PREGNANCY IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH NEPHRITIS

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ABSTRACT

Pregnancy in patients with lupus nephritis is a challenging clinical situation. Although not absolutely contraindicated, it is associated with increased risk for foetal and maternal complications, including foetal loss, preterm delivery, intrauterine growth retardation, hypertension, pre-eclampsia, nephritis flare, and, rarely, maternal death. The complication rate is further increased in the presence of antiphospholipid antibodies or the antiphospholipid syndrome. Proliferative classes of nephritis (III and IV) also appear to confer excess risk for complications. Immunosuppressives such as cyclophosphamide and mycophenolate, and antihypertensives such as angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers need to be stopped due to teratogenic effects. Agents like corticosteroids, azathioprine, and probably calcineurin inhibitors are considered compatible with gestation. Lupus activity needs to be assessed and carefully monitored. Thrombotic risk due to antiphospholipid antibodies, thrombotic events, or nephrosis needs to be evaluated and managed accordingly, with the use of aspirin and/or unfractioned or low molecular weight heparin. Differentiating between severe pre-eclampsia and lupus nephritis flare might require a renal biopsy, which might not always be feasible, for example after the 32nd gestational week or in a setting of uncontrolled hypertension or thrombocytopaenia. A 6-month history of quiescent disease on non-teratogenic agents seems to be associated with best chance for favourable outcomes. Pregnancy is optimally managed by a multidisciplinary team of experienced specialists, and close monitoring for disease activity during gestation; additionally, follow-up for maternal flare postpartum is also advised.

Keywords: Nephritis, outcome, pre-eclampsia, pregnancy, systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a potentially fatal, chronic autoimmune disorder with a prevalence that ranges from approximately 20-150 cases per 100,000 population.[1] Its pathogenesis involves aberrant apoptotic mechanisms combined with dysregulated immune responses leading to loss of self-tolerance against nuclear antigens and to autoantibody production. The result is an immune complex disease with inflammation of various organs and tissues.[2] Up to 75% of SLE patients display evidence of renal involvement.[3] Lupus nephritis (LN) manifests clinically with haematuria, proteinuria, and varying degrees of renal impairment, and is associated with increased morbidity and mortality.[4] The histological classification of LN describes the severity of renal lesions.[5] Active, proliferative lesions (Classes 3 and 4) require aggressive immunosuppression to prevent progression to end-stage kidney disease (ESKD),[5] with response rates ranging between 30-80%.[6]

Since 90% of SLE patients are female,[7] and predominantly of childbearing age, pregnancy is not unusual in this clinical setting. Chronic kidney disease (CKD) of all stages has been associated with increased risk of maternal and foetal complications,[8,9] being higher in later stages of

renal insufficiency[10] and with the lowest pregnancy success rates being observed in ESKD.[11] Early studies implied an association between SLE and poor pregnancy outcomes.[12] However, more recent data report live birth rates higher than 85%.[13,14] Besides hypertension and the antiphospholipid syndrome (APS), renal involvement in SLE has been identified as a risk factor for poor pregnancy outcomes[3,15,16] in addition to increasing morbidity and mortality both of the mother and the foetus. This review will discuss current evidence regarding the association of SLE and LN with foetal and maternal complications, as well as recommendations and treatment options for pregnant women with LN.

COMPLICATIONS

Foetal/Neonatal

Although a recent single-centre experience comparing 60 pregnancies in women without LN with 35 pregnancies in patients with previous LN reported similar foetal prognosis,[17] pregnant SLE patients show substantially lower live birth rates than the general population,[18] and active SLE during pregnancy has been associated with poor foetal outcomes.[14,19,20] A recent meta-analysis included 37 studies with 2,751 pregnancies in 1,842 patients with SLE and LN.[15] Excluding induced abortions (5.9%), 23.4% of pregnancies were unsuccessful. Foetal complications included spontaneous abortion (16%), intrauterine growth retardation (12.7%), and stillbirth (3.6%). Among all live births the premature birth rate reached 39.4%. Neonatal deaths were reported at 2.5% (Table 1). In random-effects meta-regression analysis, active LN was significantly associated with premature birth, even after controlling for maternal hypertension.[15] Other studies have also demonstrated that only active LN is associated with poorer pregnancy outcomes, such as preterm delivery and foetal loss, compared to a history of LN or SLE without renal involvement.[16,21] In the aforementioned meta-analysis the cases with biopsy proven LN showed no association between histological classification (proliferative lesions [Classes 3 and 4] versus non-proliferative lesions [Classes 2 and 5]) and unsuccessful pregnancy rates.[15] This may be attributed to scarcity of data, as well as the elapsed time between renal biopsies and relevant pregnancies, limiting the effect of histology on outcome. In these biopsy-proven cases, both active LN and a history of LN approached, but failed to reach, significant association with premature birth rate.[15]

