, immunosuppressants and SLEPDAI are already included in the DORIA/Zen and LLDAS definitions, we did not consider them although they were significant on univariate analysis. Similarly, to facilitate comparison with the PROMISSE study, we chose LA instead of other related (and thus subject to collinearity) significant variables on univariate analysis (i.e. anti-aggregants, heparin, previous thrombosis, associated APS). Of note, age at pregnancy was forced in both models, based on the current literature, as the older the maternal age, the worse the obstetric outcome. Predictors of APOs in both analyses were SLICC-Damage Index (per

1 unit increase) and positive LA in the first trimester (adjusted (a)ORs of 1.8 and 4.2 in Model 1 and 1.7 and 3.7 in Model 2, respectively) (Tables 3 and 4). Neither DORIA/Zen remission nor LLDAS predicted APOs. Multicollinearity was ruled out in both models ($VIF < 2$).

Analysis of the PROMISSE predictors of APOs

Among the 121 women of European descent (corresponding to the White women of PROMISSE) who were concomitantly antihypertensive-free, LA-negative and had a $PGA \leq 1$ in the first trimester and a platelet count $> 100 \times 10^9/l$, only eight (6.6%) had an APO at any time; one of these fetuses died *in utero* and another after birth. By contrast, among the combined group of all but those of European descent women treated with antihypertensive drugs ($n=2$) or women with positive LA ($n=41$), 15 (34.9%) had an APO at any time: two of these fetuses died *in utero* but no neonatal deaths occurred.

Discussion

After the large North American PROMISSE study, where 385 women with SLE were prospectively included between 2003 and 2012, we report the second largest prospective study carried out on 238 pregnant women with SLE included between 2014 and 2019. Overall, we found that flares, especially severe ones, were uncommon and did not influence pregnancy outcomes. APOs were also rare (14.3%) and mainly associated with positive LA and damage accrual.

In contrast to the PROMISSE study [9], which aimed to identify risk factors for and mechanisms of APOs specifically attributable to SLE and/or aPL, and because we wanted a sample closer to real-life practice, we did not apply any of the following exclusion criteria: prednisone > 20 mg/day, urinary protein-creatinine ratio > 1000 mg/g, erythrocyte casts on urine analysis, serum creatinine level > 1.2 mg/dl, diabetes mellitus or hypertension [9]. Apart from inclusion/exclusion criteria, several aspects distinguish the populations of the two studies: their genetic background, with 12.3% of African descent in our study vs 20.3% in PROMISSE, and the rate of overweight women (30.3% vs 39.7%, respectively). The frequency of several baseline characteristics, which are well-known risk factors for APOs, was similar or slightly higher in our cohort than in PROMISSE: previous biopsy-proven LN (26.1% vs 20.5%), positive LA (17.7% vs 8.8%), at least one positive aPL test (26.3% vs 12.5%) and a history of thrombosis (17.2% vs 8.1%) (the number of patients with APS in the PROMISSE study is not available for comparison). However, SLE was probably better controlled in our study: fewer patients had hypocomplementemia (26.4% vs 34.0%) and their disease activity was lower (mean SLEPDAI = 1.96 vs 2.79). This latter difference may be due to the higher percentage of our patients on HCQ (98.3% vs 64.7%) as well as to the

TABLE 1 Baseline patient characteristics associated with flares in the second and third trimesters

