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Effect of pregnancy on disease flares in patients with systemic lupus erythematosus

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Abstract

Objective—Prior studies found conflicting results about whether lupus is likely to flare during or after pregnancy. Using a large cohort of pregnant and non-pregnant women with lupus, we estimate the effect of pregnancy on disease flares in systemic lupus erythematosus.

Methods—Data were collected in the Hopkins Lupus Cohort 1987–2015. Women aged 14–45 years with >1 measurement of disease activity were included. The time-varying exposures were classified as pregnancy, postpartum, or non-pregnant/non-postpartum periods. Flares were defined as: 1) change in Physician Global Assessment (PGA) ≥1 from previous visit and 2) change in SELENA-SLEDAI ≥4 from previous visit. A stratified Cox model estimated hazard ratios with bootstrap 95% CIs.

Results—There were 1349 patients, including 398 pregnancies in 304 patients. There was an increased rate of flare defined by PGA during pregnancy (HR: 1.59; 95% CI: 1.27, 1.96), however this effect was modified by hydroxychloroquine (HCQ) use, with the HR of flares in pregnancy compared to non-pregnant/non-postpartum periods estimated to be 1.83 (95% CI: 1.34, 2.45) for patients with no HCQ use and 1.26 (95% CI: 0.88, 1.69) for patients with HCQ use. The risk of flare was similarly elevated among non-HCQ users in the 3-months postpartum, but not the women taking HCQ after delivery.

Conclusions—Our study supports and extends previous findings that the incidence of flare is increased during pregnancy and within the 3-months postpartum. Continuing HCQ in pregnancy, however, appeared to mitigate the risk of flare during and after pregnancy.

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Ethics Approval Johns Hopkins University School of Medicine Institutional Review Board and University of North Carolina at Chapel Hill Institutional Review Board.

Keywords

systemic lupus erythematosus; epidemiology; disease activity

INTRODUCTION

Systemic lupus erythematosus (SLE) is characterized by fluctuations of disease activity, with periods of high disease activity (i.e., flares) followed by periods of low activity. The effect of pregnancy on disease activity in SLE has long been debated. Previous research has found that 19 to 68% of women with SLE experience a flare during pregnancy.[1–11] Risk factors for flares during pregnancy include active disease at conception, prednisone use, kidney disease and previous flares.[2, 5, 7]

There are conflicting results about the effect pregnancy has on the health of SLE women. Some studies report an increased rate of flares during pregnancy, while others report no difference in disease activity.[8, 9, 12, 13] A study by Lockshin et al.[14] analyzed flare characteristics of pregnant and non-pregnant SLE patients and did not find a difference between women who were and were not pregnant. In contrast, Petri et al.[8] found the rate of flare was greater during pregnancy than in non-pregnant controls, and a subsequent analysis by Ruiz-Irastorza et al.[9] found the flare rates during pregnancy and 6-weeks postpartum were increased compared to non-pregnant, age-matched controls. However, as these studies of flares during pregnancy were published over 20 years ago, an updated analysis is warranted.

A limitation of the current literature is the inconsistency in which flares were defined, making it difficult to make comparisons across studies. Many previous studies were also limited by small sample size, which reduced power to determine differences in the rate of flares between pregnant and non-pregnant patients. Understanding the effect pregnancy has on disease activity is clinically significant for the patient, as high disease activity during pregnancy is associated with preterm births and pregnancy loss.[4, 15, 16] Additionally, examining the rate of flares during the postpartum period is important in determining if patients need to be more closely monitored in the months following pregnancy. The objective of the current analysis was to estimate the effect of pregnancy on disease flares in SLE.

METHODS

Study population

The Hopkins Lupus Pregnancy Cohort is a subset of the Hopkins Lupus Cohort, which has prospectively followed patients with SLE since 1987, with data available through February 2015. Patients meeting the American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria for SLE[17–19] were eligible for enrollment in the cohort following informed consent. Patients enrolled in the Hopkins Lupus Cohort and SLE patients seen in the Hopkins Obstetrics Clinics were referred to the Hopkins Lupus Pregnancy Cohort. Other patients were referred by their rheumatologists, the

Maryland Lupus Foundation and self-referral.[8] Pregnant women were seen every 4–6 weeks during pregnancy by a single rheumatologist. During each visit, lupus disease activity [Physician Global Assessment of disease activity (PGA)[20] and SELENA-SLEDAI[21–23]] was measured, medications were updated, and laboratory tests were conducted. Pregnancy outcome data were collected from patients at the first postpartum visit or by telephone or email, if a woman did not continue care at the Lupus Center.

