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Disease activity at conception predicts lupus flare up to two years after birth: A multicentre long term follow-up study

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ABSTRACT

Objective: To assess predicting factors that might influence systemic lupus erythematosus (SLE) disease activity in women in an extended follow-up period of two years after giving birth with clinical assessments every three months.

Methods: The study was design as an international retrospective study, enrolling 119 women with a first birth and with a two years follow-up.

Results: Joint involvement was present in 80% of patients, acute cutaneous in 64%, haematological in 54%, renal in 41% and 75% of patients were positive for anti-dsDNA. The mean SLE disease activity index 2000 (SLEDAI-2K) at diagnosis was 13.5±6.8 and at first birth was 2.8±4.4.

At follow-up, 51.3% of patients had at least one flare after a mean time after birth of 9±6.3 months (mean flare per patient 0.94±1.1). The most frequent flare manifestations were joint involvement (48%), renal (33%), cutaneous (28%) and haematologic (20%).

Patients with remission of disease (SLEDAI-2K=0; no clinical or laboratory manifestations of SLE) at conception had significantly lower rates of flares (18/49–37% vs. 43/70–61%; p=0.008).

Patients who experienced a flare during pregnancy (17 patients) had higher rates of flares during follow-up (76% vs. 47%; p=0.019), lower time for first flare (4.4±2.3 months vs. 10.3±6.5; p<0.001), lower rate of remission of

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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disease at conception (12% vs. 46%; p<0.001), lower rates of SLEDAI-2K at conception (5.9±5.6 vs. 2.3±4; p<0.001) and lower rates of exclusive breastfeeding (24% vs. 57%: p=0.009). Results were confirmed after performing multivariate analysis.
Conclusion: Remission at conception can influence SLE disease positively, even at long-term. Planned pregnancy counseling is fundamental when managing SLE patients.

Introduction

Autoimmune diseases, such as systemic lupus erythematosus (SLE) often concern young women during their childbearing years with heterogeneous clinical presentations and largely unpredictable course and prognosis [1,2]. In the past, pregnancy was discouraged in patients with SLE, due to the high frequency of maternal and fetal complications that can occur, especially in patients with uncontrolled disease activity and unplanned pregnancies [3–5]. Nowadays, despite the enormous progresses done in this field, the management of pregnancy in connective tissue diseases, and particularly in SLE, is a common yet challenging issue for the treating clinician and a significant burden for these young women. Immune system changes in pregnancy in women with SLE are well documented yet incompletely understood: they may interact in a positive or negative manner with the underlying autoimmune disease. Specifically, sex hormones are associated with SLE and its activity [6,7] and it is therefore not surprising that pregnancy itself, the post-partum period and breastfeeding (all situations in which sex hormones play vital roles) may affect SLE per se. It is well described that pregnancy affects the cell-mediated immunity, increased immunoglobulin-secreting cells, suppressive pregnancy-specific proteins and alterations in the Th1/Th2 cytokine balance [8–12]. The present literature reports a rate of SLE flares during pregnancy from 2, 5% to 68% [3,13–22]. However, there is less literature specifically assessing the immediate post-partum period (defined as up to six months after delivery) and the period in which women are breastfeeding.

Predisposing factors for developing flares during pregnancy are identified as active disease at conception, the use of prednisone during pregnancy, history of kidney involvement and close previous flares [16, 18,20].

While many existing studies focus on the immunological changes in women with SLE during pregnancy, there remains a paucity of data assessing SLE activity in the extended post-partum period of these women. This period may be extremely relevant, due to two reasons. Firstly, the time after pregnancy may be particularly important for women in that they may consider a further pregnancy (or not), and secondly because during this period a substantial number of women breastfeed their child.

In this study we aimed to assess predicting factors that might influence SLE disease activity in an extended follow-up period of two years after giving birth. We therefore designed an international retrospective, data-driven case collection study, involving centers with recognized expertise in the management of women with SLE during pregnancy and postpartum with a strictly monitored follow-up period of two years. Our hypothesis was that women with quiescent disease at the time of conception will experience less flares up to two years after giving birth.

Patients and methods

This multicenter retrospective study describes the fetal/perinatal and maternal outcomes of a cohort of patients with SLE who ever gave birth, who attended the following Health Institutions in a period lasting from 2000 to 2019 and with a follow-up of two years: the S. Giovanni Bosco Hospital (Turin, Italy), the Sant'Anna University Hospital (Turin, Italy), and the A.O.U. Mauriziano, Umberto I (Turin, Italy), Universidade Estadual do Rio de Janeiro (Rio de Janeiro, Brazil), Hospital Reina Sofia de Cordoba (Cordoba, Spain), Department of Experimental and Clinical Medicine, University of Firenze (Florence, Italy), Hokkaido University Hospital (Sapporo, Japan), National University of Cordoba (Cordoba, Argentina).

Data collection was performed retrospectively from clinical charts. Autoantibody detection [anti-nuclear antibodies (ANA), extractable nuclear antigens antibodies (ENA), anti-double strand DNA (anti-dsDNA) and antiphospholipid antibodies (aPL)] and laboratory profile (full blood count, creatinine, liver enzymes, complement levels, serum protein electrophoresis, immunoglobulins, electrolytes, urinalysis) were measured before conception, according to local standard of care adopted by all centers involved in the study.

