Remission or low disease activity at pregnancy onset are linked to improved foetal outcomes in women with systemic lupus erythematosus: results from a prospective observational study

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Abstract

Objective

Systemic lupus erythematosus (SLE) patients show variably increased risk for pregnancy complications. We analysed pregnancy outcomes (foetal and maternal), patterns of disease activity and use of medications in a contemporary Caucasian SLE population.

Methods

Prospective observational study, involving hospital units and private rheumatologists in Greece, of incident pregnancies (period 2015–2018) in women with SLE. Clinical and obstetrical monitoring was performed at regular intervals up to 9 months post-partum. Regression and mixed model analyses were used to determine predictors for adverse foetal outcomes and flares.

Results

We monitored 82 pregnancies in 64 SLE patients. Foetal loss, prematurity and small for gestational age neonate occurred at 15.8%, 34.1% and 8.5%, respectively; 53.7% of pregnancies were complicated with at least one adverse outcome. Patients with antiphospholipid antibodies (aPL) had increased risk (odds ratio [OR] 5.67, p=0.015), whereas those at low disease activity at pregnancy onset were protected (OR 0.20, p=0.024) against foetal complications. Persistent activity and glucocorticoid intake during pregnancy also predicted poor foetal outcomes. SLE patients experienced an average 1.08 mild/moderate and 0.27 severe flares. The latter occurred more frequently post-partum, in patients with alopecia (OR 8.92, p=0.003), hypocomplementaemia (OR 10.34, p=0.038) and nephritis (OR 7.32, p=0.052). Lupus activity post-labour was paralleled by decreased use of hydroxychloroquine, glucocorticoids and azathioprine.

Conclusion

In SLE women, foetal complications are common especially in the presence of aPL and increased activity, which corroborates the importance of pregnancy planning and tight disease control at pregnancy onset. Flares, mostly mild or moderate, can occur both during and after pregnancy.

Key words

antiphospholipid antibodies, nephritis, pregnancy, post-partum, preterm delivery, flares, remission, foetal outcomes, maternal outcomes

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease affecting mainly young women, therefore reproductive issues are particularly relevant (1). Pregnancies in women with SLE have long been considered to be "high risk" for miscarriage and other foetal and/or maternal complications. In a large US national survey, SLE pregnancies had excessive rates of premature labour (20.8% *vs*. 8.1% in non-SLE pregnancies), intra-uterine growth restriction (IUGR) (5.6% *vs*. 1.5%) and pre-eclampsia (22.5% *vs*. 7.6%) (2). Although analysis of inpatient data over the period 1998-2015 has suggested improving trends (3), a substantial proportion of SLE pregnancies are still burdened with adverse foetal or maternal outcomes (4).

Notably, this adverse risk may not be universally increased across all patients (5); observational studies have identified predictors of dismal pregnancy prognosis such as presence of lupus anticoagulant, active and/or history of lupus nephritis and high disease activity (5-13). Also, pregnancy outcomes may be influenced by social and racial/ethnic disparities, with black and Hispanic patients exhibiting higher rates of preeclampsia, preterm labour and IUGR, compared to white counterparts (14, 15). Thus, studies of lupus pregnancies in different settings are important to obtain an understanding of the disease at a regional level.

A notable aspect of SLE pregnancy is its potential to impact on the disease course by triggering exacerbation presumably due to underlying hormonal and biological changes (16, 17). The effect of pregnancy on disease activity has long been investigated, yielding, however, conflicting results (10, 12, 13, 18-23). Across studies, the frequency of flares varies between 13-74%, which corresponds to incidence rates of 0.36 to 1.80 per patient-year during pregnancy and post-partum (18). More recent studies have also suggested that pregnancy is a risk factor for SLE flares (19). Discrepancies in published evidence may be attributed to multiple factors, such as clinical setting and patient heterogeneity (ethnic/racial background, disease activity status at pregnancy onset), use of hydroxychloroquine, and methodological issues (definition of flares, retrospective design) (18, 19). Importantly, the majority of studies have focused on monitoring disease activity during (but not after) pregnancy, which, however, can lead to underestimation of flare incidents (13).

To this end, we designed and performed a prospective, multicentre observational study in a group of Greek Caucasian pregnant women with SLE, with serial visits every 3 months and extension of follow-up to 9 months postpartum. Through protocol-defined monitoring, we aimed to obtain contemporary real-life data on pregnancy outcomes pertaining both to the foetus and the mother, including patterns of activity and use of medications. Our study underscores the clinical relevance of antiphospholipid antibodies (aPL) and sufficient disease control in determining foetal outcomes in SLE women. Flares occurred frequently during gestation and post-partum, and we have identified patient subgroups at-risk for severe flares, towards facilitating patient stratification and personalised monitoring.

