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Variations of C3 and C4 Before and During Pregnancy in Systemic Lupus Erythematosus: Association With Disease Flares and Obstetric Outcomes

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ABSTRACT. ***Objective.*** To analyze complement level variations in systemic lupus erythematosus (SLE) pregnancies, focusing on disease flares and obstetric complications.

Methods. SLE pregnancies prospectively followed by multidisciplinary teams from 1987 to 2018 in 2 Italian rheumatology centers were retrospectively analyzed. As reference, pregnancy-modified ranges of normal levels of C3 and C4 were derived from 175 pregnancies from the general obstetric population (GOP), as previously described by our group.

Results. Two hundred forty-six pregnancies in 172 patients with SLE were analyzed. Eighty-nine percent were live births. Thirty-five flares were recorded in 30 pregnancies (12.2%) and obstetric complications occurred in 47 pregnancies (19.1%) including 27 pregnancy losses, 11 severely preterm births (2 resulting in perinatal death), and 15 hypertensive disorders. C3 and C4 levels were higher in the GOP than in patients with SLE, at any time point. C3 and C4 levels progressively increased during pregnancy in both GOP and SLE pregnancies without flare and obstetric complications, whereas this physiological increase was not observed in pregnancies with flares or obstetric complications. A significantly higher frequency of low C4 was found in pregnancies with flares (at preconception and in each trimester) and preterm births (at preconception). In multivariate analysis, low C4 at preconception was associated with flares (odds ratio 13.81, 95% CI 3.10-61.43, $P < 0.001$).

Conclusion. Low C4 at preconception was found to be an independent risk factor for SLE flare during pregnancy. Not only C3 and C4 levels but also their variations should be observed, as their failure to increase can be useful to predict risk of complications and suggest closer monitoring.

Key Indexing Terms: complement C3, complement C4, pregnancy, systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting mainly women of childbearing age. Although pregnancy outcomes in patients with SLE can be improved by correct planning and multidisciplinary management, these patients are still affected by a higher risk of maternal and fetal complications as compared to the general obstetric population (GOP).[1-4]

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History of lupus nephritis, positivity for antiphospholipid antibodies (aPL), poor disease control before conception, and flares during pregnancy are known risk factors for pregnancy complications.[5] There is a need for additional variables for a more sensitive preconception risk stratification, particularly biomarkers predicting obstetric complications.

The complement system has a crucial role during physiological pregnancy, promoting changes at the fetal–maternal interface.[6] In the GOP, C3 and C4 serum levels progressively increase during pregnancy.[7] Complement consumption, leading to a smaller increase of complement levels, can contribute to adverse pregnancy outcomes.[6,8-10] The utility of serum complement levels in monitoring disease activity in patients with SLE is well-established, but information on conventional serum C3 and C4 levels in the assessment of SLE flares during pregnancy is still limited and controversial.[6,11,12] Moreover, there are conflicting results about the role of complement as a predictor of obstetric complications in SLE pregnancies.[4,13,14] In the Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and SLE (PROMISSE) prospective study of pregnancies in women with SLE and/or aPL positivity, a smaller increase of C3 during pregnancy and the increase of complement

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activation products early in pregnancy predicted adverse pregnancy outcomes.[10,14]

The aim of this study was to retrospectively assess the association between complement levels in the preconception period and during pregnancy, and the occurrence of flares and obstetric complications by analyzing 2 historical cohorts of prospectively followed pregnancies in patients with SLE at 2 multidisciplinary pregnancy clinics.

METHODS

Study design and patient population. Data from prospectively followed SLE pregnancies were retrospectively retrieved from 1987 to 2018 at 2 Italian pregnancy clinics, to study C3 and C4 changes during gestation in SLE pregnancies. The study was approved by the local ethics committee (NP 2917).

Complement levels in the GOP, used for comparison, were previously described by our group.[7] All the patients fulfilled American College of Rheumatology (ACR) 1997 and/or Systemic Lupus International Collaborating Clinics 2012 classification criteria.[15,16] Six twin pregnancies were excluded from the analysis.

Data about clinical and laboratory features, including general cardiovascular (CV) risk factors (ie, obesity, cigarette smoking, type 2 diabetes, hypercholesterolemia, hypertriglyceridemia, and arterial hypertension) were collected at a preconception visit (within 6 months before conception) and during each trimester.

Disease activity was evaluated by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) at preconception and by the Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI) during each trimester.[17] A disease flare was defined as the onset of new disease features (with a consequent increase in disease activity) and/or worsening of preexisting manifestations resulting in treatment modification.