Cardiovascular risk factors (including arterial hypertension, dyslipidaemia, diabetes, hormone replacement therapy and smoking) were assessed following the National Institute for Health and Care Excellence (NICE) guidelines [23]. Adjusted Global AntiPhosPholipid Syndrome Score (aGAPSS) of the patients was also calculated to further evaluate the thrombotic risk of the cohort [24].

Inclusion criteria:

- SLE classification (ACR 1997 criteria [25] and SLICC criteria [26]) prior to pregnancy,
- first birth after year 2000,
- follow-up of at least two years after the first birth.

Definitions to determine the activity of SLE:

a) **remission of disease*** [SLE disease activity index 2000(SLEDAI-2K) = 0; no clinical or laboratory manifestations of SLE] – 49 patients (41.2%),
b) **low Disease activity****,

b1) **very low disease activity** (SLEDAI-2K= 1-2) -26 patients (21.8%),
b2) **low disease activity** (SLEDAI-2K= 3-4) -24 patients (20.2%),

c) **No remission of disease** -20 patients (16.8%)
d) Δ SLEDAI-2K***

* defined according to DORIS definition [27] with Physician Global Assessment (PGA) ≤0.5, prednisone daily dose not higher than 5 mg and/ or immunosuppressive drugs on maintenance dose.

** defined according to the definition of the Asia Pacific Lupus Consortium: SLEDAI ≤4, which allows a low level of disease activity, without activity in major organ systems or new disease activity, PGA ≤1, prednisone daily dose not higher than 7.5 mg/day and/ or immunosuppressive drugs on maintenance dose (28).

***defined as the difference of highest SLEDAI-2K observed at follow-up with SLEDAI-2K at conception

Statistics

Categorical variables are presented as number (%) and continuous variables are presented as mean (S.D.). The significance of baseline differences was determined by the chi-squared test, Fisher's exact test or the unpaired t-test, as appropriate. Significance of univariate analysis were confirmed through the use of multivariate analysis. Correlation analysis, linear regression and Cox regression were also performed. A two-sided P-value <0.05 was statistically significant. All statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY,

USA).

Results

Patients characteristics of our multicenter cohort

The analysis included 119 women diagnosed with SLE with a first birth (mean age at conception 29.9 years, S.D. ±5.8; mean age at data collection 37.6 years old, S.D. ±7.4; mean disease duration at data collection 17.2 years, S.D. ±6.7; mean follow-up at data collection 15.4 years, S.D. ±6.9).

Sixteen patients (13.5%) also fulfilled the current criteria for antiphospholipid syndrome (APS) [29], while 32 (26.9%) patients tested persistently positive for aPL, without fulfilling the clinical criteria of APS [29]. Further, 10 (8.4%) patients also were diagnosed with Sjögren's Syndrome.

At diagnosis, joint involvement represented the most frequent clinical manifestation of the cohort (95 patients; 79.8%), followed by acute cutaneous manifestations (76 patients; 63.9%), haematological manifestations (64 patients; 53.8%), renal involvement (49 patients; 41.2%) and serositis (28 patients; 23.5%).

All patients were positive for ANA and, at diagnosis, 89 of them (74.8%) were also positive for anti-dsDNA. Furthermore, 58 patients (48.7%) were also found to be positive for ENA antibodies, of which anti-Ro/SSA positivity was the most common (44 patients; 37%), either alone or in combination with others ENA antibody, in particular 7 cases (5.9%) were positive for both anti-Ro/SSA and anti-La/SSB antibodies. In 34 cases (28.6%), anti-Sm antibodies were detected, 24 patients (20.2%) tested positive for anti-RNP antibodies, one patient tested positive for anti-U1RNP antibodies and one patient for anti-Scl70 antibodies. Furthermore, 77 patients (64.7%) presented with low complement levels and 28 (23.5%) with positive direct coombs test. The mean SLEDAI-2K at diagnosis was 13.5 (S.D. ±6.78). Demographic and diagnostic characteristics of the patients included in the study are summarized in Table 1.

Previous to the first birth most of the patients were treated with hydroxychloroquine (HCQ) (104 patients; 87.4%), 49 (41.2%) only received low doses of steroids (<=7.5 mg of prednisone/daily), while 70 patients (58.8%) required medium to high doses of steroids (>7.5 mg of prednisone/daily). The most common immunosuppressive drug used in the cohort was azathioprine (AZA) (41 patients; 34.5%), followed by Mycophenolate Mofetil (27 patients; 22.7%).

Table 1
Clinical and laboratory characteristics of the cohort.