Exposures

Exposure was classified as pregnancy (yes/no), postpartum period (yes/no), or non-pregnant/non-postpartum period (unexposed). The exposure variables were included as time-varying covariates, so as to include all observations for an individual (including pre-pregnancy observations on women who became pregnant). The postpartum period was analyzed separately as lasting 3 months and 12 months.

Outcomes

Disease flares during follow-up were classified by PGA and SELENA-SLEDAI:

1. Change in PGA ≥1 from the previous visit,
2. Change in SELENA-SLEDAI ≥4 from the previous visit.

Subject selection

During the study period, there were 2417 SLE patients observed in the Hopkins Lupus Cohort, of which 2229 were female. Fifteen patients were removed due to lack of complete information on pregnancies, and an additional 350 patients were removed because SLE diagnosis occurred after age 45. In order to calculate flares, at least two disease activity measurements were required. Of the remaining patients, 1426 had more than one study visit; however, 77 of patients were observed only during pregnancy and were removed from the study population due to likely being systematically different from patients routinely followed in the cohort. The final analytic cohort consisted of 1349 women, including 304 women who had 398 pregnancies. There were 381 observed postpartum periods, with at least one visit during the postpartum period.

Analysis

All women in the cohort between the ages of 14 and 45 were included in the analysis, regardless of pregnancy status. The time of entry into the cohort was considered the initial measurement for all women. Patients were right censored and removed from the risk set at age 45, menopause, loss to follow-up, death, or the end of follow-up. If patients had a gap of more than one year in study visits, patients were considered lost to follow-up but were allowed to re-enter the cohort when study visits resumed.

If a woman had more than one pregnancy, all pregnancies and postpartum periods were included. Incidence rate ratios and 95% confidence intervals (95% CI) were calculated separately for pregnancy and postpartum periods compared to non-pregnant/non-postpartum periods. The hazard ratios (HR) of flares were estimated using a stratified Cox model based on the Prentice, Williams, and Peterson total time approach using the PHREG procedure

[24, 25]. A stratified Cox model is a conditional model that does not assume independence of multiple events of flare.[26] Instead, the model took into account that a patient was not at risk for a second flare without having experienced a first flare. Using the same model, relative hazard rates of flare were calculated between 1) pregnant and non-pregnant/postpartum periods and 2) postpartum and non-pregnant/postpartum periods. Due to repeated events of flares being counted in the same patient and patients being allowed to exit and re-enter the analytic cohort, 95% CI were estimated with 1,000 bootstrap replications sampled with replacement.[27] Potential covariates of interest included patient race, age at diagnosis, age at baseline, and duration of disease at baseline. Confounders were defined by a 10% change in beta estimates when included in the model. None of these covariates were found to be confounders and were not included in any models.

Prednisone and hydroxychloroquine (HCQ) were explored as time-varying covariates. To test whether effects were similar for HCQ users and non-users, as well as prednisone users and non-users, interaction terms between each medication with the exposure were included in the model. Models exploring effect modification by HCQ, for example, would 1) estimate the HR of flare for pregnant women taking HCQ compared to non-pregnant/non-postpartum women taking HCQ, 2) estimate the HR of flare for pregnant women *not* taking HCQ compared to non-pregnant/non-postpartum women *not* taking HCQ, and 3) compare these two HR to see if the hazard ratio for women taking HCQ differed from the HR for women *not* taking HCQ. Effect measure modification was determined by likelihood ratio test (α=0.20).