Obstetric complications were divided in 3 groups: (1) pregnancy losses, including early miscarriage (≤10th gestational week) and late pregnancy loss (>10th gestation week); (2) severely preterm births with delivery before the 34th gestational week; and (3) hypertensive disorders of pregnancy including preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, and eclampsia.

Statistical analysis. Categorical variables were expressed as numbers and percentages and were compared using the Fisher exact test. Continuous variables were expressed as median (2.5-97.5 percentile range) and were compared using the Mann-Whitney *U* test or the Wilcoxon signed-rank test for paired measurements.

To identify predictors of SLE flare during pregnancy, multivariable logistic regression analysis was performed by selecting covariates based on the research question (possible role of serum complement levels at preconception visit) and plausible independent variables, which were selected a priori among others clinical variables, such as SLEDAI score during the 6 months prior to conception and hydroxychloroquine treatment during pregnancy. Odds ratios (ORs) were calculated with 95% CIs.

RESULTS

Patients and pregnancies description. One hundred seventy-two patients with SLE were included. The median year of pregnancy was 2009 (2005-2014). Median age at diagnosis was 23.0 (10.5-35.0) years and at conception was 31.0 (22.0-40.7) years; median disease duration at conception was 7.0 (0.0-23.0) years. Demography, comorbidities, and disease features are reported in Supplementary Table S1 (available with the online version of this article).

Data for 246 pregnancies were analyzed (1 woman had 5 pregnancies, 2 women had 4 pregnancies, 8 women had 3 pregnancies, and 47 women had 2 pregnancies). There were 134 (54.5%) pregnancies in primigravidae patients; 154 (62.6%) pregnancies were planned, 232 (94.3%) were spontaneous, and 14 (5.7%) were achieved with assisted reproductive technology.

Thirty-five flares occurred in 30 pregnancies (12.2%); flares were mild/moderate in 22 cases (73.3%). In 8/30 (26.7%) pregnancies, the flare occurred during the first trimester (3 hematologic, 2 renal, 1 cutaneous, 1 articular, and 1 renal + cutaneous); in 17/29 (58.6%) during the second trimester (5 articular, 3 cutaneous, 3 hematologic, 1 renal, 1 vasculitic, 2 articular + cutaneous, 1 renal + cutaneous, and 1 hematologic + vasculitic); and in 5/28 (17.9%) during the third trimester (2 articular, 1 neurologic, 1 cerebral arterial thrombosis, and 1 macrophage activation syndrome). A higher frequency of severely preterm births was found in pregnancies with flare compared with pregnancies without flare (13.3% vs 3.2%, $P = 0.03$; Supplementary Table S2, available with the online version of this article). The SLEDAI score in the 6 months before pregnancy was low and similar in both groups (median [2.5-97.5 percentile] 2.0 [0.0-6.0] vs 2.0 [0.0-6.0], $P = 0.16$; data available in 161 and 18 pregnancies, respectively).

Live births were 219 (89%). Among these, 31 neonates were small for gestational age (SGA; 14.8%, 9 missing data). Forty-seven pregnancies (19.1%) had at least 1 obstetric complication. There were 27 (11%) pregnancy losses; 20 were early miscarriages and 7 were late miscarriages. There were 11 severely preterm births (2 perinatal deaths occurred); in 4 cases, preterm delivery was caused by preeclampsia. Hypertensive disorders of pregnancy occurred in 15 pregnancies, all defined as preeclampsia, 4 of which were complicated by HELLP syndrome; no eclampsia was recorded.

As compared with 199 uneventful SLE pregnancies (Supplementary Table S3, available with the online version of this article), the group of 27 pregnancies complicated by fetal loss was more frequently treated with immunosuppressants (63% vs 32.2%, $P = 0.004$). Eleven pregnancies complicated by severely preterm births had higher frequency of antiphospholipid syndrome (APS; 36.4% vs 9%, $P = 0.02$) and higher SLEPDAI during pregnancy (first trimester: 4.0 [0.0-6.0] vs 2.0 [0.0-6.0], $P = 0.02$; second trimester: 4.0 [0.0-13.0] vs 2.0 [0.0-6.0], $P = 0.004$; and 3rd trimester: 4.0 [2.0-14.0] vs 2.0 [0.0-4.0], $P < 0.001$). Fifteen pregnancies complicated by hypertensive disorders had higher frequency of CV risk factors (86.7% vs 38.2%, $P = 0.005$), triple aPL positivity (26.7% vs 8.5%, $P = 0.045$), corticosteroid (CCS) treatment during pregnancy (100% vs 76.4%, $P = 0.046$), and higher SLEPDAI during the second trimester (3.0 [0.0-13.0] vs 2.0 [0.0-6.0], $P = 0.01$).