Demographics	
Age at inclusion, years, mean ±S.D.	37.6 ±7.36
Age at conception, years, mean ±S.D.	29.85 ±5.75
Secondary Diagnosis	
APS, n (%)	16 (13.5)
Sjögren, n (%)	10 (8.4)
Clinical SLE characteristics at diagnosis	
Acute cutaneous , n (%)	76 (63.9)
Malar rash, n (%)	57 (48)
Subacute lesions, n (%)	7 (5.9)
Photosensitivity, n (%)	21 (17.6)
Chronic cutaneous manifestations, n (%)	11 (9.2)
Oral/nasal ulcers, n (%)	43 (36.13)
Non scarring alopecia, n (%)	41 (34.5)
Joint, n (%)	95 (79.8)
Serositis, n (%)	28 (23.5)
Pleuritis, n (%)	17 (14.3)
Pericarditis, n (%)	14 (11.8)
Renal, n (%)	49 (41.2)
Biopsy-proven Lupus Nephritis, n (%)	32 (26.9)
Neurologic, n (%)	8 (6.72)
Haematological, n (%)	64 (53.8)
Haemolytic anaemia, n (%)	19 (16)
Leukopenia, n (%)	43 (36.1)
Thrombocytopenia, n (%)	26 (21.9)
Laboratory characteristics at diagnosis	
ANA, n (%)	119 (100)
anti-dsDNA, n (%)	89 (74.8)
ENA, n (%)	58 (48.7)
anti-Sm, n (%)	34 (28.6)
anti-Ro/SSA, n (%)	44 (37)
anti-Ro/SSA and anti –La/SSB, n (%)	7 (5.9)
anti-RNP, n (%)	24 (20.2)
anti-U1RNP, n (%)	1 (0.8)
anti-Scl 70, n (%)	1 (0.8)
Antiphospholipid antibodies, n (%)	48 (40.3)
Lupus anticoagulant, n (%)	26 (21.8)
Anticardiolipin antibodies (IgG/IgM), n (%)	34 (28.6)
Anti-β2 Glycoprotein1 antibodies (IgG/IgM), n (%)	9 (7.6)
Low complement, n (%)	77 (64.7)
Positive Direct Coombs test, n (%)	28 (23.5)
Comorbidities	
Arterial hypertension, n (%)	19 (16)
Hyperlipidemia, n (%)	8 (6.7)
Diabetes, n (%)	0 (0)
aGAPSS, mean ±S.D.	2.97 ±3.6
Previous venous thrombosis, n (%)	8 (6.7)
Previous arterial thrombosis, n (%)	3 (2.5)

APS = antiphospholipid syndrome; SLE = systemic lupus erythematosus; ANA = anti-nuclear antibodies; anti-dsDNA = anti-double stranded DNA antibodies; anti-Sm = anti-Smith antibodies; ENA = extractable nuclear antigens antibodies; Adjusted Global AntiPhosPholipid Syndrome Score = aGAPSS.

First Birth, breastfeeding and other pregnancies of the cohort

During the pregnancy of the first birth, the majority of patients were treated with HCQ (101 patients; 84.9%), 66 (55.5%) received low doses of steroids (<=7.5 mg of prednisone/daily), while 28 patients (23.5%) received medium to high doses of steroids (>7.5 mg of prednisone/daily).

Fifty-two patients (43.7%) received low-dose aspirin and 29 (24.4%) cases were treated with low molecular weight heparin during pregnancy. Immunosuppressant treatment with AZA was given in 39 (32.9%) women and Cyclophosphamide (CYC), intravenous immunoglobulins and tacrolimus were used in two cases (1.7%). Further information on the treatment undergone by the patients (previous to first birth and during pregnancy of the first birth) is described in Table 2.

The mean SLEDAI-2K at conception of the first birth of the patients was 2.8 (S.D. ±4.35). Twenty patients (16.8%) were not in remission or with low disease activity at conception, as previously described. Only two patients did not achieve a resolution of clinical manifestations within 3 months of pregnancy (with a case of persistent thrombocytopenia and one of worsening of proteinuria). A total of 17 patients (14.3%) experienced a disease flare during pregnancy and required a change in the therapy. The most common affected domain of lupus flare was joint (10/17 flares), followed by renal (4/17), hematological (3/17) and cutaneous (2/17). The patients were treated with a prednisone increase >7.5 mg/daily (7/17) or ≤7.5 mg/daily (4/17), with pulses of methylprednisone (3/17), initiation of AZA (6/17) or CYC (2/17).

A total of 87 patients (73.1%) breastfed after first birth (any type of breastfeeding) for a mean duration of 10.3 ±10 months. Sixty-two patients (29%) exclusively breastfed after first birth, for a mean duration of 6.1 ±6 months.

When looking at pregnancy complications of first birth, 2 cases of intrauterine growth restriction, 2 cases of pre-eclampsia and 1 case of neonatal lupus were reported.

When considering all the reported pregnancies of the cohort, beyond first pregnancy, a total of 214 pregnancies were recorded. In more detail, we observed a live rate birth of 79% (169 total of live births out of 214 pregnancies), with a total of 37 miscarriages (17.3%) and 8 (3.7%) stillbirths.

Pregnancy outcomes of all pregnancies and relative breastfeeding data of the patients included in the study are resumed in Table 3.

Table 2
Treatment undergone by the patients (previous to first birth and during pregnancy of the first birth).