	Total (n = 238)	Flare (n = 35)	No flare (n = 203)	P-value
Maternal characteristics				
Age at pregnancy, mean (S.D.)	31.6 (4.5)	30.9 (4.9)	31.7 (4.4)	0.37
Nulliparity	88 (37.0)	15 (42.9)	73 (36.0)	0.44
Family geographical origin (n = 235)				
European descent	166 (70.6)	25 (71.4)	141 (70.5)	
African descent	29 (12.3)	4 (11.4)	25 (12.5)	
Asian descent	17 (7.2)	2 (5.7)	15 (7.5)	0.99
Others	23 (9.8)	4 (11.4)	19 (9.5)	
Overweight (BMI \geq 25 kg/m ²) (n = 234)	71 (30.3)	7 (20.0)	64 (32.2)	0.17
Active smokers (n = 233)	21 (9.0)	3 (8.6)	18 (9.1)	>0.99
Alcohol consumption (n = 226) ^a	6 (2.7)	1 (2.9)	5 (2.6)	>0.99
Previous IUFD (n = 237)	16 (6.8)	2 (5.9)	14 (6.9)	1.00
Previous thrombosis	41 (17.2)	5 (14.3)	36 (17.7)	0.81
Associated APS	34 (14.3)	5 (14.3)	29 (14.3)	>0.99
SLE duration, years, median (IQR)	7.2 (3.6–12.4)	7.7 (3.3–12.9)	7.2 (3.6–12.4)	0.92
Previous renal involvement	67 (28.2)	12 (34.3)	55 (27.1)	0.38
Laboratory characteristics				
Low platelets (<100 \times 10 ⁹ /l)	3 (1.3)	1 (2.9)	2 (1.0)	0.38
24-h proteinuria >0.5 g/d (or >0.5 g/g)	9 (3.8)	2 (5.7)	7 (3.5)	0.62
Positive anti-dsDNA (n = 222)	104 (46.9)	19 (55.9)	85 (45.2)	0.25
Hypocomplementemia (n = 216)	57 (26.4)	15 (42.9)	42 (23.2)	0.02
At least one positive aPL (n = 232)	61 (26.3)	9 (26.5)	52 (26.3)	>0.99
IgG/IgM anti- β 2GPI (n = 232)	26 (11.2)	4 (11.8)	22 (11.1)	>0.99
IgG/IgM aCL (n = 232)	37 (16.0)	4 (11.8)	33 (16.7)	0.62
LA (n = 232)	41 (17.7)	6 (17.7)	35 (17.7)	>0.99
Triple positive aPL (n = 232)	17 (7.3)	2 (5.9)	15 (7.6)	>0.99
SLE activity and damage				
PGA, median (IQR) (n = 235)	0.1 (0–0.2)	0.1 (0–0.9)	0.1 (0–0.2)	0.65
SLEPDAI, median (IQR) (n = 212)	2 (0–3)	2 (0–4)	2 (0–2)	0.06
SLICC-Damage Index, median (IQR) (n = 236)	0 (0–0)	0 (0–0)	0 (0–0)	0.87
Clinical SLEPDAI = 0	206 (86.6)	28 (80.0)	178 (87.7)	0.28
Remission (DORIA/Zen definition)	154 (64.7)	21 (60.0)	133 (65.5)	0.53
Remission (DORIS definition)	147 (61.8)	20 (57.1)	127 (62.6)	0.54
LLDAS (n = 219)	157 (71.7)	25 (71.4)	132 (71.7)	0.97
Current treatment				
Prednisone	119 (50.0)	21 (60.0)	98 (48.3)	0.20
Prednisone mg/d, median (IQR) (N = 119)	7 (5–10)	7 (5–10)	7 (5–10)	0.71
Immunosuppressive drugs ^b	56 (23.5)	12 (34.3)	44 (21.7)	0.10
HCQ ^c	234 (98.3)	34 (97.1)	200 (98.5)	0.47
Low-dose aspirin ^d	165 (69.3)	24 (68.6)	141 (69.5)	0.92
Low molecular weight heparin	61 (25.6)	8 (22.9)	53 (26.1)	0.68
Antihypertensive agents	5 (2.1)	1 (2.9)	4 (2.0)	0.55

S.D.: standard deviation; aCL: anti-cardiolipin; anti- β 2GPI: anti-beta2 Glycoprotein I; anti-dsDNA: anti-double stranded DNA; aPL: antiphospholipid; APS: antiphospholipid syndrome; IQR: interquartile range; g/d: grams per day; IUFD: intrauterine foetal death (>10 weeks); LA: lupus anticoagulant; LLDAS: lupus low disease activity state; PGA: physician global assessment; SLE: systemic lupus erythematosus; SLEPDAI: SLE Pregnancy Disease Activity Index. ^aAt least 10 units per week. ^bImmunosuppressive drugs: Azathioprine (n = 53, 22.3%) and tacrolimus (n = 5, 2.1%); two women received both. ^cAll but four women (98.3%) took HCQ; among those four, intolerance accounted for the lack of HCQ treatment for two, retinopathy for one and non-adherence for the fourth. ^dLow-dose aspirin was given to 165 women (69.3%). In particular, 52 of 67 patients (77.6%) with previous renal involvement and 56 of 61 patients (91.8%) with at least one positive aPL during pregnancy were treated with low-dose aspirin. More details on geographical origins are available in [Supplementary Table S1](#), available at *Rheumatology* online. Bold text highlights significance.

routine monitoring of HCQ levels in France, which leads to a better treatment adherence [18]. Finally, besides the difference in HCQ exposure, we had more patients on low-dose aspirin (69.3% vs 35.1%). The publication of the PROMISSE study in 2015 before the

current recommendations may explain this difference (Table 5) [1, 2, 9].