To account for the time-varying exposures (pregnancy, postpartum period, and medication use) and the possibility for each individual to experience multiple events, a new patient ID was created when the exposure changed for each patient to account for the censoring that occurred in the model with a change in exposure and clustering within an individual as well as within a certain exposure group [28]. Both the original ID, to account for correlation across all observations for an individual, and new ID, to account for correlation within each exposure period for an individual, were included in the models. In order to determine if all women in the cohort were an appropriate comparator group for women who became pregnant, we performed a sensitivity analysis that included only women with an observed pregnancy in the cohort (n=304). To determine if changes in clinical practice affected the results, models were stratified by time period: before and after 2000. All analyses were conducted in SAS 9.3 (Cary, North Carolina).

RESULTS

The median age at cohort entry was 30.6 years and 29.4 years at the first pregnancy (Table 1). The median duration of SLE at cohort entry was 2.0 years, and the median follow-up was 3.9 years. Of the 398 pregnancies, 85% were live births, of which 29% were preterm. Hydroxychloroquine was taken during 58% of pregnancies, and 80% of patients took HCQ at some point during follow-up. Forty-five percent of pregnancies occurred between 1987 and 2000. The median number of visits was 5 during pregnancy, 1 postpartum, and 11 in non-pregnant/non-postpartum periods.

PGA flares were more common during pregnancy compared to outside of pregnancy (Table 2; HR: 1.59; 95% CI: 1.27, 1.96). There was no evidence of an increased rate of flare during the 12-month postpartum period, but there was an increase in flare in the initial 3 months postpartum (HR: 1.48; 95% CI: 1.07, 1.95). In the sensitivity analysis of only patients with an observed pregnancy, the incidence of flares during non-pregnant/non-postpartum periods decreased, suggesting women who became pregnant while in the cohort had, on average, fewer flares than women without a pregnancy. During pregnancy, almost half of flares occurred during the 3rd trimester, while 24% occurred during the 1st trimester. One-third of flares during pregnancy were scored PGA 2 or higher, compared to 40% of flares during non-pregnant, non-postpartum times.

When flares were defined by SELENA-SLEDAI, results were comparable to PGA (Table 3), with a higher rate of flare during pregnancy (HR: 1.57; 95% CI: 1.25, 1.92). There was no evidence of an increased rate 12-months postpartum, but there was a non-statistically significant increase in flares in the initial 3 months postpartum (HR: 1.37; 95% CI: 0.94, 1.82). Similar to models of PGA flares, the incidence of SELENA-SLEDAI flare decreased during non-pregnant/non-postpartum periods when only women with an observed pregnancy were included. SELENA-SLEDAI flares most commonly occurred during the 3rd trimester (54% of flares). Half of flares during pregnancy and 45% of flares during non-pregnant, non-postpartum time were mild, with a score of 4–8. Only 15% of flares during pregnancy and 20% of flares during non-pregnant, non-postpartum times were scored ≥12.

Hydroxychloroquine use was found to be an effect modifier in the association of pregnancy and flares. The increase in flares during pregnancy appeared to only be present in women not taking HCQ. When flares were measured by PGA, the HR of flares in pregnancy compared to non-pregnant/non-postpartum periods was 1.83 (95% CI: 1.34, 2.45) for patients with no HCQ use and 1.26 (95% CI: 0.88, 1.69) for patients with HCQ use (likelihood ratio p-value: 0.04; Table 4). While HCQ appeared to have a similar effect in the 3-month postpartum period, with the HR of flares 1.63 (95% CI: 1.04–2.39) without HCQ and 1.25 (95% CI: 0.71–1.87) with HCQ, the difference did not meet our statistical definition for modification. When flares were measured by SELENA-SLEDAI, there was a modest decrease in the association between pregnancy and flares for women taking HCQ, but not to the extent that HCQ would be considered an effect modifier. However, when limited to only patients with an observed pregnancy in the cohort, the HR of SELENA-SLEDAI flares in pregnancy compared to non-pregnant/non-postpartum periods was 2.09 (95% CI: 1.39, 2.97) for patients with no HCQ use and 1.49 (95% CI: 0.92, 2.08) for patients with HCQ use (likelihood ratio p-value: 0.07). No differences in race, age at diagnosis, age at baseline, and duration of disease were found between HCQ users and non-users.

