Editorial

Complementing What We Know About Systemic Lupus Erythematosus Pregnancy

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Pregnancy in women with systemic lupus erythematosus (SLE) can increase the risk of disease flare, which in turn increases adverse pregnancy outcomes. Maternal adverse pregnancy outcomes include hypertensive disorders, increased cesarean deliveries, and death, whereas fetal adverse outcomes include fetal loss and death, preterm delivery, and intrauterine growth restriction (IUGR).1 With improved prepregnancy counseling and pregnancy management, adverse pregnancy outcomes in SLE have decreased, although rates of preeclampsia and fetal death remain high.2 Nonetheless, predicting those patients who will flare during pregnancy or have an adverse pregnancy outcome remains challenging. Previous studies have identified some patient characteristics and biomarkers that portend worse pregnancy outcomes: these include current or past renal disease, active disease at conception, hypertension, hematologic abnormalities, and antiphospholipid antibodies.1

Pregnancy success is dependent on modifications to the immune system to ensure that the fetus, which is a hemiallograft, can survive. The complement system plays an important role in these modifications, as complement activation needs to be regulated to circumvent adverse pregnancy outcomes. The presence of complement inhibitors at the maternal-fetal interface helps to achieve this.3 When genetic mutations cause these complement regulators to be defective, recurrent pregnancy loss can ensue.4 Dysregulation of complement can also be associated with pregnancy-induced hypertensive disorders such as preeclampsia.5 Pregnancy complications of antiphospholipid syndrome (APS), including fetal loss and preeclampsia, are thought to be mediated by complement activation. Hydroxychloroquine, the foundation of SLE treatment, inhibits complement activation, and this suggests one of the mechanisms by which pregnancy outcome is better in patients with SLE who stay on this medication in pregnancy.6 The role of complement levels as a predictor of adverse pregnancy outcomes has gained traction. In the Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISSE) study, the largest prospective study of SLE pregnancy to date, lower levels of C3 were shown to be associated with adverse pregnancy outcomes.7 Other groups have also correlated low complement levels with preterm birth.8 However, the relevance of low complement levels in pregnant patients with SLE has been difficult to interpret as these studies lack a control group of healthy pregnancies in which complement is measured.

In this issue of The Journal of Rheumatology, Crisafulli et al examine the role of C3 and C4 levels as a possible predictor of disease flare and obstetric outcomes in pregnant women with SLE.9 The authors retrospectively analyzed C3 and C4 level variation prepregnancy and in all 3 trimesters of 246 pregnancies in 172 women with SLE and associated them with pregnancy outcomes. Importantly, levels of C3 and C4 from the general obstetric population were used as controls. The authors found that levels of C3 and C4 were higher overall in the general obstetric population compared to patients with SLE. These complement levels increased over the course of 3 trimesters in the general obstetric population and in those patients with SLE without adverse pregnancy outcomes or flares. In contrast, complement levels did not increase during the course of pregnancy in patients with SLE with disease flares or adverse pregnancy outcomes that included pregnancy loss, severe preterm birth, and hypertensive disorders of pregnancy. Low C4 levels preconception were an independent risk factor for SLE flare. The authors concluded that monitoring C3 and C4 levels preconception and during pregnancy is useful in predicting pregnancy complications in patients with SLE.

The strength of the study by Crisafulli et al is the number of pregnancies in which C3 and C4 levels were able to be collected throughout pregnancy.9 This enabled the authors to compare levels of C3 and C4 in the general population to those of women

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with SLE and to further separate out those SLE pregnancies that had complications (disease flares and adverse pregnancy outcomes). The authors also had data on disease activity as measured by the SLE Disease Activity Index and SLE Pregnancy Disease Activity Index in their cohort.\textsuperscript{3} Their study population had relatively low disease activity, normal renal function, and low glucocorticoid use. The flare rate during pregnancy was low (12%), as was the rate of adverse pregnancy outcomes (19%). Interestingly, this latter rate echoes what was found in the PROMISSE study and lends credence to the idea that disease flare and adverse pregnancy outcomes affect a minority of SLE pregnancies.\textsuperscript{7} Identifying this minority, however, is an important challenge to overcome, and if levels of C3 and C4 can be used to identify these patients, measuring complement levels is crucial.

The study by Crisafulli et al\textsuperscript{9} does leave us with some unanswered questions as to whether these assays are ready for prime time in pregnancy management. Although the median levels of C3 and C4 reported in this study are different in those patients with SLE with and without pregnancy complications, there is significant overlap, suggesting there are limits to how one can use C3 and C4 levels as an initial screening test for the SLE patient population at large. Trending C and C4 over time for an individual patient may be the ideal situation; nonetheless, it is noteworthy that in this study,\textsuperscript{9} most of the disparate results did not present until the second or third trimester—a time when complications such as preeclampsia and IUGR may already be present. Similarly, although the finding that low C4 levels predict flares is intriguing, the actual 2.5 to 97.5 percentile range overlaps significantly between SLE pregnancies with and without complications (Figure 2B),\textsuperscript{9} making it less likely that this metric could be applied broadly in clinical practice.

If the findings in the study by Crisafulli et al are robust,\textsuperscript{9} in addition to identifying at-risk patients, it may point to directions for possible therapeutic interventions. The C5a blocker eculizumab has been used to treat hemolytic uremic syndrome and paradoxical nocturnal hematuria, but more recently, has also been used to treat severe preeclampsia.\textsuperscript{8,9} Arguably, if we could identify those patients with risk factors for adverse pregnancy outcomes in SLE (history of renal disease, hypertensive disorders, active disease at conception),\textsuperscript{1} we may be able to identify which patients should be monitored for complement levels early during pregnancy. Perhaps if these data could be combined with information on early markers for preeclampsia and other pregnancy complications and complement levels of pregnant patients with SLE were closely monitored, there may be a role for preemptive treatment with complement blockers to circumvent adverse pregnancy outcomes.

In their study, Crisafulli and colleagues add to our growing knowledge regarding the importance of complement in both healthy and high-risk SLE pregnancies.\textsuperscript{9} With continued exploration in this area, we will hopefully be able to better define the value of monitoring complement levels during SLE pregnancy to mitigate risk as well as better understand the pathophysiology of these complications, leading not only to prediction but also to prevention.

REFERENCES