

Editorial

Disease activity of pregnant women with systemic lupus erythematosus



Systemic lupus erythematosus (SLE) is an autoimmune and multisystemic disease with a significant female predominance, particularly during the reproductive years (ratio 15:1), affecting up to one in 1000 women of child-bearing age.¹ Pregnancy is considered a very high-risk period for women with SLE, and therefore has been strongly discouraged in those suffering from SLE for the most part until recent years.¹ A study of 13,555 deliveries of women with SLE showed that they had a 20-fold higher risk of maternal mortality and a higher rate than pregnant women without SLE of hypertension, pregestational diabetes mellitus, renal impairment, pulmonary hypertension, major infection, and hematological complications, as well as events such as bleeding, anemia, thrombocytopenia, stroke, deep vein thrombosis, and pulmonary embolism.² Therefore, the management of SLE during pregnancy remains challenging for physicians, and outcomes for both mother and baby can be less than optimal if the disease is not managed with caution.³ In this issue Dr. Yang has an article addressing this important topic—pregnancy outcomes of woman with SLE in a single institute in northern Taiwan.⁴ The authors studied 60 pregnancies of 55 women with SLE and found that the pregnancy outcome was strongly positively related to the remitted disease activity of the women with SLE prior to conception and during pregnancy; these women with SLE that was quiescent prior to conception and during pregnancy had a longer gestation period and a lower complication rate with pregnancy, and delivered newborns with higher body weight than those women with active SLE.⁴ Therefore, the authors emphasized the importance of requiring women with SLE to consult with obstetricians prior to conception, and to maintain remitted disease activity with the help of rheumatologists before and during pregnancy. In fact, teamwork in modern medical care has become one of the most important issues in providing better care for diseased patients and for improving the global health of the general population.⁵ We congratulate the authors on their success and also appreciate their contribution to this field.

There is much evidence supporting the importance of SLE quiescence prior to conception,^{1,3} although multivariate analysis from Dr. Yang's report failed to identify its value.⁴ The risk of flare appears to be dependent on disease activity 6–12 months before becoming pregnant.¹ Women without active SLE during this period have a lower risk of flare

during pregnancy, but women with active SLE during this time have a higher risk of morbidity and mortality, and this includes not only the mothers but also the fetuses and/or newborns, suggesting that pregnancy in women with SLE should be well planned and well prepared for in advance. In other words, all women with SLE should achieve complete SLE remission before they get pregnant. However, the length of such necessary remission remains uncertain. Many earlier reports recommended that at least 6 months of SLE quiescence might be required to minimize the risk of flare during pregnancy and provide a better maternal and fetal outcome.^{1,6,7} However, with the significantly increased maternal age in modern society,⁸ including the SLE population, it is not easy to wait such a long time. The average age of the study population in Yang's study was 29.7 years, ranging from 20 years to 43 years.⁴ A recent excellent review suggested that 4 months of SLE quiescence may be enough to ensure a safe pregnancy.³ However, Dr. Yang failed to investigate the period between remission of SLE and initiation of conception in the study, and therefore could not suggest the best interval between SLE quiescence and conception, but we still found the value of Dr. Yang's article in further suggesting that the silent disease activity of SLE prior to conception is strongly related to uncomplicated pregnancy.⁴ In addition, remission of SLE activity during pregnancy was strongly associated with a longer gestation period, and women with activated lupus activity during pregnancy had a threefold higher risk of preterm deliveries (<37 weeks of gestation) than did women with remission of SLE activity during pregnancy.⁴

In terms of pregnancy outcome, Dr. Yang reported that women with SLE, regardless of disease activity before and during pregnancy, had relatively fewer gestational weeks and their newborns had lower body weight than in the general population (37.4 gestational weeks vs. 38.6 gestational weeks, and 2727 g vs. 3315 g, respectively).^{4,9} That is to say, late preterm labor (defined as newborns delivered at between 34 gestational weeks and 37 gestational weeks)¹⁰ is also a substantial problem for women with SLE, regardless of their disease activity. How to manage this high-risk population (pregnant women with SLE) is still a challenge facing obstetricians, rheumatologists, and pediatricians.

Given that a single study may not adequately address all that we need to know, we would like to survey the studies from the past 3 years to provide a more complete picture of best practices. However, as shown in a recent excellent review by Peart and Clowse,³ it is not easy or possible to conduct a prospective, randomized clinical trial and subsequently interpret the available data to guide the therapeutic recommendations because of the rarity and sensitivity of pregnancies in women with SLE. It is difficult to comment on this, but there is no doubt that a longer stable duration prior to conception might result in a better pregnancy outcome.

A limitation of Dr. Yang's study was that the assessment of lupus activity was based on routine monitors, including urine routine, complete blood cell counts, erythrocyte sedimentation rate (ESR), and serum titers of C3, C4, and double-stranded DNA, as well as urinary protein loss and clearance rate of creatinine.⁴ However, during pregnancy, ESR and serum C3 and C4 levels are usually elevated due to increased liver production. Therefore, women with active lupus might have serum C3 and C4 levels within the "normal range", suggesting that relative variation rather than absolute levels of C3 and C4 should be taken into consideration. By contrast, a decrease of $\geq 25\%$ in serum C3 and C4 levels in pregnancy should be carefully evaluated, because this may be an earlier hint of SLE flare.¹¹

Another limitation of Dr. Yang's study was that lupus nephritis was not considered, although it is well known that active lupus nephritis prior to and at conception confers the highest risk of flare during pregnancy. This risk of flare during pregnancy still remains higher in women with lupus nephritis in remission.¹² Therefore, women with remitted lupus nephritis might not be good candidates to consider as well prepared for pregnancy, even though a longer duration of remitted lupus nephritis was obtained prior to conception. Any woman with SLE during the reproductive years should be managed in an intensive manner to avoid the occurrence of lupus nephritis, especially those women who still plan to become pregnant.

Conflicts of interest

The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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