Importantly, 71.6% of our patients with previous renal involvement and 91.8% of those with at least one positive aPL received low-dose aspirin. This

TABLE 2 Baseline patient characteristics associated with APOs in the second and third trimesters

	Total (n = 238)	APOs (n = 34)	No APOs (n = 204)	P-value
Maternal characteristics				
Age at pregnancy, mean (S.D.)	31.6 (4.5)	30.7 (4.8)	31.7 (4.4)	0.22
Nulliparity	88 (37.0)	11 (32.4)	77 (37.8)	0.55
Family geographical origins (n = 235)				
European descent	166 (70.6)	21 (61.8)	145 (72.1)	
African descent	29 (12.3)	7 (20.6)	22 (11.0)	
Asian descent	17 (7.2)	2 (5.9)	15 (7.5)	0.40
Others	23 (9.8)	4 (11.8)	19 (9.5)	
Overweight (BMI \geq 25 kg/m ²) (n = 234)	71 (30.3)	14 (41.2)	57 (28.5)	0.14
Active smokers (n = 233)	21 (9.0)	5 (15.2)	16 (8.0)	0.19
Alcohol consumption (n = 226) ^a	6 (2.7)	2 (6.3)	4 (2.1)	0.20
Previous IUFD (n = 237)	16 (6.8)	5 (14.7)	11 (5.4)	0.06
Previous thrombosis	41 (17.2)	10 (29.4)	31 (15.2)	0.04
Associated APS	34 (14.3)	10 (29.4)	24 (11.8)	0.01
SLE duration, years, median (IQR)	7.2 (3.6–12.4)	10.0 (3.7–15.3)	7.0 (3.5–11.9)	0.13
Previous renal involvement	67 (28.2)	13 (38.2)	54 (26.5)	0.16
Laboratory characteristics				
Low platelets (<100 × 10 ⁹ /l)	3 (1.3)	0 (0.0)	3 (1.5)	>0.99
24-h proteinuria >0.5 g/d (or >0.5 g/g)	9 (3.8)	3 (8.8)	6 (2.9)	0.12
Positive anti-dsDNA (n = 222)	104 (46.9)	21 (67.7)	83 (43.5)	0.01
Hypocomplementemia (n = 216)	57 (26.4)	13 (40.6)	44 (23.9)	0.05
At least one positive aPL (n = 232)	61 (26.3)	18 (52.9)	43 (21.7)	<0.001
IgG/IgM aCL (n = 232)	37 (16.0)	9 (26.5)	28 (14.1)	0.08
IgG/IgM anti- β 2GPI (n = 232)	26 (11.2)	6 (17.7)	20 (10.1)	0.24
LA (n = 232)	41 (17.7)	15 (44.1)	26 (13.1)	<0.001
Triple positive aPL (n = 232)	17 (7.3)	5 (14.7)	12 (6.1)	0.08
Disease activity and damage				
PGA, median (IQR) (n = 235)	0.1 (0–0.2)	0.1 (0.0–0.4)	0.1 (0.0–0.2)	0.06
SLEPDAI, median (IQR) (n = 212)	2 (0–3)	2 (2–4)	2 (0–2)	0.01
SLICC-Damage Index, median (IQR) (n = 236)	0 (0–0)	0 (0–1)	0 (0–0)	0.01
Clinical SLEPDAI = 0	206 (86.6)	28 (82.4)	178 (87.3)	0.42
Remission (DORIA/Zen definition)	154 (64.7)	17 (50.0)	137 (67.2)	0.05
Remission (DORIS definition)	147 (61.8)	17 (50.0)	130 (63.7)	0.13
LLDAS (n = 219)	157 (71.7)	19 (57.6)	138 (74.2)	0.05
Current treatment				
Prednisone	119 (50.0)	23 (67.7)	96 (47.1)	0.03
Prednisone mg/d, median (IQR) (n = 119)	7 (5–10)	7.5 (5–10)	7 (5–10)	0.13
Immunosuppressive drugs ^b	56 (23.5)	13 (38.2)	43 (21.1)	0.03
HCQ ^c	234 (98.3)	34 (100.0)	200 (98.0)	>0.99
Low-dose aspirin ^d	165 (69.3)	29 (85.3)	136 (66.7)	0.03
Low molecular weight heparin	61 (25.6)	15 (44.1)	46 (22.6)	0.01
Antihypertensive agents	5 (2.1)	2 (5.9)	3 (1.5)	0.15

