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Systemic Lupus Erythematosus and pregnancy

Aisha Lateef[a] and **Michelle Petri**[b,*]

[a]Division of Rheumatology, University Medicine Cluster, National University Health System, 1E, Kent Ridge Road, Singapore 119074. aisha_lateef@nuhs.edu.sg

[b]Division of Rheumatology, Johns Hopkins University, School of Medicine, Johns Hopkins Lupus Center, 1830 E. Monument Street, Suite 7500, Baltimore, MD 21205, USA

Abstract

Systemic lupus erythematous (SLE) is an autoimmune disease with a strong female predilection. Pregnancy remains a commonly encountered yet high risk situation in this setting. Both maternal and fetal mortality and morbidity are still significantly increased despite improvements in outcomes. Maternal morbidity includes higher risk of disease flares, pre-eclampsia and other pregnancy-related complications. Fetal issues include higher rates of pre-term birth, intra-uterine growth restriction and neonatal lupus syndromes. Treatment options during pregnancy are also limited and maternal benefit has to be weighed against fetal risk. A coordinated approach, with close monitoring by a multidisciplinary team, is essential for optimal outcomes.

Keywords

Systemic lupus erythematosus; antibodies; pregnancy; fetal loss; pre-eclampsia; neonatal lupus syndromes

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a strong female predilection. Disease onset in younger age group, coupled with improved survival, makes pregnancy a likely occurrence in the setting of SLE. Although outcomes have improved over time and successful live births can now be achieved in a large majority, pregnancy still remains a high risk situation in SLE[1-3]. Both maternal and fetal mortality and morbidity are significantly increased, along with health care utilization and costs[2-5]. A multidisciplinary coordinated approach with involvement of appropriate specialists, and close monitoring is essential for optimal outcomes. This review will discuss major issues

*Corresponding author, mpetri@jhmi.edu.

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and the management principles to guide the clinician caring for the pregnant women with SLE.

Effects of pregnancy on SLE disease activity

Although opinions differ, most of the studies have shown that risk of SLE flare is higher during pregnancy. Variable flare rates of between 25-65% have been reported, likely attributable to different study designs, patient populations and assessment tools utilized[6-8]. Multiple predictors for flares have been identified including disease activity at the time of conception, lupus nephritis, and discontinuation of medications such as hydroxychloroquine[9,10]. The majority of these flares are mild to moderate in severity and involve renal, musculoskeletal, and hematological systems[11]. Recognition and management of the flares during pregnancy can be challenging as features may be altered and therapeutic options limited.

Recognition of disease activity during pregnancy

Recognition of disease activity and flare in pregnancy can be a difficult as physiological changes of pregnancy may overlap with features of active disease (Table 1). Investigations have to be interpreted with caution: mild degrees of anemia, thrombocytopenia, proteinuria, and raised erythrocyte sedimentation rate are common during pregnancy. Complement levels become less informative with the rise in levels during normal pregnancy. The trend becomes more important, and decline in levels of complement during pregnancy has been associated with poor pregnancy outcomes [12,13]. The use of SLE disease activity indices face similar issues, as physiologic pregnancy changes were not accounted in these tools. Pregnancy-specific disease activity scales have been developed but utility remain limited. Clinical judgment of an experienced physician may the best tool to evaluate disease activity in some scenarios.

Management of disease activity pregnancy

Treatment of disease activity and flares during pregnancy require use of medications that are effective yet safe for the growing fetus. Unfortunately, patients and sometimes even physicians discontinue medications due to concerns over presumed toxicity, resulting in avoidable disease flares and associated consequences. The fear is compounded by lack of information as the data on safety of drugs during pregnancy is generally limited to registries, case reports or animal studies. However, although choices are limited and maternal benefit has to be weighed against fetal toxicity, multiple effective options exist and should be utilized [14,15](Table 2).

Steroids can be continued during pregnancy for optimal disease control but attempts should be made to minimize the exposure. High doses of steroids are associated with an increased risk of diabetes, hypertension, pre-eclampsia and premature rupture of membranes, but short-term use for flares and disease control is permissible [14]. Similarly, use of fluorinated compounds, such as dexamethasone and betamethasone should be limited to single course for fetal lung maturity in cases of premature delivery. Repeated use should be avoided in

view of association with impaired neuro-psychological development of the offspring in later life [16].

Hydroxychloroquine (HCQ) has multiple proven benefits in SLE and continued use throughout pregnancy is strongly recommended. Pregnancy specific benefits include reduction in disease activity, lower risk of flares, and reduced risk of heart block in at risk pregnancies [17-20]. HCQ discontinuation was shown to increase disease flares during pregnancy and should be discouraged [17].