Treatment Prior to pregnancy	
Statins, n (%)	4 (3.7)
HCQ, n (%)	104 (87.4)
Anti-hypertensive, n (%)	39 (32.8)
Low doses of steroids (<=7.5 mg of prednisone/daily), n (%)	76 (63.9)
Medium to high doses of steroids (>7.5 mg of prednisone/daily), n (%)	70 (58.8)
IVIG, n (%)	4 (3.4)
MTX, n (%)	15 (12.6)
AZA, n (%)	41 (34.5)
MMF, n (%)	27 (22.7)
CYC, n (%)	29 (24.4)
RTX, n (%)	6 (5)
Belimumab, n (%)	3 (2.5)
During pregnancy	
HCQ, n (%)	101 (84.9)
Low dose of aspirin, n (%)	52 (43.7)
Low molecular weight heparins, n (%)	29 (24.4)
Low dose of Steroids (<=7.5 mg of prednisone daily), n (%)	66 (55)
Medium to high dose of Steroids (>7.5 mg of prednisone daily) , n (%)	28 (23.5)
AZA, n (%)	39 (32.8)
IVIG, n (%)	2 (1.7)
Tacrolimus, n (%)	2 (1.7)
CYC, n (%)	2 (1.7)

HCQ – Hydroxychloroquine; MTX – Methotrexate, MMF – Mycophenolate Mofetil; CYC – Cyclophosphamide; RTX – Rituximab; AZA – Azathioprine; IVIG – Intravenous Immunoglobulins.

Table 3
Pregnancy outcomes of all pregnancies and relative breastfeeding data.

Pregnancy Characteristics	All (214)	%
Outcomes		
Live births	169	79
Miscarriages	37	17.3
Stillbirths	8	3.7
Maternal and Foetal Complications		
Prematurity	39	18.2
Pre-eclampsia	23	10.7
HELLP syndrome	4	1.9
Placental Infarction	12	5.6
Breastfeeding (all pregnancies)		
Any breastfeeding	109	64.5*
Exclusive breastfeeding	87	51.5*
Breastfeeding (after first birth)		
Any breastfeeding	87	73.1**
Any breastfeeding duration (months), mean ±S.D.	10.29 ±10.04	
Exclusive breastfeeding***	62	52.1**
Exclusive breastfeeding*** duration (months), mean ±S.D.	6.07±6	

* Percentages are calculated considering viable babies (total= 169)
** Percentages are calculated considering first birth (total= 119)
*** Exclusive breastfeeding was defined as feeding infants only breast milk

Flares within two years of follow-up

Patients were followed-up for two years after birth, with regular check-ups and updates every three months, including clinical visit with assessment of SLEDAI-2K and laboratory testing.

At follow-up, 61 patients (51.3%) had at least one flare of disease [30], with a total of 85 flares (mean flare per patient 0.94 ±1.1). The first flare at follow-up occurred after a mean time after birth of 9 ±6.3 months with a mean increase of SLEDAI-2K (when compared to SLEDAI-2K at conception) of 6.8 ±4.3 points and a mean duration of 5.1 ±4.1 months. In sixteen cases (26.2%) the first flares involved more than one clinical domain. The most frequent domain of the first flare were joint involvement (29 flares out of 61; 47.5%), followed by renal (20 flares; 32.8%), cutaneous (17 flares; 27.9%) and hematologic (12 flares; 19.7%) involvement. The evaluation of all 85 flares at follow-up showed a mean cumulative duration of all flares of 7.1 ±4.8 months, with a mean increase of SLEDAI-2K (when comparing SLEDAI-2K at conception with the flare with the highest SLEDAI-2K) of 7.4 ±4.4 points. The distribution of clinical domains in all flares was similar to that of the first flare during the follow-up. Flares' domains (first flare) are illustrated in Fig. 1 and in Table S1.

Patients with remission of disease at conception had significantly lower rates of flares during follow-up when compared to the others (18/49; 36.7% vs. 43/70; 61.4%; p= 0.008). The statistical difference was conserved when analyzing the difference of patients in remission and patients with low disease activity at conception compared to the others (32/75; 42.7% vs. 29/44; 65.9%; p= 0.014). Furthermore, when considering only patients that developed flares during follow-up (61 patients), patients in remission at conception (18 patients) when compared to the others (43 patients) had significantly lower number of flares at follow-up (1.1 ±0.32 vs. 1.5 ±0.7; p= 0.003), lower cumulative duration of all flares (4.8 ±3.1 months vs. 8 ±5.1; p= 0.004) and longer duration of any breastfeeding (10.1 ±11.8 months vs. 5.9 ±8.2; p= 0.024), respectively. In addition, patients that were negative for anti-dsDNA antibodies at conception had lower rate of flares during follow-up (67% vs. 82%; p= 0.008).

Patients who experienced flare during pregnancy (17 patients) also had higher rates of flares during follow-up (76% vs. 47%, respectively; p= 0.019), lower time for first flare (4.4 ±2.3 months vs. 10.3 ±6.5, respectively; p<0.001), lower rate of remission of disease at conception (12% vs. 46%, respectively; p<0.001), lower rates of SLEDAI-2K at conception (5.9 ±5.6 vs. 2.3 ±4, respectively; p<0.001) and lower rates of exclusive breastfeeding (24% vs. 57%, respectively; p=0.009).

Both remission of disease and flares during pregnancy remained significantly associated with the development of flares during follow-up after multivariate analysis. However, when considering the prediction of flares during follow-up by running a regression analysis, remission was significantly associated with flares at follow-up (standardized ß -0.205; p=0.027, CI -0.039-0.24), while the development of flares during pregnancy did not remain significant. Finally, the cumulative hazard ratio (HR) for development of flares during follow-up considering remission was of – 2 (statistically significant, with 95% confidence intervals 1.2 – 3.5). Fig. 2 shows the comparison of flares proportion of survival curves and relative confidence intervals based on remission status at conception.