When the cohort was limited to visits after the year 2000, results were similar for flares defined by PGA and SELENA-SLEDAI (Supplemental Table 1). Prior to 2000, more person-time during pregnancy was unexposed to HCQ (63.2 person-years compared to 20.9 exposed to HCQ. After 2000, the majority of patients during pregnancy, as well as most patients during non-pregnant periods, were treated with HCQ (102.6 person-years compared to 34.1 person-years unexposed to HCQ during pregnancy). When flares were measured by

PGA, the HR of flares during pregnancy remained higher in patients not taking HCQ in both time periods (Supplemental Table 2). When flares were defined by SELENA SLEDAI (Supplemental Table 3), however, the HR of flares during pregnancy was increased for patients unexposed to HCQ in the time period prior to 2000, but an opposite effect was observed in the time period after 2000.

Prednisone use was only found to be an effect modifier in the association of pregnancy and flares in the sensitivity cohort of patients with an observed pregnancy when flares were defined by SELENA-SLEDAI. The HR of flares in pregnancy compared to non-pregnant/non-postpartum periods was 1.91 (95% CI: 1.23, 2.81) in patients with no prednisone use and 1.44 (95% CI: 0.98, 2.01) in patients with prednisone use (likelihood ratio p-value: 0.16). There was no evidence for modification by prednisone use in PGA models or other SELENA-SLEDAI models.

DISCUSSION

Previous studies found conflicting results about whether lupus was more or less likely to flare in pregnancy[8–10, 13, 14, 29]. The present analysis is the largest cohort study to date and includes data collected over almost 30 years. When compared to non-pregnant women with SLE, pregnant women and recently-pregnant women did appear to flare more frequently. However, women taking hydroxychloroquine did not appear to have an increased risk of lupus flare in pregnancy or the postpartum period. Prednisone may also play a role in decreasing disease activity during pregnancy, as it was found to be an effect modifier for SELENA-SLEDAI flares in the sensitivity cohort of patients with an observed pregnancy.

The results support what has previously been reported in the literature, both within the Hopkins Lupus Cohort and in other pregnancy cohorts.[4, 8, 9, 13] The initial effort to determine the impact of pregnancy on lupus activity in this cohort was completed by Petri and colleagues in 1991[8] and found that among the first 40 pregnant patients in this cohort, the rate of flare was greater during pregnancy (1.6 flares per person-year (PY)) compared to non-pregnant controls (0.7 flares per PY). A previous analysis in this cohort by Clowse et al. [4] reported that among patients seen at least 6 months prior to pregnancy, 12.5% had high disease activity (PGA ≥2) compared to 21.3% of patients during pregnancy. Additionally, lupus activity was greater among patients who discontinued HCQ during pregnancy compared to patients who continued.[3] The current study extended previous work in the Hopkins Pregnancy Cohort by analyzing a longer follow-up period and including comparisons to postpartum periods. Interestingly, the rate of flares per person-year has dramatically decreased from the initial study, with the crude flare incidence in the entire cohort averaged around 0.6 flares per PY, ranging from 0.4 with HCQ to 0.8 without HCQ, highlighting the improvements in management of lupus during pregnancy over the past 25 years. We found that the protective effect of HCQ remained for flares measured by PGA when results were stratified prior to and after 2000. Of interest, we did not observe a similar pattern for flares measured by SELENA-SLEDAI, with a protective effect of HCQ observed in the time prior to 2000 but not after 2000.

An increased rate of flare during pregnancy has been observed in other SLE cohorts. Ruiz-Irastorza et al.[9] found the rates of flare during pregnancy and 6-weeks postpartum were increased compared to non-pregnant, age-matched controls (Table 5). A study of 29 pregnancies in Hong Kong estimated a higher rate of flares during pregnancy compared to non-pregnant patients[13] However, in contrast to our results, other studies have found no evidence of an increased rate of flare during pregnancy,[10, 14, 29] potentially due to differences in patient ethnicity, study design, sample size, or definition of flare.

