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

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

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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 systemic lupus erythematosus (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) with 230 live births. Thirty-five (14.7%) patients had at least one flare during the second/third trimester. At least one APO 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 (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 (LAC, 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: LAC and damage at conception were predictors of APOs, and hypocomplementemia in the first trimester was associated with maternal flares later in pregnancy in a cohort of pregnant patients with well-controlled SLE.

Clinical trial registration number: ClinicalTrials.gov, https://clinicaltrials.gov, NCT02450396.

Keywords: systemic lupus erythematosus, pregnancy, adverse pregnancy outcome, damage, remission.

KEY MESSAGES

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

INTRODUCTION

Systemic lupus erythematosus (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 European League Against Rheumatism (EULAR) in 2016 [1] and American College of Rheumatology (ACR) in 2020 [2] currently recommend treating women with hydroxychloroquine 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 from 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 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 (LAC), 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 since hydroxychloroquine 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 (Systemic Lupus International Collaborating Clinics-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 multicentre 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 follow 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 July 15, 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 anticardiolipin (aCL), anti-Beta2 glycoprotein type I antibodies (anti-β2GPI), and LAC. 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 LAC.

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-Salpétrière, 29/08/2012).

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 APO by a composite binary variable (the occurrence of at least one of the following events versus the non-occurrence of any of them): an otherwise unexplained intrauterine fetal death (IUFD) $\geq$ 12 weeks, a neonatal death (within 28 days after birth), placental insufficiency (fetal growth restriction, i.e. FGR, preeclampsia/eclampsia, 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 and standard deviations (SD) and medians with interquartile ranges (IQR). Incidence and 95% confidence intervals (CIs) were assessed for both maternal flares and APOs. To identify their predictors, we tested the following variables during the first trimester: 1) continuous: maternal age, disease duration, SLEPDAI, PGA, SLICC-Damage Index scores; 2) categorical: family geographical origins (European descent, African descent and Asian descent), see Supplementary Table S1, available at *Rheumatology* online), overweight (body mass index (BMI) ≥25 kg/m^2), tobacco and alcohol consumption (at least 10 units per week), associated APS, nulliparity, previous thrombosis, IUFD, or renal involvement, low platelet count (platelets <100×10^9/l), positive anti-double-stranded (ds)-DNA, hypocomplementemia, positive aPL, 24-hour (h) proteinuria, concomitant treatment, remission, and LLDAS.

Pearson's chi square 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 Figure S1, available at *Rheumatology* online). Their mean age was 31.6 (SD 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%): 1 had class I, 1 class II, 12 class III, 19 class IV, 16 class V, 1 class VI, 5 class III+V, and 7 class IV+V. Nine women had positive 24-hour 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 hydroxychloroquine, 119 (50%) prednisone, 56 (23.5%) immunosuppressive drugs, and 165 (69.3%) low-dose aspirin. Finally, five women (2.1%) received antihypertensive drugs.

The median (IQR) SLEPDAI was 2 (0-3). Remission was achieved by 200 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 2). All had been treated with prednisone, 7 (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 5 (2.1%), renal in 3 (1.3%), and/or haematological in 2 (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). Since 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 IUFD.

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, 7 (2.9%) IUFDs, 5 (2.1%, 5 missing data for the weight) SGA infants, and one (0.4%) neonatal death. Among patients with placental insufficiency leading to preterm delivery, 8 had FGR, 6 HELLP syndrome, 14 preeclampsia/eclampsia, and/or one placental abruption.

At univariate analysis, women with at least one APO were more likely to have LAC (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 skin colour (P=0.40) (Table 2).

To minimize collinearity, two different logistic regression models were tested for DORIA/Zen remission and LLDAS (Tables 3, 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 LAC 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, since 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 LAC 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 3,4). Neither DORIA/Zen remission nor LLDAS predicted APO. 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, LAC-negative, and had a PGA ≤ 1 in the first trimester and a platelet count > 100 $\times 10^9$/l, only 8 (6.6%) had an APO at any time; one of these foetuses 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 LAC (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 LAC 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 LAC (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 hydroxychloroquine (98.3% vs 64.7%) as well as to the routine monitoring of hydroxychloroquine levels in France, which leads to a better treatment adherence [18]. Finally, besides the difference in hydroxychloroquine 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 (1, 2, 9) may explain this difference (Table 5).

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 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 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 hydroxychloroquine, 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 hydroxychloroquine: 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 hydroxychloroquine vs 1.26 (95%CI: 0.88–1.69) in those who were on hydroxychloroquine [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 hydroxychloroquine during pregnancy.

We evaluated three definitions of remission and found no substantial differences between them in terms of association with maternal flares or APO. 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, LAC and damage accrual predicted APOs. The PROMISSE study [9] had previously shown that LAC 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) 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 health-care 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 since 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 LAC 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 hydroxychloroquine. These results should be helpful to physicians caring for pregnant women with SLE.

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Contributors. ML, NCC, VLG, and GGI designed the study; ML and AM performed the statistical analyses. NCC, VLG, and GGI analysed and interpreted the data. NCC, VLG, GGI, EL, NM, NA, CMH, PO, ED, FSR, and AM collected clinical data on behalf of the GR2 study group. AD helped to critically revise the manuscript for important intellectual content. NCC, VLG, GGI, and ML wrote the manuscript.