Variations of C3 and C4 levels during pregnancy. Figures 1 and 2 show C3 and C4 levels throughout pregnancy in (A) SLE pregnancies with and without flare and in (B) SLE pregnancies with and without obstetric complications. Complement levels in the GOP are shown in Supplementary Figure S1 (available with the online version of this article).[7]

In the GOP, C3 significantly increased throughout pregnancy and C4 increased from the first trimester to the second

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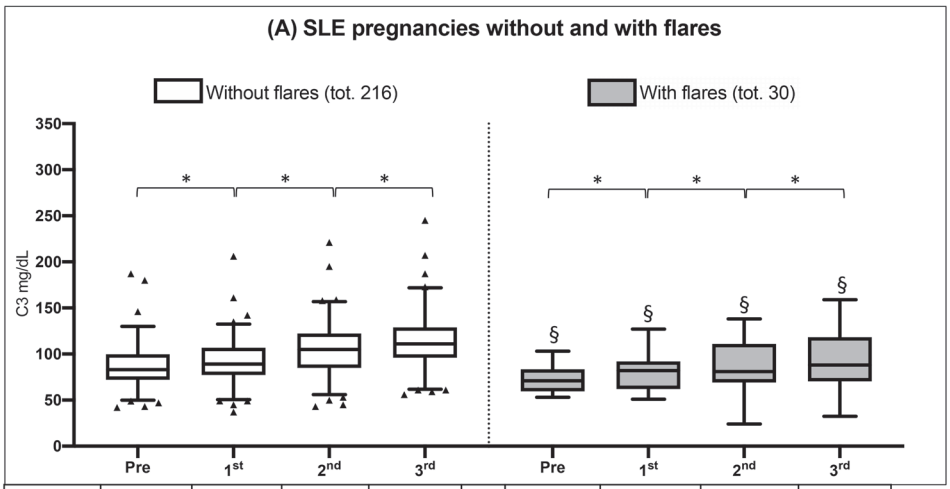
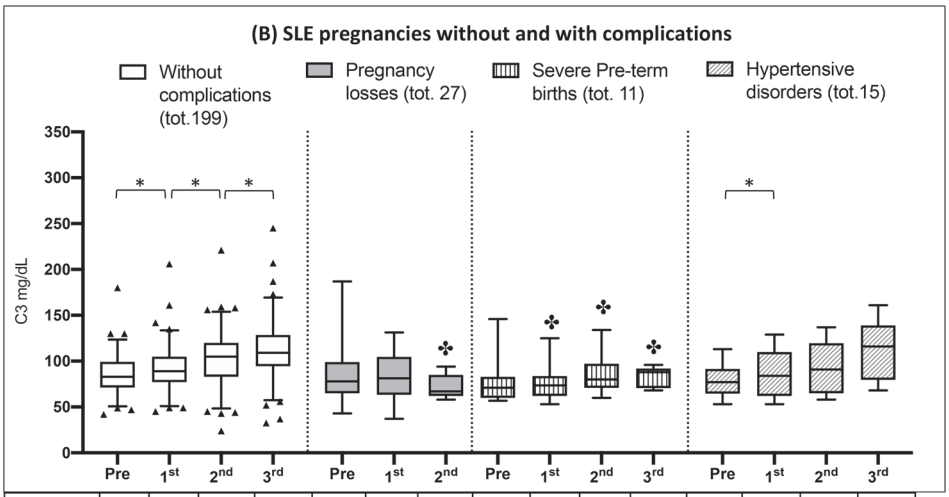


	Without flares (tot. 216)				With flares (tot. 30)			
	Pre	1st	2nd	3rd	Pre	1st	2nd	3rd
n	181	192	182	165	17	27	27	26
median	83	89	105	111	71	79	81	88
2.5-97.5 percentiles	50-130	51-133	56-157	62-172	53-103	51-127	24-138	33-159