Fewer studies have examined postpartum flares. In this same cohort, Petri et al.[8] reported a lower mean rate of flare after delivery than during pregnancy among 42 patients, with the rate of flare decreasing from 1.6 flares per PY during pregnancy to 0.7 per PY in the year after delivery. A study in Argentina observed 19% of patients flared during pregnancy, compared to 4% in the puerperium.[6] Ruiz-Irastorza et al.[9] estimated a rate of flare during pregnancy of 0.08 per person-month, compared to 0.15 per person-month 8 weeks after pregnancy outcome, which decreased to 0.05 one year postpartum. In our analysis, we defined the postpartum period according to two definitions, and observed an increase rate of flare during a 3-month postpartum period yet no increased rate during a 12-month postpartum period, suggesting the increased risk of flare experienced during pregnancy remains for several months postpartum.

We estimated hazard ratios using stratified Cox models, which take into consideration the order in which flares occurred, and allowed different baseline hazards based on the number of previous flares a patient had in the cohort.[26] Given that a patient with no history of flares likely has a different baseline hazard of flare than a patient who has had multiple previous flares, a model that takes this into account seems more appropriate. A limitation of our study design was patients were censored in the model when the exposure changed. We accounted for this by creating a new ID variable when a patient's exposure changed, and included the original and new IDs in the model. However, this caused a patient's stratum for previous flares to be limited to the current exposure period, which may result in residual confounding. Even so, we view this residual confounding to be preferable to the potentially biased estimates of a crude model or an unadjusted counting process Cox model that would not account for any previous flares.

The present analysis benefited from including two disease activity indices in the same analytic cohort, which allowed us to compare how results might differ depending on the flare index used. We found that, although more flares were observed by SELENA-SLEDAI, the hazard ratios for both indices were similar. Additionally, using data from all women enrolled in the cohort allowed us to analyze more of the disease history of patients. Because all patients may not be the most appropriate comparator group for women who became pregnant, we conducted a sensitivity analysis restricted to women with an observed pregnancy. We found that non-pregnant/non-postpartum flare rates do change depending on the group of women analyzed, with women who had a pregnancy having a lower incidence of flare during non-pregnant/non-postpartum periods. We also considered patients who had more than a one-year gap between study visits to be considered lost to follow-up, although patients were allowed to re-enter the analytic cohort. This was done to include patients who were under routine care and to allow for an appropriate comparator score for the calculation

of disease flare. The disease activity of these patients during unobserved periods is unknown, and if a gap in visits was due to remission of the disease, it is possible we underestimated the person-time for low disease activity periods. Although we did not find any differences between HCQ users and non-users, there remains a possibility that non-users were patients with an allergy to HCQ, intolerant to HCQ, or refused to take the medication. Additionally, flares captured in the analysis were based on flares observed at the Lupus Center; therefore, we were unable to include flares that occurred during hospitalizations.

Our study supports prior data suggesting hydroxychloroquine may prevent lupus flares during pregnancy, and now suggests that it also may prevent post-partum flares. While in prior decades many women with lupus were expected to flare during or after pregnancy, more recent data suggests that a large proportion of women have minimal disease activity throughout the period. We hypothesize that routine continuation of hydroxychloroquine in modern lupus pregnancies may be the driving force for the diminution in lupus activity during and following pregnancy. The results suggest we can be more optimistic with many women with lupus: they do not need to expect a lupus flare during or after pregnancy, particularly if they continue hydroxychloroquine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Demographics for SLE patients at baseline and pregnant women at time of first pregnancy in cohort in the Hopkins Lupus Cohort, 1987–2015.

	Total Cohort at Baseline n =1349	**Pregnant Women at First Pregnancy in Cohort n =304**
Race	n (%)	n (%)
White	656 (48.6%)	173 (56.9%)
Black	546 (40.5%)	102 (33.6%)
Other	147 (10.9%)	29 (9.5%)
	Median (IQR)	*Median (IQR)*
Age, years	30.6 (25.5–36.8)	29.4 (26.1–33.2)
Duration of SLE, years	2.0 (0.3–6.7)	4.8 (1.7–9.6)

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Table 2

Association of pregnancy and lupus flares defined by PGA[A]: the Hopkins Lupus Cohort, 1987–2015 (n=1349).

