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Editorial

Pregnancies in women with Systemic Lupus Erythematosus and Antiphospholipid Antibodies

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Editorial

The pregnancy outcome in women with Systemic Lupus Erythematosus (SLE) has unquestionably improved with a significant decrease in pregnancy morbidity over the last five decades from 40% in the early 1960's to less than 15% in recent years [1]. Indeed, pregnancy was discouraged in women with SLE until fairly recently. The twenty-first century brought renewed interest in research focusing on pregnancy outcomes in women with SLE, with new concepts challenging previously assumed theories.

Buyon et al joined this fascinating debate in a recent issue of *Annals of Internal Medicine* 2015 Jun 23rd, publishing the results of the PROMISSE study (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus); PROMISSE is so far the largest multicentre cohort study of pregnant women with underlying stable SLE [2]. The study included 385 women with a diverse ethnic and socioeconomic background recruited from 9 centres in total (8 centres across the United States and one in Canada) that was followed prospectively during pregnancy. Outcome measures were adverse pregnancy outcomes defined as foetal or neonatal death, birth before 36 weeks due to placental insufficiency, hypertension or preeclampsia; and Small-for-Gestational-Age (SGA) neonate (birth weight < the fifth percentile). Disease activity was assessed with the Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI) and the Physician's Global Assessment (PGA). The aim of the study was to identify risk factors for adverse pregnancy outcomes due to SLE or/and the presence of Antiphospholipid Antibodies (aPL).

It is well-known that SLE has preponderance for women in their childbearing age; consequently pregnancy has always been an important issue of concern for the patient and the treating physician. Based upon numerous reports on successful pregnancy outcomes in the past decades, the initial advice against pregnancy in the 1950s [3], has been replaced by a common understanding that women with SLE often have successful pregnancy outcomes and clinicians therefore advise on pregnancy planning, including possible drug adjustments, timing and close surveillance [4,5].

The PROMISSE study has given answers to some long discussed questions based on a scarce number of studies mainly of retrospective design or small number of patients. However, it is important to note that the PROMISSE cohort included patients with quiescent SLE embarking pregnancy. Patients with a urine protein-creatinine ratio > 1000 mg/g, creatinine level greater than 1.2 mg/dL and prednisone use greater than 20 mg/d and twin pregnancies were therefore excluded from participation.

The flare rate of SLE patients during pregnancy for example has been a subject of such debate. In the PROMISSE cohort flare rates in the second and third trimester were 2.5% and 3% respectively, which is much lower than other studies previously have reported. This emphasises the importance and reassures common clinical practice, namely the recommendation of pre-pregnancy counselling and conceiving during a disease quiescent phase. This in turn highlights the importance of specialist clinics and pregnancy counselling [5] and once again draws attention to the confidential enquiry into maternal deaths in the United Kingdom, which recommends that pregnancy counselling should be provided for women with underlying pre-existing medical illnesses. This was in response to the identification of maternal mortality in women who had not received pre-pregnancy advice [6]. In 81% of the study participants Buyon et al found women to have a successful pregnancy outcome, in other words, the child was born alive delivered after 36 weeks' of gestation and was in at least the fifth percentile for birth weight.

The PROMISSE study also highlights the remarkable difference in pregnancy outcomes across ethnic groups. Attributes of women with successful pregnancy outcomes were: non-Hispanic white origin, a negative lupus anticoagulant, not treated for hypertension at study entry, no or low

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disease activity and a platelet count of at least 100 10^9 cells/L. In comparison, women who were not of non-Hispanic white origin had more than double the risk of developing one or more adverse pregnancy outcomes; In women of African (N = 78) and Hispanic (N = 58) decent, poor foetal outcomes were found in 27.4% and 20.6%, respectively.

Other predictors of poor pregnancy performance were antihypertensive use at baseline, the presence of lupus anticoagulant, severe clinical flare of SLE during pregnancy, mild or moderate clinical flare, moderate clinical disease activity at baseline and thrombocytopenia. Interestingly, commonly used serologic variables to anticipate clinical outcomes, such as complement levels and anti-dsDNA positivity were not associated with adverse pregnancy outcomes. However, anti-dsDNA was analysed as a dichotomised variable, whereas the clinical use mainly is based in the titre tendency. Complement levels in turn are difficult to interpret in pregnancy due to the influence of oestrogen in particular and in the PROMISSE cohort, low complement levels at baseline were more often seen in patients with adverse pregnancy outcomes.

Data from the PROMISSE cohort will hopefully in the future identify serological biomarkers, possibly genes and in addition give valuable information about underlying disease mechanisms. These data will also need external validation. Moreover, due to study design, the issue of first-trimester loss was not addressed in the PROMISSE study.

In conclusion, this study provides reassurance for women with stable disease and their responsible clinicians that pregnancy outcomes are favourable. It also highlights the importance of pre-pregnancy counselling. In the United Kingdom a recent systematic review supported by the British Society of Rheumatology provides clear comprehensive guidance with regards to drug safety for clinicians treating pregnant and lactating women with underlying rheumatic disease (BSR & BHPR guideline on prescribing drugs in pregnancy and breastfeeding. Part I & II [7,8].

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