	Without complications (tot.199)				Pregnancy losses (tot. 27)			Severe Pre-term births (tot. 11)				Hypertensive disorders (tot.15)			
	Pre	1st	2nd	3rd	Pre	1st	2nd	Pre	1st	2nd	3rd	Pre	1st	2nd	3rd
n	156	179	187	177	27	21	5	7	10	10	7	13	15	13	9
median	83	89	105	109	78	81	67	71	74	80	88	77	84	91	116
2.5-97.5 percentiles	51-124	51-134	49-154	57-169	43-187	37-131	58-94	57-146	53-125	60-134	68-96	53-113	53-129	58-137	68-161

Figure 1. C3 levels at different time points (preconception visit and each trimester of pregnancy) in (A) SLE pregnancies with and without flare and (B) SLE pregnancies with and without obstetric complications. Data are represented as median (box: 25-75 percentile; whiskers: 2.5-97.5 percentile). * Wilcoxon sign-rank test: $P < 0.05$. Mann-Whitney *U* test: § $P < 0.05$ (vs "without flare"); ❖ $P < 0.05$ (vs "without complications"). 1st: first trimester; 2nd: second trimester; 3rd: third trimester; Pre: preconception visit; SLE: systemic lupus erythematosus.

trimester. Similarly, in SLE pregnancies without flare or without obstetric complications, C3 significantly increased from the preconception period to the first trimester and throughout pregnancy and C4 increased from the preconception period to the second trimester. In the other SLE groups, complement levels showed different trends: no increase of C4 from preconception to the first trimester in SLE pregnancies with flare; no increase throughout pregnancy in SLE pregnancies with fetal losses or with severely preterm births; and no increase in the second and third trimesters in SLE pregnancies with hypertensive disorders (Figure 1 and Figure 2).

C3 and C4 levels: comparison between groups. In each trimester, C3 and C4 levels were higher in the GOP than that in each of the SLE pregnancy groups, including those without flares and without complications (Figure 1 and Figure 2; Supplementary Figure S1, available with the online version of this article).

In turn, SLE pregnancies without flares showed higher C3 and C4 levels than pregnancies with flares, at preconception and in each trimester (Figure 1A and Figure 2A).

SLE pregnancies without complications had higher C3 and C4 levels in the second trimester compared to pregnancies with fetal losses and showed higher C3 levels than the severely

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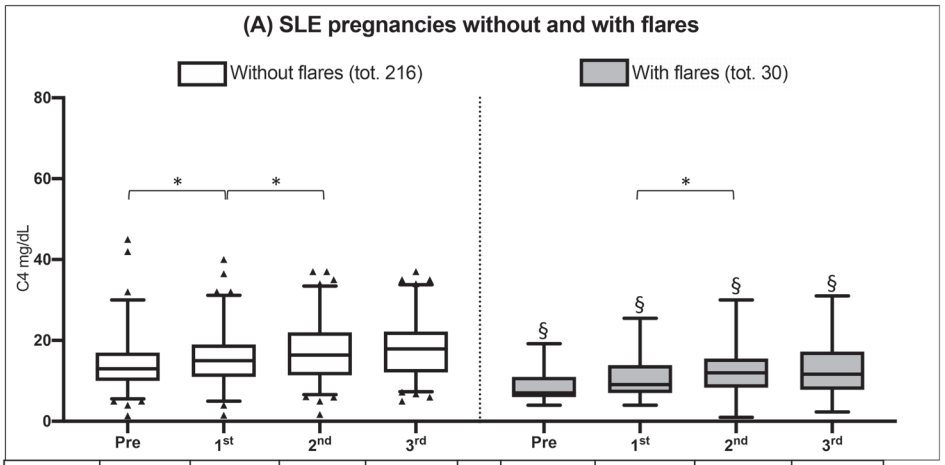
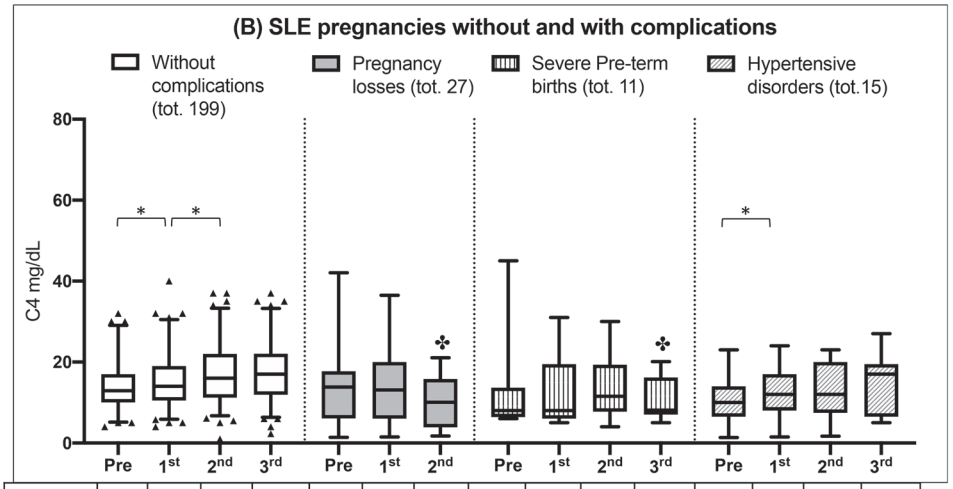