S.D.: standard deviation; aCL: anti-cardiolipin; anti- β 2GPI: anti-beta2 Glycoprotein I; anti-dsDNA: anti-double stranded DNA; aPL: antiphospholipid; APO: adverse pregnancy outcome; APS: antiphospholipid syndrome; g/d: grams per day; IQR: interquartile range; IUFD: intrauterine foetal death (>10 weeks); LAC: lupus anticoagulant; LLDAS: lupus low disease activity state; PGA: physician global assessment; SLEPDAI: SLE Pregnancy Disease Activity Index. ^aAt least 10 units per week. ^bImmunosuppressive drugs: Azathioprine (n = 53, 22.3%) and tacrolimus (n = 5, 2.1%); two women received both. ^cAll but four women (98.3%) took HCQ; among those four, intolerance accounted for the lack of HCQ treatment for two, retinopathy for one and non-adherence for the fourth. ^dLow-dose aspirin was given to 165 women (69.3%). In particular, 52 of 67 patients (71.6%) with previous renal involvement and 56 of 61 patients (91.8%) with at least one positive aPL during pregnancy were treated with low-dose aspirin. More details on geographical origins are available in [Supplementary Table S1](#), available at *Rheumatology* online. Bold text highlights significance.

finding might explain the lower rate of APOs in our cohort, and confirms the good application of current guidelines [1, 2].

Severe maternal flares occurred in three women (1.2%) in our study: among them only one woman

gave birth preterm, due to placental insufficiency at 28 weeks (with preeclampsia/eclampsia and HELLP syndrome); by contrast, both women with severe renal flares gave birth to healthy children at term. In the multicentre PROMISSE study [9], 5.5% patients had

TABLE 3 Risk factors for APOs: multivariate analysis

Variables	Model 1 ^a		
	Crude OR (95% CI)	aOR (95% CI)	P-value
Age at pregnancy	0.9 (0.9, 1.0)	1.0 (0.9, 1.1)	0.45
DORIA/Zen remission	0.5 (0.2, 1.1)	0.5 (0.2, 1.2)	0.11
SLICC-Damage Index (per 1-unit increase)	1.9 (1.2, 3.0)	1.8 (1.1, 2.9)	0.02
Positive LA in the 1st trimester	5.2 (2.4, 11.5)	4.2 (1.8, 9.7)	0.001

^aMultivariate analysis performed on complete cases for the tested variables: $n=230$. aOR: adjusted odds ratio; LA: lupus anticoagulant; OR: odds ratio. Age at pregnancy was also forced into the analysis, as a known risk factor for APO. We included LA, and because of high collinearity, we excluded associated APS, at least one positive aPL test and treatments such as low-dose aspirin and low molecular weight heparin (as most women with APS or carrying aPL were treated with these drugs) from our regression models. Finally, we excluded prednisone dose, immunosuppressants, SLEPDAI, hypocomplementemia and anti-dsDNA from both models, as both the DORIA/Zen definition of remission and LLDAS are composite scores that already include these factors (see [Supplementary Material](#), available at *Rheumatology* online). Bold text highlights significance.

TABLE 4 Risk factors for APOs: multivariate analysis

Variables	Model 2 ^a		
	Crude OR (95% CI)	aOR (95% CI)	P-value
Age at pregnancy	0.9 (0.9, 1.0)	1.0 (0.9, 1.1)	0.45
LLDAS	0.5 (0.2, 1.1)	0.5 (0.2, 1.1)	0.07
SLICC-Damage Index (per 1-unit increase)	1.9 (1.2, 3.0)	1.7 (1.1, 2.8)	0.03
Positive LA in the 1 st trimester	5.2 (2.4, 11.5)	3.7 (1.6, 8.7)	0.002