Commonly used immunosuppressive agents such as cyclophosphamide, methotrexate, and mycophenolate have teratogenic potential and ideally should be discontinued before conception. Safe immunosuppressants for pregnancy use include azathioprine and calcineurin inhibitors, tacrolimus and cyclosporine [14,15]. Multiple studies have shown them to be safe and effective therapies for use during pregnancy. An association between maternal azathioprine therapy and late developmental delays (specifically, increased utilization of special education services) in offspring was suggested by one study but remains to be confirmed[21]. Some risk of fetal cytopenias and immune suppression has been reported with higher doses and it is recommended to limit the dose to maximum of 2mg/kg/day[14]. Although safety of inadvertent exposure to leflunomide (usually followed by cholestyramine washout) has been reported, data is limited[22,23]. It should be discontinued before pregnancy with consideration of wash out procedure[15]. Use of biologic drugs during pregnancy is increasing but is still limited to anti TNF agents which are not an option for SLE [15,24]. Data on other biologic agents such as rituximab and belimumab are very limited, and use should be limited to situations where no other pregnancy safe option is viable [15]. Intravenous immunoglobulin (IVIG) and plasmapheresis remain alternative options in selected situations [15,25].

Effect of SLE on pregnancy outcomes

The interaction of SLE, an immune mediated disease, and immunological adaptations of pregnancy lead to unique challenges in this setting. Both mother and the baby are at high risk of adverse pregnancy outcomes (APO) including pre-eclampsia, pre-term delivery, pregnancy loss, and intra-uterine growth restriction (IUGR). The predictors of APO include active maternal disease, nephritis, proteinuria, hypertension, thrombocytopenia, and presence of anti-phospholipid antibodies (aPLs), especially lupus anticoagulant (LAC)[10,26-30]. Ethnic differences have also been reported, likely reflective of racial differences in disease and access to health care [10,31].

Pregnancy loss has declined significantly over the decades and live birth rates of 80-90% have been reported [1,25]. Pre-term births are now the most frequent problem, occurring in up to half of the pregnancies with poor prognostic markers listed above. Additionally, thyroid disease is associated with pre-term birth in SLE pregnancy [32].

Higher rates of maternal death, thrombosis, infection, and hematologic complications during SLE pregnancy have been reported, although non- pregnant SLE patients also have higher risks of these medical complications and mortality [2,3]. Neurodevelopmental disorders in

offspring of mothers with SLE represent an emerging concern that requires further study.[33,34].

Pre-eclampsia in SLE pregnancy

Pre-eclampsia affects 16-30% of SLE pregnancies compared to 5-7% in healthy women. In addition to the general predisposing factors (advanced maternal age, previous personal or family history of preeclampsia, pre-existing hypertension or diabetes mellitus, obesity), SLE specific predictors for pre-eclampsia include active or history of lupus nephritis, presence of anti-phospholipid antibodies, thrombocytopenia, declining complement levels, and mutations in complement regulatory proteins [35-37].

The high risk of pre-eclampsia in SLE pregnancy is compounded by the difficulty in differentiating it from lupus nephritis. Both conditions can manifest with increasing proteinuria, deteriorating renal function, hypertension, and thrombocytopenia, and can even co-exist. Guidelines and biomarkers have been proposed but have limited utility. Ultrasound findings such as abnormal uterine artery waveforms have shown good utility as diagnostic tools, and predictive modeling has been attempted for early recognition [38-40]. However, all these measures have limitations and differentiation may be extremely difficult. Renal biopsy could guide management in selected cases and is safe in experienced hands [41]. However, at times, delivery of the baby may be the only definitive answer.

Management guidelines for pregnancy in SLE

Ideally, pregnancy should be timed during period of disease quiescence as active disease at the time of conception is known to be one of the strongest predictor of APO. In reality, unplanned pregnancies are common, highlighting the often neglected need for contraceptive counseling in this group of women [42]. Effective contraceptive choices include combined oral contraceptives in women with stable disease and negative aPL, progesterone only contraceptives, and intra-uterine devices, while barrier methods are ineffective with high failure rate [43]. (See Chapter 1). Caution is required when making decisions regarding contraception in women with aPL and active disease in view of limited data.