The presence of antiphospholipid antibodies (APAs) has been associated with poor foetal outcomes.[13,22] The aforementioned meta-analysis reported about one-quarter of pregnancies being positive for APAs.[15] Their presence, although not

Table 1: Foetal and maternal complications associated with systemic lupus erythematosus.

Foetal complication	Rate %*
Induced abortion	5.9
Spontaneous abortion	16.0
Stillbirth	3.6
Neonatal death	2.5
Unsuccessful pregnancy	23.4
Intrauterine growth retardation	12.7
Premature birth rate	39.4
Maternal Complication	
Severe (stroke, eclampsia, death)	1.0
Hypertension	16.3
Pre-eclampsia	7.6
Active nephritis	16.1
Flare	25.6

*Estimated event rate from random effect analysis.
Modified from Smyth et al.[11]

associated with the rate of active LN, did correlate significantly with premature birth rate and increased induced abortion rate.[15]

Neonatal SLE may be caused by trans-placental passage of maternal anti-SSA/Ro anti-SSB/La antibodies, causing dermatological, hepatic, haematological, or cardiac manifestations,[23] including potentially fatal congenital heart block.[24]

Maternal

The maternal complications of SLE patients during pregnancy include hypertension, lupus flare, LN, and pre-eclampsia, as well as more severe complications including eclampsia/HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, stroke, and maternal death. The SLE subjects included in the aforementioned meta-analysis[15] experienced lupus flare (25.6%), hypertension (16.3%), LN (16.1%), and pre-eclampsia (7.6%), with severe complications amounting to ~1%.[15] Deaths mainly result from sepsis, opportunistic infections, and pulmonary embolism, in the setting of renal failure, pre-eclampsia/HELLP or aggressive immunosuppression.[12,14-16,20,22,25-27] One case of pregnancy associated cardiomyopathy and one of adrenal failure after abrupt steroid withdrawal, both resulting in maternal death, have also been reported.[28] All three reported fatalities with biopsy proven LN had proliferative lesions.[16,25,27] Single-centre studies have shown an association of active LN, defined by the presence of an active urine sediment and/or proteinuria >0.5 g per 24 hours with or without elevated creatinine, with higher incidence of maternal complications, while renal quiescence at the start of the pregnancy has been associated with favourable maternal outcome.[16,22] However, a recent meta-analysis demonstrated both active LN and a history of LN to be associated with maternal hypertension and pre-eclampsia.[15] The same study reported an association between positive APAs and maternal hypertension, potentially increasing the risk of pre-eclampsia, which is a known complication of the APS.[15]

IMPACT OF PREGNANCY ON LN

During pregnancy there is an increase in the levels of progesterone and estradiol, and although a link between oestrogen and progesterone administration in postmenopausal women and lupus flare has been suggested,[7] the impact of those hormones on aggravating lupus during pregnancy is still unclear.[1] Maternal tolerance to the foetus during normal pregnancy requires immunological alterations, including increased numbers of regulatory T cells (Tregs) and a shift to a Th2 antibody-mediated immune response.[3,21] Since SLE is an antibody mediated disease also characterised by dysregulated Treg responses, pregnancy might theoretically affect disease activity. Lupus flares can occur from any time during pregnancy to several months after delivery.[29] Although the results of studies comparing flare rates between pregnant and non-pregnant SLE patients appear inconclusive, similar studies referring to the patients' own course during and without pregnancy showed an increase of LN flares during pregnancy.[3] In a recent meta-analysis the frequencies of SLE and LN flares were reported at 25.6% and 16.1%, accordingly.[15] Although few women will reach ESKD, about 25% of LN flare cases during pregnancy will prove resistant to treatment, showing progressive renal function decline after delivery.[29] Given the high risk of adverse foetal and maternal adverse events associated with active LN during pregnancy, including maternal death,[28] the importance of close monitoring for disease activity cannot be overemphasised.[3]