^aMultivariate analysis performed on complete cases for tested variables: $n=212$. aOR: adjusted odds ratio; LA: lupus anticoagulant; LLDAS: lupus low disease activity state; OR: odds ratio. Age at pregnancy was also forced into the analysis, as a known risk factor for APOs. We included LA, and because of high collinearity, we excluded associated APS, at least one positive aPL test, and treatments such as low-dose aspirin and low molecular weight heparin (as most women with APS or carrying aPL were treated with these drugs) from our regression models. Finally, we excluded prednisone dose, immunosuppressants, SLEPDAI, hypocomplementemia and anti-dsDNA from both models, as both the DORIA/Zen definition of remission and LLDAS are composite scores that already include these factors (see [Supplementary Material](#), available at *Rheumatology* online). Bold text highlights significance.

severe flares, even though patients with severe disease at conception were excluded. As we did not exclude such women in our study, a higher rate of flares (mild/moderate and severe) might theoretically be expected. Nevertheless, more than 60% of our patients were in remission/LLDAS in the first trimester, possibly because nearly all of our patients were on HCQ, as recently recommended [1, 19]. Antimalarials have been widely demonstrated to mitigate the risk of flares both during pregnancy and in the postpartum period [1, 20]. A recent retrospective study of 398 pregnancies in 304 patients reported a higher flare rate during pregnancy (HR: 1.59; 95%CI: 1.27, 1.96), but this was no longer true for patients on HCQ: the HR for flares during pregnancy compared with non-pregnant/non-postpartum periods was 1.83 (95%CI:

1.34, 2.45) in patients not treated with HCQ vs 1.26 (95%CI: 0.88, 1.69) in those who were on HCQ [20].

Maternal flares were associated with hypocomplementemia ($P = 0.02$), consistently with previous reports [9, 21]. Notably, flares during the second and third trimesters were not associated with APOs ($P > 0.99$), in contrast to older cohorts and the PROMISSE study [9, 22]. The discrepancies between our study and prior cohorts are probably due to the low rate of patients with severely active SLE in our study, which likely prevented us from finding an association between disease activity and APOs. This difference may be due also to the improvement in the management of SLE; both physicians and patients now understand the importance of achieving remission/LLDAS before conception as well as of maintaining HCQ during pregnancy.

TABLE 5 Major differences between GR2 and PROMISSE [9] studies

	GR2	PROMISSE [9]
Time frame	2014–2019	2003–2012
Exclusion criteria	Twin pregnancy	Twin pregnancy UPCR >1000 mg/g Creatinine level >1.2 mg/dl Prednisone >20 mg/d
Ethnicity (African descent/Black)	12.3%	20.3%
History of thrombosis	17.2%	8.1%
Positive LA	17.7%	8.8%
At least one positive aPL	26.3%	12.5%
Previous renal involvement	28.2%	20.5%
HCQ exposure	98.3%	64.7%
Mean SLEPDAI at 1 st trimester	1.96	2.79

aPL: anti-phospholipid; LA: lupus anticoagulant; HCQ: hydroxychloroquine; SLEPDAI: SLE Pregnancy Disease Activity Index; UPCR: urinary protein creatinine ratio.

We evaluated three definitions of remission and found no substantial differences between them in terms of association with maternal flares or APOs. This could be due to the high frequency of patients on remission in the first trimester and consequently, to a lack of power. It may also be explained by the fact that the definitions of remission that were assessed are indeed relatively close and partially use the same variables. Hence, analyses of wider cohorts are needed to test each remission sub-class during pregnancy, including those with serologically active but clinical quiescent disease.

Overall, 230 (96.6%) women had liveborn infants who survived to discharge. APOs were observed in 14.3% of women, whereas they occurred in 19% of patients in the PROMISSE study. This difference might be due to the different definition of SGA (below the third percentile in our cohort vs the fifth in PROMISSE) and the high proportion of patients treated with aspirin (69.3% vs 35.1%).

In our study, LA and damage accrual predicted APOs. The PROMISSE study [9] had previously shown that LA is a predictor of APOs, pinpointing that the risk of pregnancy complication in women with SLE is due to aPL antibodies more than SLE itself. In addition, we demonstrated for the first time that damage accrual is associated with APOs. Analysis of patients with damage ($n = 30$, [Supplementary Table S4](#), available at *Rheumatology* online) showed diverse irreversible damage, driven both by disease activity and glucocorticoid treatment, but also aPL status and/or associated APS. This finding suggests that damage should be considered in preconception counselling and in early pregnancy. It also reinforces the importance of achieving remission/LLDAS to prevent the accrual of additional damage [23–25].