n	181	192	182	165		17	27	27	26
median	13	15	16	18		7	9	12	12
2.5-97.5 percentiles	6-30	5-31	7-33	7-34		4-19	4-26	1-30	2-31



n	156	179	187	177	27	21	5	7	10	10	7	13	15	13	9
median	13	14	16	17	14	13	10	8	8	12	8	10	12	12	17
2.5-97.5 percentiles	5-29	6-31	7-33	6-33	1-42	2-37	2-21	6-45	5-31	4-30	5-20	1-23	2-24	2-23	5-27

Figure 2. C4 levels at different time points (preconception visit and each trimester of pregnancy) in (A) SLE pregnancies with and without flares and (B) SLE pregnancies with and without obstetric complications. Data are represented as median (box: 25-75 percentile; whiskers: 2.5-97.5 percentile). *Wilcoxon sign-rank test: $P < 0.05$. Mann-Whitney U test: $^{\S}P < 0.05$ (vs "without flare"); $^{✣}P < 0.05$ (vs "without complications"). 1st: first trimester; 2nd: second trimester; 3rd: third trimester; Pre: preconception visit; SLE: systemic lupus erythematosus.

preterm birth group in each trimester, whereas higher C4 was observed only in the third trimester (Figure 1B and Figure 2B). There were no differences in C3 and C4 levels comparing pregnancies without obstetric complications and pregnancies with hypertensive disorders.

By comparing C3 and C4 levels in patients with or without CV risk factors, we found a higher level of C3 at the third trimester in the group with CV risk factors (113.0 [61.0-187.0] mg/dL vs 105.5 [55.3-157.2] mg/dL, $P = 0.02$).

Frequency of low levels of C3 and/or C4. At preconception, pregnancies with flare showed a higher frequency of low C3 and C4 compared with pregnancies without flares (Supplementary Table S4, available with the online version of this article). Using the range for normal values that was previously derived from healthy pregnancies,[7] SLE pregnancies with flare had a higher frequency of low C4 in each trimester as compared with pregnancies without flares (Supplementary Table S4).

By comparing pregnancies with and without obstetric complications, only the preterm birth group showed, in the preconception period, a significantly higher rate of low C4 compared with uneventful pregnancies. No other differences were found throughout pregnancy (Supplementary Table S5, available with the online version of this article).

There was no difference in the frequency of CV risk factors

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between patients with low or normal complement levels at preconception (38.3% vs 46.7%, $P = 0.29$).

Multivariate analysis. In multivariate analysis (Table), low C4 at preconception was associated with flare during pregnancy (OR 13.81, 95% CI 3.10-61.43, $P < 0.001$).

Due to the small number of obstetric complications, the multivariate analysis for their association with complement levels could not be performed.

DISCUSSION

Our study on a large series of SLE pregnancies shows that the physiological pattern of C3 and C4 variations during pregnancy is conserved in pregnancies without flare and/or obstetric complications. In fact, levels of C3 increase throughout pregnancy and levels of C4 until the second trimester in these pregnancies. However, it must be noted that C3 and C4 levels are consistently lower in SLE pregnancies compared with the GOP.[7] The importance of our study is indeed the use of pregnancy-modified normal ranges for C3 and C4 levels.

Currently, as suggested by the current European Alliance of Associations for Rheumatology recommendations on pregnancy in patients with SLE[18] and ACR guidelines for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases,[19] women are advised to start a pregnancy when the disease is in remission or in stable low disease activity. Accordingly, the large majority of patients in our study showed a very low disease activity at preconception evaluation. Therefore, flares were observed only in 12.2% of cases. Although this frequency is rather small, identifying predictors of flare during pregnancy may be relevant for clinical practice.

The lack of increase in C4 levels during the first trimester in SLE pregnancies with disease flares suggests that clinicians might use this variable as a way to predict this potential complication.