Differences in SLEDAI-2K at conception positively correlated with the number of flares developed during follow-up (Pearson correlation 0.381; p= 0.002), cumulative duration of all flares (Pearson correlation 0.274; p= 0.033), and with total Δ SLEDAI-2K, defined as the difference of highest SLEDAI-2K observed at follow-up with SLEDAI-2K at conception (Pearson correlation 0.409; p= 0.001). Furthermore, SLEDAI-2K at conception negatively correlated with the cumulative duration of any breastfeeding undergone by patients (Pearson correlation -0.226; p= 0.015). A graphical representation of the correlation analysis performed is showed in Fig. S1.

When considering possible differences in first flares domains, we observed significant differences between patients in remission at conception when compared to the others for the occurrence of hematological flares (4% vs. 14%, respectively; p= 0.047), cutaneous flares (6% vs. 20%, respectively; p= 0.021), joint flares (10% vs. 34%, respectively; p= 0.002), while no differences were observed when considering renal flares (16% vs. 17%, respectively; non-significant). No differences regarding renal involvement were also observed when considering all the flares at follow-up between groups (16% vs. 23%, respectively; non-significant), while the significance was maintained for all the other flare domains and was observed also for the serositis domain (0% vs. 7%, respectively; p= 0.024). Interestingly, we observed a statistically significant correlation between the occurrence of first renal flare at follow-up and renal involvement at diagnosis (Pearson 0.516; p <0.001). A similar observation was noted when considering

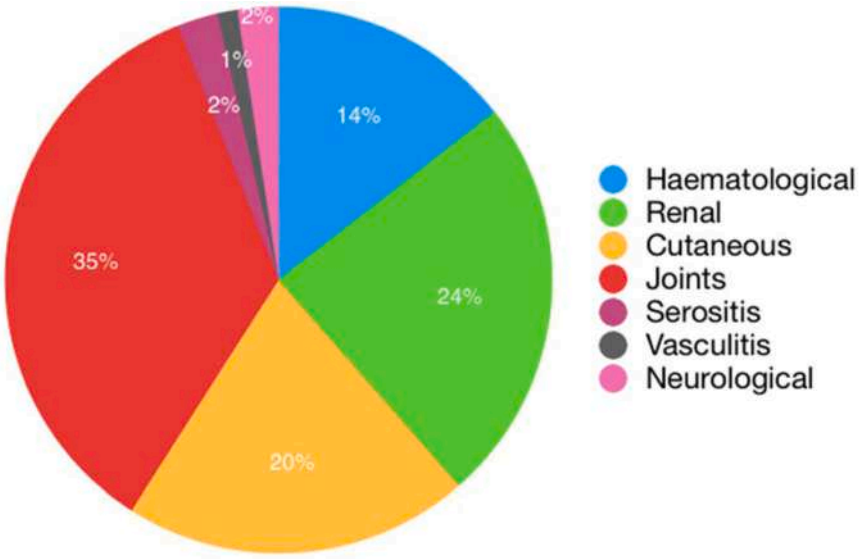

Fig. 1. Graphical representation of flares' domains (first flare) experienced by the patients included in the study during the follow-up.

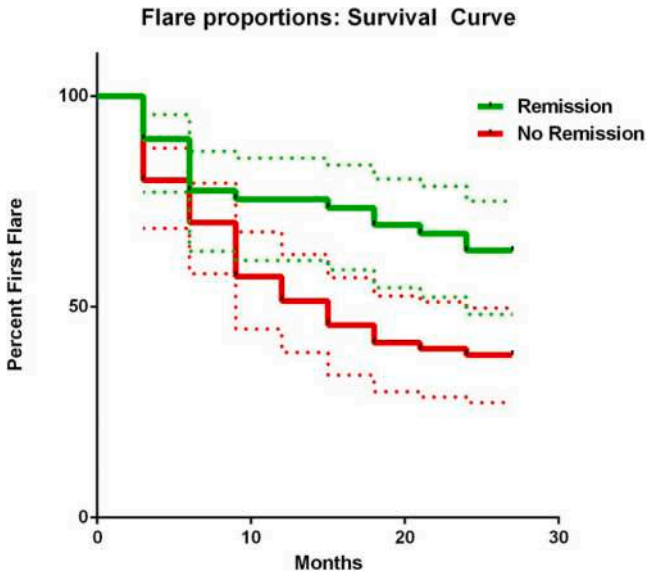

Fig. 2. Flare proportion: Survival Curve based on remission status at conception of the patients included in the study.

cutaneous involvement (Pearson 0.261; p = 0.004).

Discussion

Herein we present the results of our multicenter cohort of women with SLE. Approximately half of our patients experienced at least one flare at follow-up of 2 years and the first flare occurred after a mean time after birth of 9 ±6.3 months with a mean increase of SLEDAI-2K (when compared to SLEDAI-2K at conception) of 6.8 ±4.3 points and a mean duration of flare of 5.1 ±4.1 months.