	Flares	PY	Crude incidence per 100 PY	Crude IRR (95% CI)	Stratified Cox[B] HR (95% CI)
12-Month Postpartum Period					
All patients (n=1349)					
Not pregnant/postpartum	2246	5583.2	40.2	1.0 (ref)	1.0 (ref)
Pregnancy	134	220.8	60.7	1.51 (1.27, 1.80)	1.59 (1.27, 1.96)
12-months postpartum	148	370.9	39.9	0.99 (0.84, 1.17)	1.02 (0.83, 1.25)
Patients with ≥1 observed pregnancy in the cohort (n=304)					
Not pregnant/postpartum	642	1790.4	35.9	1.0 (ref)	1.0 (ref)
Pregnancy	134	220.8	60.7	1.69 (1.40, 2.04)	1.88 (1.48, 2.49)
12-months postpartum	148	370.9	39.9	1.11 (0.93, 1.33)	1.24 (0.96, 1.66)
3-Month Postpartum Period					
All patients (n=1349)					
Not pregnant/postpartum	2336	5786.3	40.4	1.0 (ref)	1.0 (ref)
Pregnancy	134	220.8	60.7	1.50 (1.26, 1.79)	1.57 (1.26, 1.92)
3-months postpartum	58	95.6	60.7	1.50 (1.16, 1.95)	1.48 (1.07, 1.95)
Patients with ≥1 observed pregnancy in the cohort (n=304)					
Not pregnant/postpartum	732	1993.5	36.7	1.0 (ref)	1.0 (ref)
Pregnancy	134	220.8	60.7	1.65 (1.38, 1.99)	1.79 (1.40, 2.42)
3-months postpartum	58	95.6	60.7	1.65 (1.26, 2.16)	1.71 (1.11, 2.52)

[A] Flare defined as change in ≥1 from PGA score at previous visit

[B] Stratified Cox model is a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced

CI: confidence interval; HR: hazard ratio; IRR: incidence rate ratio; PGA: Physician Global Assessment of disease activity; PY: person-years; SLE: systemic lupus erythematosus

Table 3

Association of pregnancy and lupus flares defined by SELENA SLEDAI[A]: the Hopkins Lupus Cohort, 1987–2015 (n=1349).

	Flares	PY	Crude incidence per 100 PY	Crude IRR (95% CI)	Stratified Cox[B] HR (95% CI)
12-Month Postpartum Period					
All patients (n=1349)					
Not pregnant/postpartum	2641	5583.0	47.3	1.0 (ref)	1.0 (ref)
Pregnancy	140	220.8	63.4	1.34 (1.13, 1.59)	1.57 (1.25, 1.92)
12-months postpartum	170	370.9	45.8	0.97 (0.83, 1.13)	1.09 (0.89, 1.32)
Patients with ≥1 observed pregnancy in the cohort (n=304)					
Not pregnant/postpartum	708	1790.4	39.5	1.0 (ref)	1.0 (ref)
Pregnancy	140	220.8	63.4	1.60 (1.34, 1.92)	1.82 (1.34, 2.38)
12-months postpartum	170	370.9	45.8	1.16 (0.98, 1.37)	1.32 (1.03, 1.69)
3-Month Postpartum Period					
All patients (n=1349)					
Not pregnant/postpartum	2748	5786.3	47.5	1.0 (ref)	1.0 (ref)
Pregnancy	140	220.8	63.4	1.34 (1.13, 1.58)	1.36 (1.06, 1.69)
3-months postpartum	63	95.6	65.9	1.39 (1.08, 1.78)	1.37 (0.94, 1.82)
Patients with ≥1 observed pregnancy in the cohort (n=304)					
Not pregnant/postpartum	815	1993.5	40.9	1.0 (ref)	1.0 (ref)
Pregnancy	140	220.8	63.4	1.55 (1.30, 1.86)	1.61 (1.16, 2.16)
3-months postpartum	63	95.6	65.9	1.61 (1.25, 2.08)	1.61 (1.02, 2.40)

[A] Flare defined as change in ≥4 from SELENA-SLEDAI score at previous visit

[B] Stratified Cox model is a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced

CI: confidence interval; HR: hazard ratio; IRR: incidence rate ratio; PY: person-years; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index

Table 4

Modification[A] by hydroxychloroquine of hazard ratios for the association of pregnancy and lupus flares: the Hopkins Lupus Cohort, 1987–2015 (n=1349).