Materials and methods

Study design

A prospective observational (non-interventional) study was performed by a collaborative network of five Rheumatology hospital units and private rheumatologists in Greece, covering from primary to tertiary care. During the enrolment period (01/2015 to 01/2018), consecutively seen pregnant women with SLE diagnosis who met the revised 1997 American College of Rheumatology (ACR) (24) or 2012 Systemic Lupus International Collaborating Clinics (SLICC) (25) classification criteria, were asked to participate following informed consent. In case a patient had multiple pregnancies, each pregnancy was registered individually. Structured questionnaires and forms were used to collect prespecified demographic and clinical variables, as outlined below. Patients were managed at the discretion of the treating physician and in accordance to the EULAR recommendations (26), which emphasise the importance

of pregnancy planning and tight control of disease activity at pregnancy onset. The study was approved by the Ethics Committee of the University Hospital of Heraklion (protocol no. 13985).

Screening and follow-up visits

Patients were examined at inclusion visit (typically within 2–3 weeks since pregnancy confirmation) and then followed every 3 months (or earlier if necessary) until last pregnancy status (in case of pregnancy loss), or 9 months postpartum (in case of live birth). Data were collected in structured forms on: i) demographics (age, years of education, smoking [non-, ex-, current smokers), body mass index (BMI; kg/m^2), ii) disease manifestations and classification criteria (24, 25), iii) obstetrical history (detailed below) and conception method (spontaneous, assisted), iv) laboratory (complete blood count, liver and renal function, urinalysis) and immunological [anti-dsDNA, C3/C4, antiphospholipid antibodies (aPL)] tests, v) disease activity (27) (SLEDAI-2K (28), SELENA-SLEDAI Physician Global Assessment [PGA](29)), vi) comorbid diseases and vi) use and dosage of medications. At the end of pregnancy, the type of delivery (normal or caesarean section, spontaneous or programmed), sex, birth weight, birth week and APGAR score of the newborn were recorded. Data were entered into a secure electronic database installed on the Rheumatology Clinic, University Hospital of Heraklion protected server and network. The operation and maintenance of the database was strictly supervised by the scientifically accountable protocol and access was granted only to authorised users/researchers. All principles of anonymity, confidentiality and non-traceability of data are adhered to.

Adverse foetal outcomes

These included: 1) foetal loss, including early miscarriage (before 10th week of gestation), late miscarriage (between 10th and 20th week of gestation) and stillbirth (after 20 weeks of pregnancy), 2) preterm delivery or termination of pregnancy prior to 36 weeks due to maternal of foetal complications not explained by anatomical or chromosomal abnormalities, further classified as: i) early (28th-33rd week of gestation) or ii) moderate (34th-36th week of gestation), 3) small for gestational age (SGA) neonate, defined as birthweight below the 10th percentile without anatomical or chromosomal abnormalities, 4) IUGR, defined as less than 10% of predicted foetal weight for gestational age and, 5) neonatal death.

Adverse maternal outcomes

Adverse maternal outcomes were recorded and ascertained based on patient-reported interview, review of medical and hospital discharge notes, following confirmation by the treating obstetrician-gynaecologist. These included: 1) hypertension (blood pressure >140/90 on two occasions at least 6 hours apart); new-onset after 20 weeks' gestation, without presence of protein in the urine or other signs of pre-eclampsia (30), 2) gestational diabetes; confirmed by i) fasting plasma glucose level >126 mg/dl or a casual plasma glucose >200 mg/dl confirmed on a subsequent day, or ii) abnormal oral glucose tolerance test (31), 3) thrombotic events, 4) infections, 5) pre-eclampsia; onset of high blood pressure and evidence of target-organ damage beginning after 20 weeks of pregnancy and confirmed by obstetrician/gynaecologist, 6) eclampsia; pre-eclampsia complicated with grand mal seizures and/or unexplained coma during pregnancy or postpartum, 7) HELLP syndrome; characterised by haemolysis, elevated liver enzymes and low platelet count, 8) placental abruption; separation of placenta from the uterus before childbirth, 9) oligohydramnios; decreased amniotic fluid volume than expected for gestational age, 10) polyhydramnios; excess accumulation of amniotic fluid, 11) SLE flares (see below).

Disease activity states and flares

SLE activity was grouped into the following categories: no activity (SLEDAI=0), mild activity (SLEDAI=1–3), moderate activity (SLEDAI=4–10) and high activity (SLEDAI>10) (32). Lupus Low Disease Activity State (LLDAS) was defined as: (1) SLEDAI-2K ≤4, with no activity in major systems, no haemolytic anaemia or gastrointestinal activity; (2) no new lupus disease activity compared with previous assessment; (3) a SELENA-SLEDAI PGA (scale 0–3) ≤1; (4) current prednisolone (or equivalent) dose ≤7.5 mg daily; and (5) tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents (33). Remission was defined according to the DORIS definition (34) as: (1) clinical SLEDAI-2K=0; (2) dose of prednisone ≤5 mg/day; and (3) with/without stable dose of immunosuppressants, biologicals, antimalarials. Flares were classified into mild/moderate and severe according to the SELENA-SLEDAI Flare Index (29).

