

# Dispelling the Preconceived Notion That Lupus Pregnancies Result in Poor Outcomes

Given that pregnancy is the physiologic state in which estrogens reach their highest level, it is not hard to understand why physicians would be pessimistic about the course of a disease that predominantly affects women. Moreover, since immunologic adaptations take place to assure the acceptance of a semi-allograft, such adaptations might be predicted to adversely affect certain immunologic diseases. Such reasoning likely gave birth to the preconceived notion that systemic lupus erythematosus (SLE) inherently confers a poor outcome for both mother and baby. With regard to maternal disease, a compounding difficulty in ascertaining the effect of pregnancy on maternal health is the challenge in differentiating lupus activity per se from physiologic changes in pregnancy and diseases of pregnancy such as preeclampsia that can mimic active nephritis<sup>1</sup>. With regard to pregnancy outcome is the concern that the placenta and fetus may become targets of specific attack by maternal autoantibodies or some as-yet unknown factors such as cytokines, resulting in prematurity, a generalized failure of the pregnancy, or specific syndromes of passively acquired neonatal lupus.

In this issue of *The Journal*, Clark and colleagues focus on the fetal/neonatal side of the pregnancy equation<sup>2</sup>. Their results and conclusions are based on a comparison between pregnancy outcomes over the last 3 years in patients managed in their own clinic, and studies published in the past 40 years. The take-home message is that the rate of loss in SLE pregnancies has decreased from a mean as high as 43% before 1975 to 17% in 2000–2003 (a frequency that approximates the loss rate in the general population and includes both early and late losses). Specifically, 73 of 83 (88%) pregnancies in Clark's cohort resulted in a live birth. Similar high rates of live births (86% of 267 lupus pregnancies) have been recently reported by Clowse, *et al*, in the Johns Hopkins Lupus Pregnancy Cohort<sup>3</sup>. While it is clearly acknowledged that obstetrical care in general has improved

over the last 4 decades, pregnancy loss rates in the US have remained relatively stable since 1960<sup>4</sup>. Accordingly, secular trends of normal pregnancies do not account for the favorable prognosis in the pregnancies with SLE.

As pointed out by Clark, *et al*<sup>2</sup>, it is quite likely that the decrease in loss may be due in large part to identification and treatment of patients with antiphospholipid antibodies. Moreover, it has become dogma that women with SLE are advised to consider pregnancy only when disease is stable. This point is further reinforced by Clowse, *et al*<sup>3</sup>, who recently reported that fewer live births occurred among women with high-activity lupus compared to those with low-activity lupus (77% vs 88%;  $p = 0.063$ ). High-activity lupus in the first and second trimesters led to a 3-fold increase in pregnancy loss. These results unfortunately also reinforce the point that patients can and do get pregnant even when their disease is active.

However, the news on live births is as good as it gets, because preterm delivery (< 37 weeks) in patients with SLE has only marginally decreased over the last 4 decades and continues to be nearly triple the frequency reported in the general US population. Specifically, Clark and colleagues report a modest, albeit insignificant, trend towards a decrease in preterm deliveries from 1980 to 2000 (37.5% to 32%, respectively)<sup>2</sup>. One of the difficulties in evaluating preterm deliveries relates to etiology. Early delivery might be spontaneous, e.g., premature rupture of membranes and/or preterm labor, or the result of planned induction because of deteriorating maternal or fetal well-being. Clark, *et al*<sup>2</sup> strictly defined preterm delivery as spontaneous in their own cohort, but assurances of that distinction in the literature were not possible. The effect of maternal disease activity as it related to gestational age at birth was also addressed in the Hopkins study<sup>3</sup>. Not surprisingly, full-term delivery was achieved in 26% of lupus pregnancies among women with high-activity lupus, compared with 61%

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*See* Decrease in pregnancy loss rates in SLE over a 40-year period, *page 1709*

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achieving full-term in those with no or mild lupus activity ( $p < 0.001$ ). It remains unclear whether this implies that babies were delivered because of poorly controlled maternal disease and/or that active maternal disease translates to an unfavorable *in utero* environment. A decade ago, Rahman, *et al*<sup>5</sup> reported that in 73 SLE patients with 141 pregnancies between 1970 and 1995, renal disease was the only statistically significant predictor for fetal loss ( $p < 0.012$ ) and hypertension for poor fetal outcome ( $p < 0.024$ ), using univariate analysis.

On the side of optimism, preterm birth might represent a “rescued baby” that would otherwise have been a fetal demise if not delivered early when biophysical profiles screamed of imminent danger. This optimism notwithstanding, preterm infants do not always survive, those that do may have other medical problems, and the cost of caring for these neonates can be extraordinary.

Although the study of Clark, *et al*<sup>2</sup> did not formally address whether pregnancy adversely affects maternal disease, the authors do imply in their discussion that patients who do not have severe organ disease or a history of life-threatening complications in previous pregnancies should have a favorable course. While this wisdom is generally accepted, it is worthy of mention that Lockshin and colleagues were instrumental in this regard over 20 years ago when they compared disease activity in pregnant patients with SLE and non-pregnant patients matched for disease severity<sup>6</sup>. There were no statistically significant differences in the frequency of any disease activity marker studied, including proteinuria, hypocomplementemia, anti-DNA antibodies, and therapy. Few earlier studies evaluating pregnancy in patients with lupus included control groups.

On balance, Clark and her team are appropriate in advocating that the conventional description of pregnancy in SLE be replaced by a more optimistic view, with the caveat that a history of arterial thrombosis, severe renal insuffi-

ciency, and pulmonary hypertension are contraindications. However, optimism does not obviate the critical need for judicious obstetrical care and the search for biomarkers such as complement activation products [Salmon JE. Personal communication (Re: NIH Grant No. 5R01AR049772-02, Predictors of Pregnancy Outcome in SLE and Antiphospholipid Syndrome)] that would help predict poor outcomes beyond the influence of maternal disease or specific autoantibodies.

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