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Review article

A comprehensive review of the clinical approach to pregnancy and systemic lupus erythematosus

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ABSTRACT

Nowadays, most of the young women affected by Systemic Lupus Erythematosus (SLE) can carry out one or more pregnancies thanks to the improvement in treatment and the consequent reduction in morbidity and mortality. Pregnancy outcome in these women has also greatly improved in the last decades. A correct timing for pregnancy (tailored on disease activity and established during a preconception counselling), together with a tight monitoring during the three trimesters and the post-partum period (to timely identify and treat possible obstetric complications or maternal disease flares), as well as the concept of multidisciplinary management, are currently milestones of the management of pregnancy in SLE patients. Nevertheless, the increasing knowledge on the compatibility of drugs with pregnancy has allowed a better treatment of these patients, by choosing medications that control maternal disease activity without harming the foetus. However, particular attention and strict monitoring should be dedicated to SLE pregnant women in particular clinical settings: patients with lupus nephritis and patients with aPL positivity or Antiphospholipid syndrome, who are at higher risk for maternal and foetal complications, but also patients with anti-Ro/SSA and/or anti-La/SSB antibodies, because of the risk of neonatal lupus. A discussion on family planning, as well as counselling on contraception, should be part of the everyday-practice for physicians caring for SLE women during their reproductive age. Another issue is the possible reduction of fertility in these women, that can be due to different reasons. Consequently, the request for assisted reproduction techniques has been increasing in the last years, so that rheumatologists and gynaecologists should be prepared to counsel SLE patients also in this particular setting.

Contents

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1. Maternal and foetal outcome in SLE pregnancy

Systemic lupus erythematosus (SLE) is a chronic multi-organ autoimmune disease, with a remitting and relapsing course. It mainly affects young women during their childbearing age, so that pregnancy and family planning are topics of major interest for these patients. In the past, pregnancy was discouraged in women affected by SLE, because of frequent reports of severe flares during pregnancy and poor obstetric outcomes, and therefore termination of pregnancy was frequently recommended [1–4]. In the last decades the diagnostic and therapeutic strategies for SLE have greatly improved, and consequently the management of pregnancy. The main concerns are about the effects of pregnancy on maternal diseases and the impact of SLE itself on obstetric/foetal outcome [5].

A systematic review of literature from 1960 to 2000 reported a decrease in foetal loss rate from 40% to 17% [6] and the most recent studies observed a pregnancy loss rate of 10–25% [7–15]. Early pregnancy losses (EPL) can be determined by several factors, including chromosomal and anatomical abnormalities or hormonal dysfunctions, and influenced by maternal characteristics (age, ethnicity, co-morbidities). In addition to these risk factors, common in the general population, those specific for SLE have to be considered: proteinuria, thrombocytopenia, antiphospholipid antibody (aPL) positivity/antiphospholipid syndrome (APS), systemic arterial hypertension and high SLE disease activity, as defined by clinical scores or serological aspects (increased anti-dsDNA titre, low complement levels) [7,15].

Hypertensive complications, including pregnancy-induced hypertension, pre-eclampsia (PE)/eclampsia and HELLP, are a main concern for SLE pregnant patients, in particular for those with aPL positivity/APS and lupus nephritis (LN) [16–22]. Active/flaring SLE at conception or in the 4–6 months before has also been associated with adverse pregnancy outcomes (APO) other than EPL: late pregnancy losses (LPL), neonatal death, preterm delivery/prematurity, hypertensive complications and probably intrauterine growth restriction (IUGR) and small for gestational age (SGA) newborns [16,22–27]. Even though the disease could be in remission at the time of conception, major organ involvements such as renal or neurological, should be considered as risk factors for APO [13,21,28,29].