Statistical analysis

Descriptive statistics (median [interquartile range)) were calculated for continuous variables. The chi-squared test was used to compare categorical variables. The longitudinal course of disease activity was analysed using an ordinal (SLEDAI-2K>0 *vs*. SLEDAI-2K=0) logistic mixed model treating sequential visits as repeated measures and patients as random effect covariates. Logistic regression was used to identify baseline factors independently associated with adverse foetal outcomes (defined as any of the following complications: foetal loss, preterm delivery, SGA neonate) and SLE flares. Possible predictors (including general risk factors for pregnancy complications) were first evaluated by univariate analysis and variables associated with p-value <0.100 were considered for multivariate analysis (stepwise backward selection method). Models were assessed based on tests for linearity, interactions and goodness of fit. To address the effect of both time-varying and baseline factors, we utilised Generalised Estimated Equation (GEE) treating adverse foetal outcome as dependent variable (Logit link function). Within-subject (repeated measures) effects were considered with autoregression correlation matrix structure. Statistical significance was indicated as a two-sided p<0.05. All statistical analyses were performed using SPSS v. 25.0.

Results

Clinical characteristics and foetal outcomes in SLE pregnant women

We monitored 82 incident pregnancies in 64 women with SLE (48 patients with a single pregnancy, 14 patients with two pregnancies, 2 patients with three pregnancies). Twenty-seven patients had previous obstetric history with an average 1.4 pregnancies prior to enrollment (Table I). At the time of the first pregnancy monitored prospectively, patients were 33.5 (6.8) years old and had 3.7 (6.7) years disease duration. In terms of clinical characteristics, 20.3% had history of LN, 29.7% were aPL positive and 37.5% had anti-Ro/SSA autoantibodies. Twenty-six patients (40.6%) had been previously treated with at least one immunosuppressive or biological agent. Of 82 pregnancies, 83.0% were live births, of which 41.1% were preterm and 56.1% were delivered with a caesarean section (Table II). Foetal losses were mostly (11.0%) early abortions before the 10th week of gestation. Altogether, more than half of pregnancies (53.7%) were complicated with at least one adverse foetal outcome, including pregnancy loss, prematurity and/or SGA. Median APGAR score at 5 minutes was 9 (data from n=36 newborns). Excluding late prematurity (≥37th gestational week), foetal complication rate was 39.0%. There were no cases of neonatal death, congenital heart block or medical termination of pregnancy due to foetal abnormalities.

Maternal outcomes and patterns of disease activity during gestation and postpartum

Next, we assessed for adverse maternal outcomes in our cohort. There was a low frequency of hypertensive and metabolic complications (1.2% each), placental abruption, oligo- or polyhydramnios (3.7%, 4.9% and 1.2%, respectively) (Supplementary Table S1). Pregnancy can impact on SLE course and, *vice versa*, active lupus may predispose to adverse pregnancy outcomes (35, 36), so we examined disease activity patterns during pregnancy and 9 months postpartum (Fig. 1A). At pregnancy onset, 35.6% of patients had

Table I. Demographic and clinical characteristics of pregnant SLE women (n=64) [1]

Characteristic	Median (IQR) or %
Age at conception (years) [2]	33.5 (6.8)
SLE duration until conception (years)	3.7 (6.7)
SLICC 2012 criteria items	
Acute cutaneous lupus erythematosus	75.0%
Chronic cutaneous lupus erythematosus	3.1%
Mucosal ulcers	35.9%
Non-scarring alopecia	31.3%
Arthritis	79.7%
Serositis	9.4%
Renal disease	20.3%
Neurologic disease	1.6%
Haemolytic anaemia	6.3%
Leukopenia	37.5%
Thrombocytopenia	12.5%
ANA	100%
Anti-dsDNA	48.4%
Anti-Sm	10.9%
Anti-phospholipid antibodies (aPL)	29.7%
Hypocomplementaemia [3]	71.9%
Direct coombs	15.6%
Autoantibodies at the time of conception	
Anti-Ro/SSA	37.5%
Anti-La/SSB	17.2%
Anti-dsDNA	10.9%
Anti-Sm	3.1%
Anti-phospholipid antibodies [4]	
Anti-cardiolipin IgG	14.1%
Anti-cardiolipin IgM	7.8%
Anti-β2-glycoprotein IgG	12.5%
Anti-β2-glycoprotein IgM	4.7%
Lupus anticoagulant	9.4%
Past SLE treatment	
HCQ	93.8%
Methotrexate	17.2%
Azathioprine	34.4%
Mycophenolate	14.1%
Cyclosporin	6.3%
Cyclophosphamide	9.4%
IVIg	1.6%
Rituximab	3.1%
Belimumab	3.1%
Comorbidities	
Arterial hypertension	6.3%
Diabetes mellitus	0.0%
Thyroid disorder	29.7%
Chronic kidney disease [5]	0.0%
Tobacco use	12.5%
Assisted reproduction (IVF [6])	11.0% [7]
Previous obstetric history	
Primigravida	57.8%
Average no. pregnancies [8]	1.4
Adverse foetal outcome	26.6%