Pregnancy may carry a very high maternal risk in a subset of SLE patients, and should be avoided in these women (Table 3). However, successful pregnancy is possible for a large majority of women with SLE, albeit with a higher risk. Pre-pregnancy evaluation with assessment of auto-antibody profile, end organ function, disease activity, and medication use helps to risk stratify, identify optimal timing and plan the management strategy for each pregnancy (Figure 1).

All pregnant women with SLE should be closely monitored during pregnancy, preferably by a multidisciplinary team of appropriate specialists. A recent large study showed reduction in immunosuppression use and rheumatologist visits despite overall increased health care utilization during SLE pregnancies [4]. This again emphasizes the need for team-based approach in care of these high risk pregnancies. Ante-natal monitoring should be tailored to the individual needs of the particular patient but generally requires frequent review,

especially in the presence of poor prognostic markers. Presence of certain specific antibodies poses special risk and deserves closer attention.

Anti-phospholipid antibodies in SLE pregnancy

Anti-phospholipid antibodies (aPL) are present in a quarter to half of SLE patients. Some of these patients are asymptomatic, while others develop thrombotic or obstetric complications, termed the antiphospholipid syndrome (APS). The presence of aPL significantly increases the risk of APO, even in asymptomatic women.

Management of exposed pregnancies depends on the risk profile and can be categorized into 3 main groups. Asymptomatic carriers are women with positive aPL but no prior clinical event. Low dose aspirin has been recommended but multiple studies have failed to show the benefit of this approach[44-46]. However, use of prophylactic aspirin in this setting remains common. The second group includes women with recurrent pregnancy losses but no systemic thrombosis, termed obstetric anti-phospholipid syndrome (OB-APS). Combination therapy with aspirin and prophylactic doses of heparin significantly reduces the risk of pregnancy loss in this group [46,47]. The third group is comprised of patients with APS and prior systemic thrombosis. These women should receive full therapeutic doses of heparin throughout pregnancy. Heparin should be continued for 6 weeks post-partum. Low molecular weight heparin (LMWH) can be used in place of unfractionated heparin as it has comparable efficacy but less adverse effects with easier monitoring.

The outcomes of aPL-exposed pregnancies have significantly improved with current therapies, and live birth rates of over 80% can be achieved. However, some patients remain refractory and continue to have recurrent losses. Management of this group remains challenging; steroids, IVIG, and plasmapheresis have been tried with some benefit, but data are limited [48-50]. Therapy has to be individualized and the patient counseled accordingly.

Anti Ro/La antibodies and Neonatal Lupus Syndromes

Pregnancies exposed to anti-Ro and anti-La antibodies have higher risk of developing neonatal lupus syndromes (NLS), a form of passively acquired fetal autoimmunity from maternal antibodies that cross the placenta. The majority of the manifestations, such as rash, hematologic and hepatic abnormalities, tend to resolve with clearance of the maternal antibodies by six to eight months of life[51]. However, injury to the developing fetal cardiac conduction pathway by these antibodies can lead to permanent damage. The cardiac manifestations include conduction defects, structural abnormalities, cardiomyopathy and congestive cardiac failure but the most feared complication is development of complete heart block (CHB)[52].

Affecting up to 2% of exposed pregnancies, but with recurrence rates of 16-20% after the first event, CHB is associated with high fetal mortality of 20%. The majority (up to 70%) of survivors require pacemaker insertion[53]. CHB development is generally preceded by lower degrees of conduction delays although rapid development without warning signs has been described[53]. The majority of the events occur between 16-26 weeks of gestation but late cases do occur and even post-partum development of CHB has been reported. Early detection and treatment initiation might halt this progression but reversal of established CHB

has not been reported. Multiple monitoring tools have been proposed for early detection of milder forms of conduction defects including doppler echocardiography, tissue-velocity based fetal kinetocardiogram, and trans-abdominal fetal electrocardiogram[54].

Fetal doppler echocardiography remains the most commonly used method. Based on the most vulnerable period, recommended approach is to monitor all exposed fetuses weekly between 16–26 weeks of gestation, and bi-weekly thereafter[52,55,56]. Detection of an early conduction defect such as prolonged PR interval should prompt a discussion about prophylactic therapy. Although results have not been consistent, maternal administration of fluorinated corticosteroids and beta agonists has shown fetal survival benefit in some studies[55,57-59]. In absence of any other therapy of known benefit, this remains the treatment of choice but any expected benefit has to be weighed against the risk of IUGR and preterm birth. Treatment of established CHB remains an unresolved issue with minimal benefit with any available approach.