	Patients Exposed to HCQ				Patients Unexposed to HCQ			
	Flares	**PY**	**Crude Incidence per 100 PY**	**HR[B] (95% CI)**	**Flares**	**PY**	**Crude Incidence per 100 PY**	**HR[B] (95% CI)**
PGA[C]								
12-Month Postpartum Period								
Not pregnant/postpartum	1458	3843.0	38.0	1.0 (ref)	788	1740.3	45.3	1.0 (ref)
Pregnancy	52	123.4	42.1	1.26 (0.88, 1.69)	82	97.3	84.3	1.83 (1.34, 2.45)
12-months postpartum	75	212.2	35.3	1.02 (0.72, 1.32)	73	158.7	46.0	0.98 (0.67, 1.31)
3-Month Postpartum Period								
Not pregnant/postpartum	1510	3967.3	38.1	1.0 (ref)	826	1819.0	45.4	1.0 (ref)
Pregnancy	52	123.4	42.1	1.24 (0.86, 1.73)	82	97.3	84.3	1.84 (1.37, 2.44)
3-months postpartum	23	51.6	44.6	1.25 (0.71, 1.87)	35	44.0	79.5	1.63 (1.04, 2.39)
SELENA-SLEDAI[D]								
12-Month Postpartum Period								
Not pregnant/postpartum	1765	3843.0	45.9	1.0 (ref)	876	1740.3	50.3	1.0 (ref)
Pregnancy	64	123.4	51.9	1.35 (0.92, 1.81)	76	97.3	78.1	1.59 (1.17, 2.09)
12-months postpartum	100	212.2	47.1	1.13 (0.88, 1.44)	70	158.7	44.1	0.91 (0.64, 1.20)
3-Month Postpartum Period								
Not pregnant/postpartum	1834	3967.3	46.2	1.0 (ref)	914	1819.0	50.2	1.0 (ref)
Pregnancy	64	123.4	51.9	1.32 (0.91, 1.79)	76	97.3	78.1	1.61 (1.20, 2.10)
3-months postpartum	31	51.6	60.1	1.53 (0.96, 2.25)	32	44.0	72.7	1.45 (0.87, 2.11)

[A] To test whether effects were similar for hydroxychloroquine (HCQ) users and non-users, an interaction term between each medication with the exposure was included in the model. Effect measure modification was determined by likelihood ratio test (α=0.20).

[B] Estimated by stratified Cox model, a conditional model that does not assume independence of multiple events of flares and allows different baseline hazards based on the number of previous flares a patient experienced

[C] Flare defined as change in ≥1 from PGA score at previous visit

[D] Flare defined as change in ≥4 from SELENA-SLEDAI score at previous visit

CI: confidence interval; HCQ: hydroxychloroquine; HR: hazard ratio; PGA: Physician Global Assessment of disease activity; PY: person-years; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index

Table 5

Incidence of flares in SLE pregnancy

Reference	Country	Pregnancies	Flare Definition	Incidence of Flare per Person-Month		
				Non-Pregnant Patients	Pregnancy	Postpartum
Mintz 1986[29]	Mexico	102	Onset of new signs of active disease in a previously inactive organ system, measured by clinical and laboratory variables	0.04	0.06	--
Petri 1991[8]	US	40	Change of ≥1.0 in PGA score since the preceding visit or during the last 93 days	0.05	0.14	0.05
Wong 1991[13]	China	29	Evidence of acute synovitis; pleuritis or pericarditis with radiographic or echocardiographic changes; new neurologic or psychiatric symptoms; thrombocytopenia (<100x 10^9/L); leukopenia (<4 x 10^9/L); hemolytic anemia (positive antiglobulin [Coombs'] test); new cutaneous lesions; or active kidney disease (with abnormal urinalysis results, increasing proteinuria, and/or low C3 and C4 levels)	0.04	0.08	--
Ruiz-Irastorza 1996[9]	UK	78	Increase of ≥0.26 or more from the minimum Lupus Activity (LAI) score during follow-up	0.04	0.08	0.15
Present analysis	US	398	Change of ≥1.0 in PGA score since the preceding visit	0.03	0.05	0.03–0.05
			Change of ≥4 in SELENA-SLEDAI score since the preceding visit	0.04	0.05	0.04–0.06