[1]For women with >1 pregnancies, data referring to the first pregnancy are included;
[2]first pregnancy monitored prospectively in the cohort study;
[3] within patients with history of hypocomplementaemia, median (IQR: interquartile range) serum C3 and C4 concentrations at conception were 77 (32) mg/dL and 11 (7) mg/dL, respectively;
[4]within patients with positive anti-cardiolipin and anti-β2-glycoprotein antibodies, median (IQR) IgG/IgM titres at conception were 120 (73) IU/mL and 44 (61) IU/mL, respectively;
[5]defined as estimated glomerular filtration rate <60 ml/min;
[6]*in vitro* fertilisation method; [7] IVF was used in 9 out of 82 pregnancies (no other methods of assisted reproduction were used);
[8]within women with previous pregnancy.

Table II. Foetal outcomes of SLE pregnancies (n=82).

Outcome	Median (IQR) or %
Live birth	83.0%
Elective abortion	1.2%
Foetal loss	
Early miscarriage (<10th week)	11.0%
Late miscarriage (10th-20th week)	2.4%
Stillbirth (>20th week)	2.4%
Preterm delivery	
Early (28th-33rd week)	2.4%
Moderate (34th-36th week)	17.1%
Late (≥37th week)	14.6%
Birth weight (g)	2850 (805)
Small for gestational age (<10th percentile weight for gestational age)	8.5%
Intra-uterine growth retardation	6.1%
Caesarean section delivery	56.1%
Any adverse foetal outcome [1]	53.7%

[1]Any of foetal loss, preterm delivery, SGA neonate.