It is well established that quiescent disease at conception is a predictor for favorable pregnancy outcomes in patients with SLE and low disease state or remission should be achieved when planning a pregnancy [31,32]. In fact, major risk factors for adverse maternal outcomes, as well as fetal, are known to include active SLE disease (especially if renal involvement is present or there is an history of renal disease) as stated by the EULAR recommendations for pregnancy in SLE [32]. However, it is still a matter of discussion how quiescent the disease should be and what should be the optimal way for clinicians to define it. Importantly, definitions of remission such as DORIA and DORIS [27,33] combine physician's assessment (defined with PGA), disease specific scoring (SLEDAI score) and ongoing immunosuppressive therapy to differentiate between different grades of remission. Importantly, quiescent disease ranges from clinical remission (either on treatment or not) to complete remission and understanding that difference is pivotal. Franklyn et al. introduced the concept of Lupus Low Disease Activity State (LLDAS), defined as patients with a SLEDAI-2K score of ≤4 with no major organ involvement, no new activity compared to previous assessment and PGA ≤1 [28].

Is it relevant to differentiate between low disease activity to very low disease activity (in our study defined as SLEDAI-2K = 1-2) and remission of the disease when considering SLE patients that are planning a pregnancy? Our results show that patients with complete remission of the disease, even when compared to patients with low and very low disease activity (assessed with SLEDAI-2K) were the patients with the lowest rates of flares during follow-up and the cumulative HR for development of flares during follow-up considering remission was two-fold decreased (CI 1.2 – 3.5). We then decided to focus on the extended post-partum period of these women in order to assess the importance of quiescent disease and its impact on an extended period of time. An extended remission of disease deeply influences patients' life, as it can influence their decision of breastfeeding or they may or may not plan further pregnancies within 2 years of a childbirth. It has previously been shown that pregnancy negatively influences the incidence of flares of an SLE patient [22,34,35], when we designed the study, we postulated that any flare prior to a pregnancy potentially not only affects the immediate pregnancy but also subsequent family planning and potential pregnancies. Further, our data show that flares' domain prior to pregnancy also affect the duration of breastfeeding post-partum. In our cohort, patients who developed flares during follow-up (61 patients), patients in remission at conception (18 patients) had significantly lower number of flares at follow-up (p= 0.003), lower cumulative duration of all flares (p= 0.004) and longer duration of any breastfeeding (p= 0.024).

Furthermore, while some evidence exists on the quality of lupus flares during pregnancy and it is hypothesized that lupus in pregnancy mimics lupus prior to pregnancy [36], our results showed that when focusing on organ flares, patients with previous renal involvement experienced more renal flares during follow-up and, interestingly, the occurrence of flares at follow-up occurred independently of remission.

Our flare rate is at the high end of the previously reported flare rates

of other cohorts, who assessed flare rates during pregnancy [3,14–22]. The high flare rate in our cohort may be partially due to the heterogeneity of the cohorts of the participating centres. Cultural influence might also play a pivotal role, especially when considering breastfeeding in our study. Our numbers were however too small to stratify the analysis according to the enrolling centre, but one should consider that all centers that participated in the study are specialized in the management of rheumatic patients in pregnancy. Importantly, one should mention that all patients received pregnancy counseling, were managed during pregnancy by multidisciplinary teams and strictly followed-up, which alone might influence the findings of our study[37].

Our data contribute to the currently available evidence further highlighting the importance of pregnancy counseling and disease control prior to conception as disease flares potentially have impact on a significant period of time post-partum. Our data also support the concept of close follow-up during pregnancy, as flares during pregnancy were associated with higher flares during follow-up. We also show that breastfeeding is affected by flares that happen pre-pregnancy, drawing attention to the fact that maternal disease activity not only has a direct impact on the mother, but also directly affects the baby and possibly also the bond between mother and child. We will need adequately designed studies to assess whether our finding translates to prospective studies and as to which extend a single flare pre-pregnancy affects the subsequent period post-partum, the choice of having a further child, breastfeeding patterns and perhaps even the bond between mother and child.

Despite the retrospective design of our study, the extreme importance of disease control prior to pregnancy once more receives attention.

This study has some limitations. First, the design of the study is retrospective in nature, and this might have a considerable impact when considering the reproducibility of the results. Second, an intrinsic potential enrollment bias cannot be excluded. Third, as reported above, the population of the included patients was heterogeneous, both in terms of socioeconomic status that in severity of disease and organ involvement. Some strengths need also to be acknowledged. First, the large number of SLE patients, that were regularly followed-up every three months by specialized centers with multidisciplinary teams tailored to the care of pregnancy in rheumatic diseases. Second, according to the stringent inclusion criteria of the study, pregnancy only from 2000 to 2019 were included, in order to reflect current standard of care of pregnancy in women with SLE and overall to improve the homogeneity of obstetric care in the cohort.

In conclusion, our study has some important messages. First the results of our study highlight how remission at conception can truly positively influence SLE disease course, even at long-term follow-up. Second, we demonstrate the importance of planned pregnancy counseling when managing patients with SLE and show the importance that pregnancy counseling and close follow-up during pregnancy may have for future pregnancies in these women.

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Data availability

Data will be available upon reasonable request.

Patients and public involvement statement

Patients were not involved in this study.

Declaration of Competing Interest

None declared.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.152113.