Disease activity at conception and in the previous months (both by the clinical and the serological side) is a key predictor not only of obstetrical complications, but also of maternal outcome in term of SLE flares during pregnancy. In fact, active SLE during the pregestation period is associated with increased risk of flare during pregnancy and particular attention should be given to the type of organ involvement, as active organ involvement in the 6 months before conception predicts the same involvement during pregnancy, especially for renal, haematological and skin activity [15–18,20,30–40]. Moreover, SLE activity before and during pregnancy also predicts damage accrual [36,41]. Present or past history of LN should be regarded as a 'red flag' for pregnancy as the worst maternal outcomes have been observed in these patients. Notably, all deaths of SLE pregnant patients have been reported in those with active LN during pregnancy: disease complications and opportunistic infections were the two leading causes [42,43]. The implications of LN during pregnancy will be discussed in a dedicated paragraph (number 3).

2. Preconception counselling and pregnancy monitoring

Preconception counselling is crucial in SLE women. Observational studies and every day clinical practice showed that planned pregnancies are associated with lower risk of flare during pregnancy, as compared to unintended pregnancies [44,45]. The EULAR recommendations for women's health and the management of family planning/pregnancy in SLE and/or APS women [46] have proposed a useful 'check-list' of factors to be considered for preconception counselling and risk stratification (synthesized and adapted in Table 1). Disease-related risk factors for unfavourable maternal/foetal outcome include increased SLE activity or flares at conception or in the 6–12 months before [15,17,25,36] and serological activity (decreased serum C3/C4, increased anti-dsDNA titres) [34,36,47,48]. Moreover, some 'critical' clinical and serological phenotypes of SLE patients have to be considered at increased risk for complications and should deserve a particular management and follow-up during pregnancy and the post-partum period:

- patients with past or present history of LN
- patients with anti-Ro/SSA and/or anti-La/SSB antibodies positivity
- patients with aPL positivity or SLE associated APS

The main issues related to these subgroups of SLE patients will be discussed in the next paragraphs (number 3,4, and 5).

Moreover, the counselling of SLE patients should include general risk factors, similarly to the general population, that should be considered together with disease-specific factors to better define the risk profile of each single patient [20,34,44,49–53] (see Table 1).

The other main aspect of counselling is the treatment of SLE patients around the conception period and during pregnancy: which drugs are compatible or not with pregnancy and which should be added or modified to obtain or maintain remission, that is crucial for the good outcome of pregnancy. This will be discussed extensively in paragraph number 6.

SLE women in their reproductive age should always be asked about their desire of pregnancy and family planning, not only to counsel against pregnancy in periods of high disease activity or during the assumption of teratogenic drugs, but also to answer to some common questions that patients are often afraid to ask: "Will my baby be healthy? Will he/she have SLE too? Is pregnancy dangerous for me or I have reduced probability to be pregnant because of the disease itself or for the drugs? Will I be able to take care of the child?". Some recent studies have addressed this issue through patient-reported questionnaires inquiring 'women health' through all its aspects, highlighting some 'gaps' in the clinician-patient communication about these important topics that appear under-investigated by rheumatologists and poorly known by patients [54].

As part of the counselling, SLE patients should be informed about the follow-up they will receive during pregnancy, which includes regular visits (every 4–6 weeks, according to our experience) to early recognize signs of disease flare or pregnancy complications. The evaluation should include physical examination, with particular attention to blood pressure, and regular blood tests including blood count, renal and hepatic function, urine analysis and anti-dsDNA and complement (at least every trimester). Erythrocyte sedimentation rate (ESR) is usually raised during normal pregnancy, so that it is not considered a valid activity marker.

Women with a history of renal involvement or hypertensive disorders, should be encouraged to frequently monitoring their blood pressure at home and should repeat 24-h urine analysis regularly. Moreover, from the obstetric point of view, SLE pregnant women should undergo regular US monitoring, following the local guidelines for pregnancies at high risk of hypertensive disorders [46,55]. Umbilical and uterine arteries Doppler sonography starting at early stages (20–24 weeks) and throughout the third trimester of