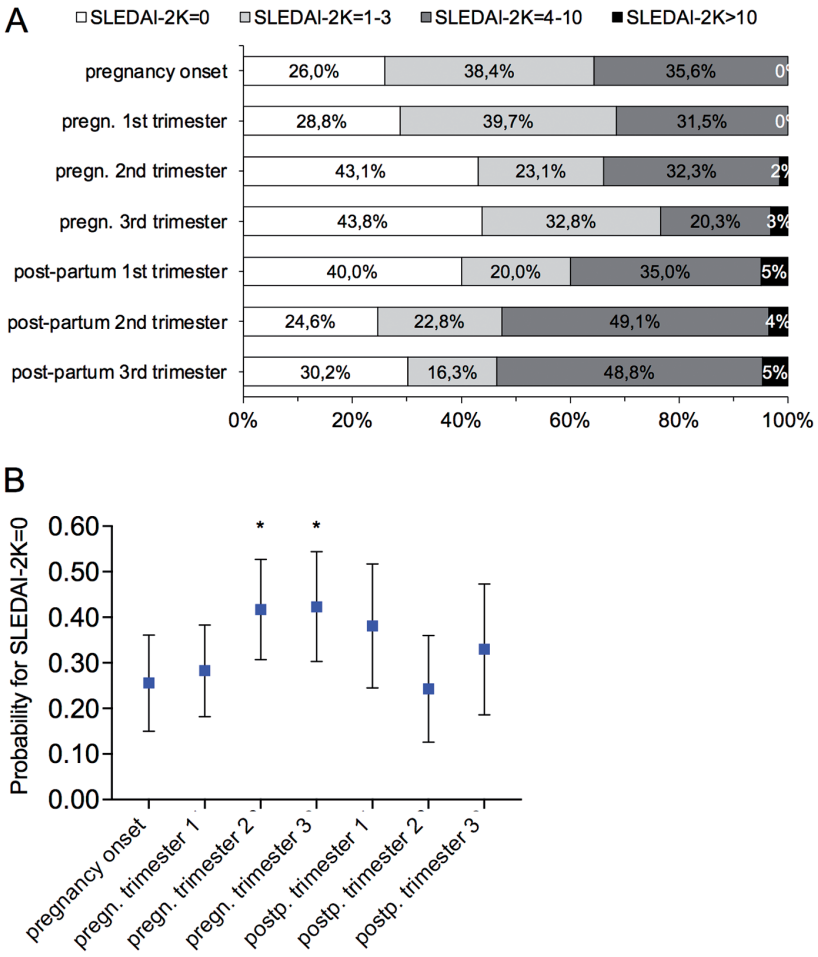

Fig. 1. Patterns of disease activity during pregnancy and post-partum in women with SLE.
A: SLEDAI-2K groups during pregnancy and post-partum; Data from n=73 (conception and 1st trimester), n=65 (2nd trimester), n=64 (3rd trimester), n=60 (post-partum trimester 1), n=57 (post-partum trimester 2) and n=43 (post-partum trimester 3).
B: Probability for complete remission (SLEDAI-2K=0) in women with SLE during pregnancy and post-partum; Linear mixed models treating sequential visits (conception to post-partum trimester 3) as repeated measures of SLEDAI-2K=0. Patients were introduced in the model as random effects. Plots represent the estimated marginal means ± 95% confidence intervals. *p<0.05 as compared to conception (F-test = 2.565; p=0.024).

SLEDAI-2K >3 and 9.9% had PGA >1. The majority (78.3%) met the LLDAS definition and 20.8% were in complete remission on-treatment. During pregnancy, the proportion of patients with SLEDAI-2K >3 at conception gradually decreased to 23.3% (3rd trimester), but increased postpartum reaching 53.8% at 6 to 9 months after birth. To obtain probability estimates for inactive SLE (SLEDAI-2K=0) during pregnancy and postpartum, while accounting for random interpatient variability, we used ordinal logistic mixed model analysis. The likelihood for inactive disease increased from 0.256 (mean estimate) to 0.417 and 0.423 at the 2nd and 3rd pregnancy trimester (p<0.05 for both comparisons), but decreased to 0.243 at the 2nd trimester postpartum (Fig. 1B). Collectively, our data indicate a tendency for SLE activity to decline during pregnancy, but may aggravate after labour.

Predictors for adverse foetal outcomes

In view of the high burden of foetal complications, we explored for respective risk factors at pregnancy onset. At univariate level, aPL positivity and increased disease activity (quantified by the SLEDAI-2K or PhGA) were associated with significantly increased odds for adverse foetal outcomes (foetal loss, preterm delivery, SGA neonate) (Table III), whereas other general risk factors shown non-significant trends (Suppl. Table S2). History of previous adverse foetal outcome and glucocorticoid intake showed non-significant trends (p<0.1). In accordance, attainment of LLDAS or remission were protective against adverse foetal outcomes. Specifically, patients on LLDAS at pregnancy onset were less likely to have foetal complications (48.1% *vs*. 80.0%, p=0.028), and those in remission had even lower risk (26.7% *versus* 59.6% for those not in remission, p=0.023) (Suppl. Fig. S1). In the multivariable-adjusted model, aPL positivity (OR 5.67) and LLDAS (OR 0.20) were retained as independent predictors (Table III).

Furthermore, we took advantage of the prospective study design to determine the effects of time-varying factors on the risk for adverse foetal outcome

in SLE women. Mixed models were implemented to account for partially matched data due to cases of pregnancy loss. In addition to aPL antibodies (β coefficient = 1.336), significant effects were revealed for longitudinal values of glucocorticoid intake (β=0.066 for dosage ≤7.5 mg/day, β=0.086 for dosage >7.5 mg/day prednisone equivalent) and disease activity (β=0.041 for PGA >1.0), independent of other covariates (Suppl. Table S3). Together, our results suggest that the risk for adverse foetal outcomes in SLE pregnancies may be determined by both fixed (aPL) and modifiable (disease activity, intake of glucocorticoids) factors.

SLE flares during pregnancy and postpartum and analysis of predictors

We addressed the incidence of flares in our cohort by analysing consecutive patient assessments spanning the gestation through 9 months postpartum. Approximately 70% of patients experienced at least one flare according to the SELENA-SLEDAI index, the majority of which were mild or moderate. The incidence rate (per 100 patient-years) was estimated to 77.2 and 17.7 for mild/moderate and severe flares, respectively (Table IV). Mild/moderate flares were distributed almost evenly across trimesters of pregnancy and postpartum (Fig. 2) and included mostly skin (48%) and musculoskeletal (51%) disease accompanied by addition/increase in hydroxychloroquine (26%) and/or glucocorticoids (37%). Severe flares occurred mostly after labour (Fig. 2) and were classified due to renal activity (proteinuria: 41%), vasculitis or increases in overall disease activity prompting the use of high-dose glucocorticoids, immunosuppressive or biological agents (65%).

As a next step, we sought to identify predictors for disease flares during gestation and postpartum. Disease activity at pregnancy onset (including attainment of LLDAS or remission) and use of medications, such as hydroxychloroquine, were not significantly associated. Nonetheless, the risk of flare could be predicted by certain disease features (classification criteria items) including history of alopecia, positive Coombs, low complement, and nephritis (OR range 5.09–10.34) (Table V).