References

[1] Somers EC. Pregnancy and autoimmune diseases. Best Practice and Research: Clinical Obstetrics and Gynaecology, 64. Bailliere Tindall Ltd; 2020. p. 3–10. Available from: https://pubmed.ncbi.nlm.nih.gov/32173263/.
[2] Tincani A, Nalli C, Khizroeva J, Bitsadze V, Lojacono A, Andreoli L, et al. Autoimmune diseases and pregnancy. Best Practice and Research: Clinical Endocrinology and Metabolism, 33. Bailliere Tindall Ltd; 2019. Available from: https://pubmed.ncbi.nlm.nih.gov/31542218/.
[3] Clowse MEB, Magder LS, Witter F, Petri M. The impact of increased lupus activity on obstetric outcomes. Arthritis Rheum 2005;52(2):514–21. Available from: https://pubmed.ncbi.nlm.nih.gov/15692988/.
[4] Georgiou PE, Politi EN, Katsimbri P, Sakka V, Drosos AA. Outcome of lupus pregnancy: a controlled study. Rheumatology (Oxford) 2000;39(9):1014–9. Available from: https://pubmed.ncbi.nlm.nih.gov/10986308/.
[5] Clark CA, Spitzer KA, Nadler JN, Laskin CA. Preterm deliveries in women with systemic lupus erythematosus. J Rheumatol 2003;30(10):2127–32. Available from: https://pubmed.ncbi.nlm.nih.gov/14528505/.
[6] Christou EAA, Banos A, Kosmara D, Bertsias GK, Boumpas DT. Sexual dimorphism in SLE: above and beyond sex hormones. Lupus 2019;28(1):3–10. Available from: https://pubmed.ncbi.nlm.nih.gov/30501463/.
[7] Singh RP, Bischoff DS. Sex hormones and gender influence the expression of markers of regulatory T cells in SLE patients. Front Immunol 2021;12:619268. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7966510/.
[8] Gluhovschi C, Gluhovschi G, Petrica L, Velciov S, Gluhovschi A. Pregnancy associated with systemic lupus erythematosus: immune tolerance in pregnancy and its deficiency in systemic lupus erythematosus - an immunological dilemma. J Immunol Res 2015;2015. Hindawi LimitedAvailable from: https://pubmed.ncbi.nlm.nih.gov/26090485/.
[9] Doria A, Cutolo M, Ghirardello A, Zen M, Villalta D, Tincani A, et al. Effect of pregnancy on serum cytokines in SLE patients. Arthritis Res Ther 2012;14(2). Available from: https://pubmed.ncbi.nlm.nih.gov/22417776/.
[10] Doria A, Ghirardello A, Iaccarino L, Zampieri S, Punzi L, Tarricone E, et al. Pregnancy, cytokines, and disease activity in systemic lupus erythematosus. Arthritis Care Res 2004;51(6):989–95. Available from: https://pubmed.ncbi.nlm.nih.gov/15593367/.
[11] Björkander S, Bremme K, Persson JO, van Vollenhoven RF, Sverremark-Ekström E, Holmlund U. Pregnancy-associated inflammatory markers are elevated in pregnant women with systemic lupus erythematosus. Cytokine 2012;59(2):392–9. Available from: https://pubmed.ncbi.nlm.nih.gov/22633082/.
[12] De Carolis S, Moresi S, Rizzo F, Monteleone G, Tabacco S, Salvi S, et al. Autoimmunity in obstetrics and autoimmune diseases in pregnancy. Vol. 60, Best Practice and Research: Clinical Obstetrics and Gynaecology. Bailliere Tindall Ltd 2019:66–76. Available from: https://pubmed.ncbi.nlm.nih.gov/31133364/.
[13] Kim MY, Guerra MM, Kaplowitz E, Laskin CA, Petri M, Branch DW, Lockshin MD, Sammaritano LR, Merrill JT, Porter TF, Sawitzke A, Lynch AM, Buyon JP, Salmon JE. Complement activation predicts adverse pregnancy outcome in patients with systemic lupus erythematosus and/or antiphospholipid antibodies. Ann Rheum Dis 2018;77(4):549–55. Available from: https://pubmed.ncbi.nlm.nih.gov/29371202/.
[14] Urowitz MB, Gladman DD, Farewell VT, Stewart J, Mcdonald J. Lupus and pregnancy studies. Arthritis Rheum 1993;36(10):1392–7. Available from: http://doi.wiley.com/10.1002/art.1780361011.
[15] Carvalheiras G, Vita P, Marta S, Trovão R, Farinha F, Braga J, et al. Pregnancy and systemic lupus erythematosus: review of clinical features and outcome of 51 pregnancies at a single institution. Clin Rev Allergy Immunol 2010;38:302–6. Available from: https://pubmed.ncbi.nlm.nih.gov/19603147/.
[16] Chakravarty EF, Colón I, Langen ES, Nix DA, El-Sayed YY, Genovese MC, et al. Factors that predict prematurity and preeclampsia in pregnancies that are complicated by systemic lupus erythematosus. Am J Obstet Gynecol 2005: 1897–904. Am J Obstet GynecolAvailable from: https://pubmed.ncbi.nlm.nih.gov/15970846/.
[17] Clowse MEB, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum 2006;54(11):3640–7. Available from: https://pubmed.ncbi.nlm.nih.gov/17075810/.
[18] Cortes-Hernandez J, Ordi-Ros J, Paredes F, Casellas M, Castillo F, Vilardell-Tarres M. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: a prospective study of 103 pregnancies. Rheumatology (Oxford) 2002;41(6):643–50. Available from: https://pubmed.ncbi.nlm.nih.gov/12048290/.
[19] Cavallasca JA, Laborde HA, Ruda-Vega H, Nasswetter GG. Maternal and fetal outcomes of 72 pregnancies in Argentine patients with systemic lupus erythematosus (SLE). Clin Rheumatol 2008;27(1):41–6. Available from: https://pubmed.ncbi.nlm.nih.gov/17516127/.