In contrast to PROMISSE [9], we did not find any significant association between APOs and active disease or ethnicity. This finding may be due to different healthcare systems and socioeconomic status of patients included in both cohorts [9].

Our study has some limitations. First, the assessment of aPL/anti-dsDNA antibodies was not centralized as in the PROMISSE study due to the real-life design of our study and the large number of centres. This limitation is at least partially offset by the fact that all laboratories in France require regular accreditation. The exact impact of disease activity in the first trimester could not be assessed because patients had to have an ongoing pregnancy at 12 weeks to be included, and it could be hypothesized that some active patients were excluded because their pregnancies ended spontaneously during the first trimester. This limitation also applies to the PROMISSE study as we chose to have a similar design to enable comparison.

In conclusion, we confirmed that positive LA predicts APOs and observed for the first time that chronic irreversible damage in the first trimester also predicts APOs. Neither remission nor LLDAS appeared to influence APOs in this cohort of women with stable, well-controlled SLE treated with HCQ. These results should be helpful to physicians caring for pregnant women with SLE.

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Contributors of the GR2 group: Béatrice Banneville, Antoine Baudet, Constance Beaudouin-Bazire, Cristina Belizna, Rakiba Belkhir, Ygal Benhamou, Alice Berezne, Sabine Berthier, Emilie Berthoux, Holy Bezanahary, Lisa Biale, Boris Bienvenu, Claire Blanchard-Delaunay, Anne Calas, Pascal Cathebras, Claire Cazalets, Benjamin Chaigne, Olivia Chandesris, Jérémy Chatelais, Emmanuel Chatelus, Elodie Chauvet, Fleur Cohen, Pascal Coquerelle, Marion Couderc, Mathilde de Menthon, Claire de Moreuil, Juliette Delforge, Azeddine Dellal, Catherine Deneux-Tharoux, Amélie Denis, Emmanuelle Dernis, Alban Deroux, Sandra Desouches, Guillaume Direz, Maxime Dougados, Marine Driessen, Aurélie Du Thanh, Laetitia Dunogeant, Cécile Durant, Isabelle Durieu, Elisabeth Elefant, Marc Fabre, Olivier Fain, Nicole Ferreira-Maldent, René-Marc Flipo, Aline Frazier, Antoine Froissart, Sophie Georgin-Lavialle, Elisabeth Gervais, Bertrand Godeau, François Goffinet, Anne Gompel, Laure Gossec, Phillipe Goupille, Claire Grange, Constance Guillaud-Danis, Eric Hachulla, Aurélie Hummel, Moez Jallouli, Patrick Jego, Stéphane Jobard, Laurence Josselin-Mahr, Noémie Jourde-Chiche, Anne-Sophie Korganow, Marc Lambert, Vincent Langlois, Delphine Lariviere, Claire Larroche, Céline Lartigau-Roussin, Augustin Latourte, Christian Lavigne, Thomas Le Gallou, Gaëlle Leroux, Hervé Levesque, Frédéric Lioté, Laurence Loeuillet, Jonathan London, Valentine Loustau, Emmanuel Maheu, Matthieu Mahevas, Hélène Maillard, Xavier Mariette, Hubert Marotte, Nicolas Martin-Silva, Nihal Martis, Agathe Masseur, François Maurier, Arsène Mekinian, Sara Melboucy-Belkhir, Martin Michaud, Marc Michel, Jacques Morel, Guillaume Moulis, Jérémy Ora, Elisabeth Pasquier, Jean-Loup Pennaforte, Antoinette Perlat, Hélène Petit Bauer, Laurent Perard, Evangéline Pillebout, Jean-Maxime Piot, Geneviève Plu-Bureau, Vincent Poindron, Agnès Portier, Gregory Pugnet, Loïc Raffray, Alexis Regent, Christophe Richez, Mélanie Roriz, Gaëtan Sauvetre, Léa Savey, Nicolas Schleinitz, Jeremy Sellam, Raphaele Seror, Vincent Sobanski, Christelle Sordet, Martin Soubrier, Katia Stankovic-Stojanovic, Nathalie Tieulé, Thierry Thomas, Marie-Agnès Timsit, Vassilis Tsatsaris, Maria Letizia Urban, Geoffrey Urbanski, Cécile Yelnik.

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Data availability statement

The data underlying this article are available in the article and in its online [supplementary material](#). The data will be shared on reasonable request to the corresponding author.

Supplementary data

[Supplementary data](#) are available at *Rheumatology* online.

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