Table III. Predictors at pregnancy onset for adverse foetal outcomes in patients with SLE.

Independent predictor	Univariate analysis Odds ratio (95% confidence interval), *p*-value	Multivariate analysis
Previous adverse foetal outcome	2.49 (0.85–7.32), p=0.097	–
Anti-phospholipid antibodies [1]	4.86 (1.46–16.20), *p*=0.010	5.67 (1.39–23.10), *p*=0.015
SLEDAI-2K		–
0	1.00 (reference)	
1–3	1.71 (0.52–5.64), *p*=0.375	
4–10	3.86 (1.11–13.46), *p*=0.034	
PhGA		–
<0.50	1.00 (reference)	
0.50–1.00	3.92 (1.28–12.05), *p*=0.017	
1.01–2.00	3.68 (0.68–21.19), *p*=0.145	
Glucocorticoids use		–
None	1.00 (reference)	
≤7.5 mg/day	2.02 (0.60–6.82), *p*=0.260	
>7.5 mg/day	6.72 (0.76–59.72), *p*=0.087	
LLDAS (yes *vs*. no)	0.23 (0.06–0.92), *p*=0.037	0.20 (0.05–0.81), *p*=0.024
Remission	0.25 (0.07–0.87), *p*=0.029	–

Logistic regression (backwards elimination model) treating adverse foetal outcome (any of foetal loss, preterm delivery, SGA neonate) as an outcome. Possible predictors (including general risk factors for pregnancy complications) were first evaluated by univariate analysis and variables associated with *p*-value <0.100 were considered for multivariate analysis (see also Supplementary Table S2).
[1]Any of anti-cardiolipin IgG or IgM, anti-β2-glycoprotein IgG or IgM, lupus anticoagulant.
[2]PhGA, physician global assessment. [3] LLDAS, low disease activity state as defined in (33).
[4]Remission defined as: (1) clinical SLEDAI-2K=0; (2) dose of prednisone ≤5 mg/day; and (3) with/without stable dose of immunosuppressants, biologicals, antimalarials (34).

Table IV. Disease flares during pregnancy and post-partum in SLE women. [1]

	Mild/moderate flares	Severe flares
Frequency (% patients with ≥1 flare)	59.2%	18.3%
no. flares per patient	0.96	0.22
Incidence rate (per 100 patient-year)		
Total observation period	77.2	17.7
Pregnancy	69.8	11.3
Post-partum	82.3	25.1
Distribution of flares episodes		
Trimester 1	12	1
Trimester 2	16	3
Trimester 3	9	2
Post-partum 1	12	4
Post-partum 2	13	4
Post-partum 3	11	3

[1]Classified according to the SELENA SLEDAI Flare Index.

Use of lupus medications during gestation and postpartum

The observation of increased disease activity and flares postpartum prompted us to examine the longitudinal patterns of medications in our study sample. At pregnancy onset, the majority of patients (74.3%) were receiving hydroxychloroquine, whereas glucocorticoids and immunosuppressives (mostly azathioprine) were used by 28.4% and 26.6%, respectively (Suppl. Table S4). The proportion of patients who reported use of the aforementioned treatments remained stable (or slightly increased) during gestation, however, it decreased post-labour. During the second and third trimester postpartum, the use of glucocorticoids and hydroxychloroquine remained almost unchanged but there was

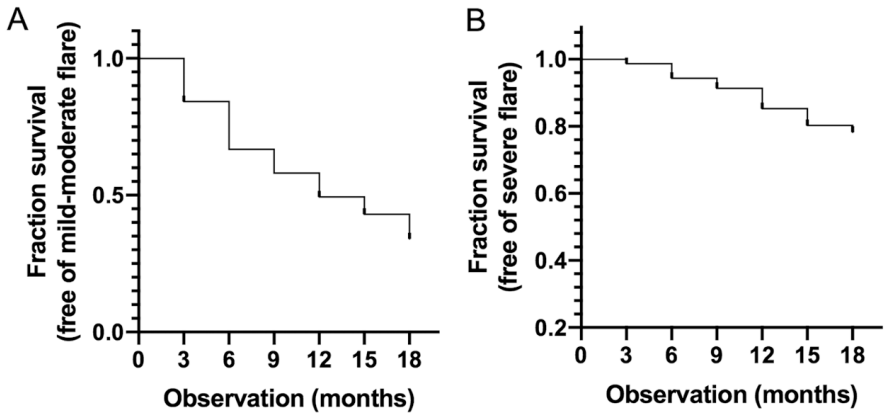

Fig. 2. Survival plots (flare-free) in SLE women during pregnancy and post-partum. Flare-free period of (**A**) mild/moderate and (**B**) severe flares.