The high risk of recurrence in subsequent pregnancies has prompted the quest for prophylactic therapy for at risk pregnancies. Beneficial effects of IVIG were reported in open label studies, but two large randomized controlled trials were negative[60,61]. Both trials have been criticized for methodology, and use of IVIG in this setting can still be considered as an option. However, the patient should be informed about the limited data and involved in the decision-making process.

HCQ again deserves special mention. Multiple studies have shown that HCQ reduces the risk of cardiac NLS in at-risk fetuses and possible recurrences[62]. In view of multiple beneficial effects of HCQ, need for continued use in all and especially at-risk pregnancies cannot be over-emphasized.

Medication use during pregnancy

An important aspect of pregnancy management in SLE is optimization of medication use during this period. The choices of effective yet safe immunosuppressants have been discussed above.

The management of blood pressure can also become quite challenging as most of the antihypertensive drugs are contraindicated during pregnancy. The safe options include hydralazine, methyl-dopa, nifedipine, and labetalol [63,64]. Beta-blocker use has been associated with IUGR and fetal bradycardia, and caution is required. Angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers are associated with specific malformations, neonatal arterial hypotension, and renal failure, and should be avoided [63,65].

Non-steroidal anti-inflammatory drugs (NSAIDS) are generally considered safe during the first and second trimesters [14]. Recently, associations between NSAID use in first trimester and specific birth defects were reported, along with potential risk of impaired fetal renal function with use after 20 weeks of gestation[66]. Hence, caution is required for use during early pregnancy. NSAIDSs should be discontinued by 32 week of gestation in view of the significantly higher risk of premature closure of the ductus arteriosus. Cyclo-oxygenase 2

inhibitors should be avoided during pregnancy as data are very limited for safety evaluation[14].

Antiplatelet agents considered safe for use during pregnancy include aspirin and clopidegrol [67]. However, clopidegrol has to be discontinued at least 7 days prior to delivery to avoid the increased risk of excessive hemorrhage. Heparin remains the anticoagulant of choice during pregnancy with data emerging on safety of direct factor Xa inhibitor, fondoparinux [67]. LMWH is easier to use and has similar efficacy and safety to unfractionated heparin [68]. Warfarin is teratogenic and should be avoided during pregnancy, especially during the first trimester.

Calcium supplementation is mandatory for all pregnant women with SLE, especially those receiving corticosteroids and heparin. Although Low vitamin D levels during pregnancy have been associated with poor outcomes, supplemental vitamin D during pregnancy did not reduce the risk [69,70]. Bisphosphonates have long half-lives and use in women with reproductive potential should be carefully considered.

Summary

Pregnancy in women with SLE remains a high risk condition despite considerable improvement in outcomes. Disease flares may occur during the pregnancy, recognition and effective treatment is difficult but a realistic goal. High maternal and fetal mortality and morbidity are related to higher incidence of complications such as pre-eclampsia, pregnancy loss, pre-term births, IUGR, and neonatal lupus syndromes including CHB. Close monitoring, tailored approach according to specific risks involved, and judicious use of appropriate therapies are the key to achieve optimal outcomes.

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Key points

- Outcomes for pregnancy in the setting of SLE have considerably improved but the maternal and fetal risks still remain high
- Disease flares, pre-eclampsia, pregnancy loss, pre-term births, intra-uterine growth restriction and neonatal lupus syndromes (especially heart block) remain the main complications
- Specific monitoring and treatment protocols need to be employed for situations such as presence of specific antibodies (aPL and anti-Ro/La)
- Safe and effective treatment options exist and should be used as appropriate to control disease activity during pregnancy
- Close monitoring, tailored multidisciplinary care, and judicious use of medications are the key to achieve optimal outcomes