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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, Prof N. Costedoat-Chalumeau (ORCID 0000-0002-1555-9021).

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

Maternal characteristics	Total (N=238)	Flare (N=35)	No flare (N=203)	*P* value
Age at pregnancy, mean (SD)	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≥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)§	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 (<100×10^9/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-β2GPI (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
LAC (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*	56 (23.5)	12 (34.3)	44 (21.7)	0.10
Hydroxychloroquine**	234 (98.3)	34 (97.1)	200 (98.5)	0.47
Low-dose aspirin***	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

SD: standard deviation; BMI: body mass index; IUFD: intrauterine fetal death (>10 weeks); APS: antiphospholipid syndrome; SLE: systemic lupus erythematosus; IQR: interquartile range; g/d: grams per day; anti-dsDNA: anti-double stranded DNA; aPL: antiphospholipid; aCL: anti-cardiolipin; anti-β2GPI: anti-

beta2 Glycoprotein I; LAC: lupus anticoagulant; PGA: physician global assessment; SLEPDAI: Systemic Lupus Erythematosus Pregnancy Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics; LLDAS: lupus low disease activity state.

§: at least 10 units per week.

***:** Immunosuppressive drugs: azathioprine (n=53, 22.3%) and tacrolimus (n=5, 2.1%); two women received both.

****:** All but four women (98.3%) took hydroxychloroquine; among those four, intolerance accounted for the lack of hydroxychloroquine treatment for two, retinopathy for one, and non-adherence for the fourth.

*****:** Low-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. Bold text highlights significance.

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

Maternal characteristics	Total (N=238)	APO (N=34)	No APO (N=204)	*P* value
Age at pregnancy, mean (SD)	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≥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)§	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-β2GPI (N=232)	26 (11.2)	6 (17.7)	20 (10.1)	0.24
LAC (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*	56 (23.5)	13 (38.2)	43 (21.1)	**0.03**
Hydroxychloroquine**	234 (98.3)	34 (100.0)	200 (98.0)	>0.99
Low-dose aspirin***	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

APO: adverse pregnancy outcome; SD: standard deviation; BMI: body mass index; IUFD: intrauterine fetal death (>10 weeks); APS: antiphospholipid syndrome; SLE: systemic lupus erythematosus; IQR: interquartile

range; g/d: grams per day; anti-dsDNA: anti-double stranded DNA; aPL: antiphospholipid; aCL: anti-cardiolipin; anti-β2GPI: anti-beta2 Glycoprotein I; LAC: lupus anticoagulant; PGA: physician global assessment; SLEPDAI: Systemic Lupus Erythematosus Pregnancy Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics; LLDAS: lupus low disease activity state.

§: at least 10 units per week.

***:** Immunosuppressive drugs: azathioprine (n=53, 22.3%) and tacrolimus (n=5, 2.1%); two women received both.

****:** All but four women (98.3%) took hydroxychloroquine; among those four, intolerance accounted for the lack of hydroxychloroquine treatment for two, retinopathy for one, and non-adherence for the fourth.

*****:** Low-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. Bold text highlights significance.

Table 3. Risk factors for APO: multivariate analysis

Variables	Model 1§		
	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 LAC in the 1st trimester	5.2 (2.4-11.5)	4.2 (1.8-9.7)	**0.001**

§: *multivariate analysis performed on complete cases for the tested variables: N=230.* OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; LAC: lupus anticoagulant; SLICC: Systemic Lupus International Collaborating Clinics. Age at pregnancy was also forced into the analysis, as a known risk factor for APO. We included LAC, and because of high collinearity, we excluded associated APS, at least one positive aPL test, and treatments such as low-dose aspirin and LMWH (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, since both the DORIA/Zen definition of remission and LLDAS are composite scores that already include these factors (see Supplementary Material). Bold text highlights significance.

Table 4: Risk factors for APO: multivariate analysis

Variables	Model 2§		
	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 LAC in the 1st trimester	5.2 (2.4-11.5)	3.7 (1.6-8.7)	**0.002**

§: *multivariate analysis performed on complete cases for tested variables: N=212.* OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; LLDAS: lupus low disease activity state; LAC: lupus anticoagulant; SLICC: Systemic Lupus International Collaborating Clinics. Age at pregnancy was also forced into the analysis, as a known risk factor for APO. We included LAC, and because of high collinearity, we excluded associated APS, at least one positive aPL test, and treatments such as low-dose aspirin and LMWH (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, since both the DORIA/Zen definition of remission and LLDAS are composite scores that already include these factors (see Supplementary Material). Bold text highlights significance.

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 LAC	17.7%	8.8%
At least one positive aPL	26.3%	12.5%
Previous renal involvement	28.2%	20.5%
Hydroxychloroquine exposure	98.3%	64.7%
Mean SLEPDAI at 1st trimester	1.96	2.79

UPCR: urinary protein creatinine ratio; LAC: lupus anticoagulant; aPL: anti-phospholipid; SLEPDAI: Systemic Lupus Erythematosus Pregnancy Disease Activity Index.