Table V. Predictors at pregnancy onset for disease flares during pregnancy and post-partum in patients with SLE.

Independent predictor	Multivariate analysis Odds ratio (95% confidence interval), *p*-value
Outcome: mild/moderate flare	
Alopecia [1]	5.09 (1.48–17.55), *p*=0.010
Coombs test +ve [1]	5.17 (1.00–25.76), *p*=0.050
Outcome: severe flare	
Alopecia [1]	8.92 (2.06–38.54), *p*=0.003
Low complement [1]	10.34 (1.13–94.34), *p*=0.038
Biopsy-proven nephritis [1]	7.32 (0.98–54.61), *p*=0.052

Logistic regression (backwards elimination model) treating mild/moderate (top model) and severe (bottom model) flares as outcome. Possible predictors were first evaluated univariate analysis and variables associated with *p*-value <0.100 were considered for multivariate analysis.
[1]According to the 2012 SLICC classification criteria definition (25).

a gradual increase in the proportion of patients who were treated with immunosuppressive or biological agents, correlating with the corresponding increases in SLE activity (Fig. 1A-B, Fig. 2).

Discussion

We conducted a prospective study of 82 SLE pregnancies in a southern European population focusing on foetal and maternal outcomes (including disease flares) and the identification of associated risk factors. Contrary to previous studies evaluating the gestation period (10, 12, 21, 22), our monitoring extended up to 9 months postpartum, thus enabling to track disease and treatment changes during and after pregnancy. Although our patient sample may be considered as 'low risk' (Caucasian women with relatively low frequency of aPL antibodies, lupus nephritis, active/severe lupus at baseline), we observed a considerable burden of foetal complications and lupus flares, albeit of mild to moderate severity in the majority. Notably, attainment of low disease activity or remission at pregnancy onset was found to be protective against foetal complications but not lupus exacerbations, the latter being mostly predicted by disease phenotypic features.

The incidence of adverse foetal outcomes in lupus pregnancy varies among different studies (5, 7, 15, 37-45), which might reflect heterogeneity in cohort characteristics (14), study design and administered patient care. Importantly, most data originate from mixed populations and there are only a few reports in Caucasians. In our study, pregnancy loss (15.8%), pre-term birth (<37 weeks gestational age; 19.5%), IUGR (6.1%) and SGA neonate (8.5%) occurred at comparable rates with studies from Italy (11.4%, 25.7%, 5.0%, 22.8%, respectively) (45) and Portugal (5.7%, 24.3%, 13.2%, respectively) (46). We did not observe any neonatal deaths which is line with the very low rates reported elsewhere (46-48). Our results reiterate previous reports (35) underscoring that despite significant improvements (3, 49), still a considerable proportion of contemporary lupus pregnancies manifest poor foetal outcomes, especially miscarriages, premature and SGA births.

Identification of predictors for foetal complications is essential for risk stratification and optimised monitoring of SLE pregnancies (26). Our multivariate analysis revealed aPL positivity as the single predictor independently associated with adverse foetal outcomes, which corroborates previous observations (5, 8, 10, 26, 39, 46, 50-54). Notably, the prognostic impact of aPL stands out despite the fact that >80% of our aPL-positive/APS SLE patients received treatment with low-dose aspirin (alone or in combination with LMWH) since the early gestational stages, therefore emphasising an important therapeutic unmet need (26, 50).

A large body of evidence has emphasised the deleterious effect of active lupus on foetal prognosis (5, 7, 8, 26, 39, 46, 48, 55). In agreement, we found that patients on LLDAS (33) or remission (34) at pregnancy onset had better foetal outcomes (Table III, Suppl. Fig. S1). Additionally, our GEE model (Suppl. Table S3) demonstrated that active disease during longitudinal pregnancy assessments conferred increased risk for foetal complications. A similar effect was revealed for intake of glucocorticoids as previously described (11, 39, 47), although this association might as well be confounded by increased lupus activity. Our results are in line with a multicentre retrospective study in 212 pregnancies that reported a trend between complete SLE remission and reduced rates of adverse pregnancy outcomes (56). Together, these data further support the treat-to-target concept in SLE by extending its potential relevance to the disease management during gestation, although further studies will be required.