Moreover, multivariate analysis demonstrated that flares during pregnancy were independently associated with low C4 levels before pregnancy (OR 13.81), but, notably, not SLEDAI at that time, indicating that even in patients with low disease activity, the presence of reduced C4 should be carefully considered. This could reflect either a persistent serological activity in otherwise inactive disease or a genetic complement defect, which is not rare in SLE.[6,20]

Table. Predictors of flare during pregnancy in multivariable logistic regression analysis.

	OR (95% CI)	*P*
Disease activity in the 6 mos before pregnancy (SLEDAI)	0.89 (0.60-1.30)	0.54
Hydroxychloroquine during pregnancy (yes/no)	0.46 (0.14-1.55)	0.21
Low C3 at the preconception visit (yes/no)	1.68 (0.46-6.13)	0.17
Low C4 at the preconception visit (yes/no)	13.81 (3.10-61.43)	**< 0.001**

Values in bold are statistically significant. OR: odds ratio; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

The association of low C4 and disease flares is not surprising. Disease activation in patients with SLE is associated mainly with classical pathway activation, which yields a decrease in C4 (and C3) circulating levels and an increase in split products.[6] In fact, measurements of C3 and C4 have been included not only in the classification criteria for SLE, but also in the disease activity indexes. As a whole, preconception C4 levels seem to be a good marker for predicting flares in SLE pregnancy.

The second issue addressed in our study is regarding SLE pregnancies with obstetric complications. We recorded that 19.1% of pregnancies had at least 1 obstetric complication; although these data are comparable with those reported in the PROMISSE study,[14] the different nature of the 2 studies (retrospective and prospective) and the slightly different definitions used for the population and complications should be considered. Our data demonstrated that C3 and C4 levels failed to increase and remained stable throughout the pregnancy in patients with SLE suffering from fetal losses, as well as in those with severely preterm birth. Notably, fetal losses occurred more frequently in patients taking immunosuppressive drugs, potentially related to more severe disease. We did not find a significantly higher frequency of aPL positivity and/or APS diagnosis in pregnancies with fetal losses compared with pregnancies without complications. This could be due to the relatively low occurrence of this complication in our cohort and the fact that most of these pregnancies were treated with low-dose acetylsalicylic acid and/or low molecular weight heparin.

Our results confirm and reinforce the data from the PROMISSE study, which showed that SLE pregnancies with an adverse pregnancy outcome (ie, late miscarriages; neonatal death secondary to prematurity and/or placental insufficiency; preterm delivery or termination of pregnancy before the 36th gestational weeks due to hypertension, preeclampsia, or placental insufficiency; or SGA infants) had higher frequency of low C3 and/or C4 at baseline evaluation (up to the 12th gestational week) and lower increase of C3 during the second trimester than other SLE pregnancies.[14] It should be noted, however, that in this study, women with potential causes of adverse pregnancy outcomes other than SLE (eg, high-dose CCSs, high serum creatinine, high blood pressure at screening, or diabetes) were excluded. On the contrary, patients with acquired CV risk factors were included in our study, thus better reflecting real-world experience. It is not surprising that a higher frequency of these risk factors was observed in the group of patients who had a pregnancy complicated by hypertensive disorders but without any association with low complement levels. Nevertheless, all the CV risk factors should be assessed during preconception counseling, given the multifactorial nature in the pathogenesis of pregnancy complications.

Finally, in patients with SLE with hypertensive disorders during pregnancy, C3 and C4 serum levels increased only between preconception and the first trimester, and remained stable thereafter, at variance with what happened in uncomplicated SLE pregnancies. Notably, it has been reported that women with early onset preeclampsia are more likely to carry

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deficiency in C4A or C4B, suggesting that C4 may play a role in the prevention of the onset of preeclampsia.[6]

Another strength of our work is the classification of obstetric complications according to their possible pathogenic mechanism. This enabled us to highlight the different effect of complement in different pathological situations.

One limitation of our study is its retrospective nature, which allowed only the analysis of data that were requested as per clinical practice. To better define the association between complement and complications in SLE pregnancies, a prospective collection of data and biological samples would be the best, as already performed in the PROMISSE study.[10]

In conclusion, our results suggest that C3 and C4 levels should be further investigated as possible predictors of maternal and fetal complications in SLE pregnancies, as they may reflect complement involvement at the placental level. In clinical practice, measuring C3 and C4 levels at preconception and in each trimester as well as observing their failure to increase throughout pregnancy might become a simple and inexpensive way to identify women at higher risk of complications.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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