[20] Gladman DD, Tandon A, Ibañez D, Urowitz MB. The effect of lupus nephritis on pregnancy outcome and fetal and maternal complications. J Rheumatol 2010;37 (4):754–8. Available from: https://pubmed.ncbi.nlm.nih.gov/20231194/.
[21] Petri M, Howard D, Repke J. Frequency of lupus flare in pregnancy: the hopkins lupus pregnancy center experience. Arthritis Rheum 1991;34(12):1538–45. Available from: https://pubmed.ncbi.nlm.nih.gov/1670196/.
[22] Ruiz-Irastorza G, Lima F, Alves J, Khamashta MA, Simpson J, Hughes GRV, et al. Increased rate of lupus flare during pregnancy and the puerperium: a prospective study of 78 pregnancies. Br J Rheumatol 1996;35(2):133–8. Available from: https://pubmed.ncbi.nlm.nih.gov/8612024/.
[23] D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham heart study. Circulation 2008;117(6):743–53. Availablefrom, https://pubmed.ncbi.nlm.nih.gov/18212285/.
[24] Sciascia S, Radin M, Sanna G, Cecchi I, Roccatello D, Bertolaccini ML. Clinical utility of the global anti-phospholipid syndrome score for risk stratification: a pooled analysis. Rheumatology (Oxford) 2018;57(4):661–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29342292.
[25] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40(9). Available from: https://pubmed.ncbi.nlm.nih.gov/9324032/.
[26] Petri M, Orbai A-M, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64 (8):2677–86. Available from: https://pubmed.ncbi.nlm.nih.gov/22553077/.
[27] van Vollenhoven R, Voskuyl A, Bertsias G, Aranow C, Aringer M, Arnaud L, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). Ann Rheum Dis 2017;76(3): 554–61. Available from: https://pubmed.ncbi.nlm.nih.gov/27884822/.
[28] Franklyn K, Lau CS, Navarra SV, Louthrenoo W, Lateef A, Hamijoyo L, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). Ann Rheum Dis 2016;75(9):1615–21. Available from: https://pubmed.ncbi.nlm.nih.gov/26458737/.
[29] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4(2):295–306. Available from: https://pubmed.ncbi.nlm.nih.gov/16420554/.
[30] Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus 1999;8(8):685–91. Available from: https://pubmed.ncbi.nlm.nih.gov/10568907/.
[31] Tani C, Zucchi D, Haase I, Larosa M, Crisafulli F, Strigini FAL, et al. Are remission and low disease activity state ideal targets for pregnancy planning in systemic lupus erythematosus? A multicentre study. Rheumatology (Oxford) 2021;60(12): 5610–9. Available from: https://pubmed.ncbi.nlm.nih.gov/33590843/.
[32] Andreoli L, Bertsias GK, Agmon-Levin N, Brown S, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis 2017;76(3):476–85. Available from: https://pubmed.ncbi.nlm.nih.gov/27457513/.
[33] Zen M, Iaccarino L, Gatto M, Bettio S, Nalotto L, Ghirardello A, Punzi L, Doria A. Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. Ann Rheum Dis 2015;74(12):2117–22. Available from: https://pubmed.ncbi.nlm.nih.gov/26223434/.
[34] Petri M, Howard D, Repke J. Frequency of lupus flare in pregnancy. The Hopkins Lupus Pregnancy Center experience. Arthritis Rheum 1991;34(12):1538–45. Available from: https://pubmed.ncbi.nlm.nih.gov/1670196/.
[35] Eudy AM, Siega-Riz AM, Engel SM, Franceschini N, Howard AG, Clowse MEB, Petri M. Effect of pregnancy on disease flares in patients with systemic lupus erythematosus. Ann Rheum Dis 2018;77(6):855–60. Available from: https://pubmed.ncbi.nlm.nih.gov/29463519/.
[36] Tedeschi SK, Massarotti E, Guan H, Fine A, Bermas BL, Costenbader KH. Specific systemic lupus erythematosus disease manifestations in the six months prior to conception are associated with similar disease manifestations during pregnancy. Lupus 2015;24(12):1283–92. Available from: https://pubmed.ncbi.nlm.nih.gov/25972367/.
[37] Braun J, Krause A, Aringer M, Burmester G, Bessler F, Engel JM, et al. [Standards of care for people with rheumatoid arthritis in Europe : Translation and comments of the eumusc.net recommendations supported by EULAR performed by a national task force of the professional organisations DGRh and VRA supported by "Deutsche Rheu. Z Rheumatol 2016;75(4):416–28. Available from: https://pubmed.ncbi.nlm.nih.gov/27138788/.