The risk for adverse foetal outcomes in lupus pregnancies may be modified by additional factors such as autoantibodies (39, 45), pre-existing or new-onset hypertension (5, 11, 37, 39, 57, 58),

high BMI (57-59) and renal involvement (past or ongoing) (7, 37, 42, 46, 55, 57, 58, 60). Such associations were not confirmed in our analysis, probably because of the low prevalence of the aforementioned features (hypertension 6.3%, lupus nephritis 20.3%) and the relatively small cohort size. The low rates of renal disease in our sample might be due to short disease duration (median 3.7 years), recruitment of cases seen not only in hospital/tertiary clinics but also in primary care, and inclusion of exclusively white patients known to have lower frequency of kidney involvement as compared to other racial groups. Notably, prevalence of nephritis ranged from 13.0% to 21.3% in contemporary lupus registries from Greece (61, 62). To this end, underrepresentation of lupus nephritis may have influenced favourably the pregnancy outcomes in our study.

An important finding was the high frequency of exacerbations consisting mostly of mild/moderate (59.2% of patients) rather than severe (18.3%) flares. Despite conflicting reports (20, 21, 38, 41, 46, 47), possibly due to differences in patient characteristics and history of active disease, study methodology, definition of flares and duration of follow-up, recent controlled (19, 48) and uncontrolled (39, 45, 55, 63) studies have demonstrated a tendency for increased SLE activity during and after pregnancy. We observed a higher incidence of flares during postpartum, in particular, rates of severe flares were more than 2-fold increased as compared to the gestation period. A similar trend has been illustrated by some (10, 19, 45) but not all (18, 63) studies, which however, focus on the first trimester post-partum. Our findings are in line with Götestam Skorpen *et al*. (13) who analysed 145 lupus pregnancies and found higher disease activity 6 and 12 months postpartum compared to the third trimester and 6 weeks postpartum. In agreement with previous reports, we identified history of lupus nephritis (12, 43, 64, 65) as a determinant for disease flares, together with alopecia, hypocomplementaemia (18, 22, 23, 58, 64, 66) and positive direct Coombs test, suggesting that the aforementioned patient groups require closer follow-up for the early detection and management of active disease. An association between flares and anti-Ro/SSA autoantibodies was previously shown (45), which implies that pregnant SLE patients with multiple immunological features may be at higher risk for relapse.

Evidence supports that treatment with antimalarials may mitigate the propensity of lupus to flare during pregnancy and/or post-labour (10, 19, 55, 56, 63, 64). In accordance, the European League Against Rheumatism (EULAR) recommends hydroxychloroquine in pregnant and/or lactating patients with SLE or APS (26, 67, 68). In our cohort, we did not detect a protective effect of the drug at pregnancy onset (*data not shown*), probably due to the relatively high proportion (74.3%) of patients receiving it. Remarkably, the use of hydroxychloroquine and azathioprine was reduced during puerperium (Suppl. Table S4). Although we did not specifically address the reasons for this change, it might have been driven by drug safety concerns over breastfeeding. Discontinuation of the aforementioned drugs predated increases in SLE activity observed during the second and third trimester postpartum (Fig. 1A-B, Table IV), although direct causal inferences cannot be drawn. These observations underscore the importance of routine disease assessments during pregnancy and the need for personalised treatment modifications decided upon a shared patient-physician basis (26).

Previously, Georgiou *et al*. (69) performed a single-centre, case-control study in 47 Greek SLE patients with 59 pregnancies monitored during the period 1982–1997. Notwithstanding some important differences in the baseline characteristics of those patients (all but one in remission, average age 24.3 years, 10% nephritis at conception), foetal loss (22.0%) and prematurity (17.0%) rates were comparable to our findings. A total 8 flares (n=6 with kidney involvement) were reported (13.6%) although follow-up was until 6 months post-delivery (69).

Our study has certain limitations to be acknowledged, such as the lack of a control group of non-pregnant SLE patients or healthy pregnant women, which precludes the estimation of relative risks for flares and other outcomes. To this end, our primary goal was to determine the frequencies of pregnancy complications and identify predictors within SLE pregnant women. As this was a multicentre study capturing data across different settings (from primary to tertiary), it would be challenging to assemble a control group of healthy pregnant women managed at the same settings. Moreover, although consecutive patients from multiple hospital and private rheumatology units were recruited, selection bias cannot be entirely excluded. Finally, our sample size is considered sufficient to determine the frequency and predictors of main study endpoints, however it may be underpowered to detect statistically significant associations with less frequent outcomes.

In conclusion, our study provides updated estimates of the outcomes of pregnancy and its effect on maternal prognosis in Greek patients with SLE. In a relatively 'low-risk' cohort, we demonstrated frequent adverse foetal outcomes, predominantly miscarriages, preterm delivery and SGA neonates, especially in patients who did not attain low disease activity or remission at pregnancy onset. SLE flares may occur during gestation but also, up to 9 months post-labour, although the majority are of mild or moderate severity. Our findings reiterate the recommendation for pregnancy planning and tight disease control at pregnancy onset in patients with SLE. Regular assessment of the foetus and the mother during pregnancy and postpartum is important to enhance the early detection of complications and optimise treatment modifications.

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