Assessing SLE activity during pregnancy is challenging.[29] The utility of complement levels, erythrocyte sedimentation rate, and C-reactive protein for monitoring lupus activity has not been established during pregnancy, and even higher levels of anti-double stranded-DNA (anti-dsDNA) antibodies alone did not predict pregnancy outcomes in SLE patients.[29] On the other hand, a doubling of proteinuria may be indicative of LN flare, while haemolytic anaemia and/or a platelet count of 100,000 may result from both increased SLE activity and severe pre-eclampsia/HELLP syndrome. Apart from possibly occurring simultaneously, both severe pre-eclampsia and LN flare share many clinical and laboratory findings, such as hypertension, proteinuria, oedema, and increasing creatinine.[3] Distinguishing between the pre-eclampsia and LN flare (Table 2), especially after the 20th week of gestation, may prove difficult, if not impossible, without a renal biopsy,[30] which may not be feasible after the 32nd week of gestation.[3,31] A renal biopsy will differentiate a LN flare with the need for immunosuppression from pre-eclampsia requiring delivery,[3] but it may be of extremely high risk in the setting of uncontrolled hypertension, anaemia, and thrombocytopaenia, leaving delivery as the main treatment option.[30]

Table 2: Clinical and laboratory features aiding the discrimination between pre-eclampsia and lupus nephritis flare.

	Pre-eclampsia	Lupus nephritis flare
Gestational age	After week 20	Throughout
Hypertension	Present	May be present
Increased creatinine	Usually absent	May be present
Increased serum uric acid	Increased	Normal (unless CKD)
Anti-dsDNA antibodies	Absent	Present
Low C3, C4	Absent	May be present
Leukopaenia	Absent	Present
Thrombocytopaenia	Absent (unless HELLP)	Present
Active urine sediment	Absent	Present

CKD: chronic kidney disease; HELLP: haemolysis, elevated liver enzymes, low platelets; anti-dsDNA: anti-double stranded DNA; C3: complement 3.

PHARMACOLOGICAL TREATMENT

Cyclophosphamide and mycophenolate mofetil (MMF) are the standard immunosuppressive agents for the treatment of proliferative LN (active Classes 3 and 4). Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, commonly utilised as antiproteinuric agents in LN.[32] All, however, are teratogenic and therefore their use is contraindicated during pregnancy, although cyclophosphamide has been administered as rescue treatment during the third trimester. Azathioprine and corticosteroids may be safely administered, with the caveat that dexamethasone and betamethasone cross the placenta and have been associated with hypertension and cognitive deficits in the offspring, limiting their use for obstetric indications only.[29] Corticosteroids are the only immunosuppressive agents compatible with breastfeeding.[3] Switching from MMF to azathioprine has been reported not to increase risk of renal flares in patients with quiescent LN planning to become pregnant.[33] The administration of cyclosporine and tacrolimus also presents a rather safe alternative for immunosuppression during pregnancy, with safety data being more robust regarding cyclosporine. Dosing should be guided by trough levels and may have to be increased due to the expanded volume of distribution during advanced pregnancy.[3] Hydroxychloroquine should be administered to all patients with LN, according to the latest guidelines, as its use is considered safe during pregnancy.[32] Lymphopaenia has been reported at birth after *in utero* exposure of rituximab,[34] and there are still insufficient data supporting its safe administration during pregnancy.[3]

RECOMMENDATIONS

In order to decrease the risk for foetal and maternal complications, including LN flare, pregnancy should at best be planned in patients with stable inactive lupus for at least 6 months on a treatment regimen that can be safely continued throughout gestation. Baseline testing for proteinuria/urinalysis, serum creatinine, full blood count, APAs and serum levels of anti-ds DNA antibodies, complement (C3 and C4) and liver function tests should be repeated regularly during pregnancy. Presence of anti-SSA/Ro and anti-SSM/La antibodies should prompt frequent evaluations of foetal heart rhythm especially from gestational weeks 16-32. A history of proliferative LN (Class 3 or 4) should receive special attention because of the increased risk for flare and complications. Thromboembolic risk should be assessed and treated accordingly. Postpartum regular follow-up is essential, due to the increased risk for LN flare.[3] Pregnancies are best managed by experienced multidisciplinary teams.[3,29]

SUMMARY

Although at increased risk of complications, pregnancy is not contraindicated in patients with LN. A stable inactive disease with optimal treatment for at least 6 months before conception presents the best clinical setting for a successful pregnancy. Thorough preconception counselling and evaluation, close surveillance during gestation, and continued postpartum follow-up by an experienced multidisciplinary team may be able to favourably manage the risk of foetal/neonatal and maternal complications.

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