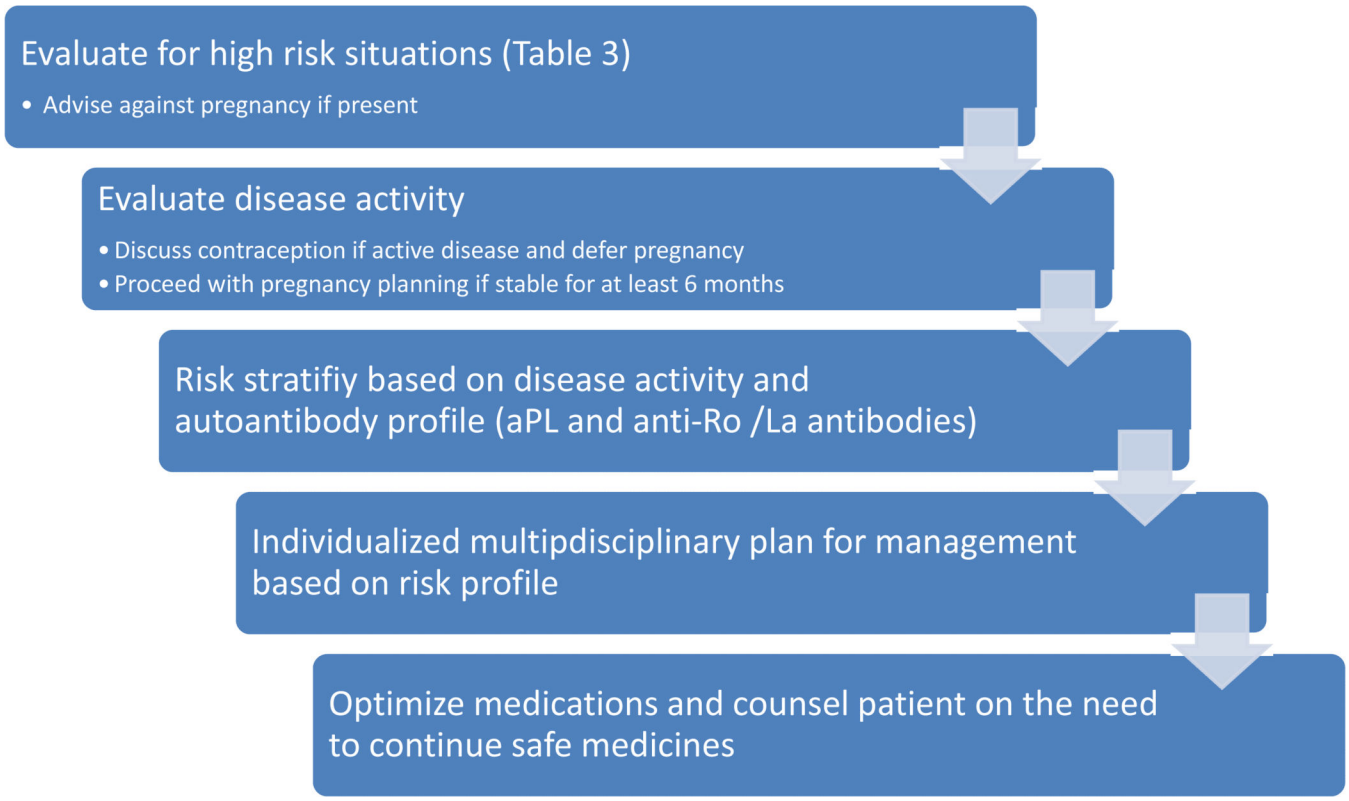

Figure 1.
Pre-pregnancy evaluation for SLE patients

Table 1

Overlapping features of pregnancy and SLE

	Pregnancy changes	**SLE activity**
Clinical Features	Facial flush Palmar erythema Arthralgias Fatigue Mild edema Mild resting dyspnea	Photosensitive rash Oral or nasal ulcers Inflammatory arthritis Fatigue, lethargy Moderate to s evere edema Pleuritis
Laboratory Features	Mild anemia, Mild thrombocytopenia Mildly raised ESR Physiologic proteinuria <300mg/day	Immune hemolytic anemia Thrombocytopenia Leucopenia, lymphopenia Raised Inflammatory markers Proteinuria >300mg/day Active urinary sediment

Table 2

Immunosuppressant use during SLE Pregnancy

Drugs	Comments
Corticosteroids • Prednisolone/ Pulse methyl prednisolone • Flourinated compounds (Betamethasone/ dexamethasone)	Use lowest possible dose Higher doses can lead to maternal complications Pulse therapy can be used for acute flares Limit to one course, for fetal lung maturation Repeated use associated with impaired neuropsychological development of the child with
Antimalarials • Hydroxychloroquine	Reduced risk of disease flares, CHB and NLS Should be continued in all SLE pregnancies
Immunosuppressants • Azathioprine • Calcineurin inhibitors (cyclosporine/ tacrolimus)	Limit azathioprine dose to 2mg/kg/day

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Table 3

High maternal risk situations for pregnancy in SLE

Avoid pregnancy if:
Severe pulmonary hypertension (systolic pulmonary artery pressure > 50mm Hg)
Severe restrictive lung disease (Forced vital capacity <1 L)
Advanced renal insufficiency (creatinine >2.8 mg/dL)
Advance heart failure
Previous severe preeclampsia or HELLP despite therapy
Stroke within the previous 6 months
Severe disease flare within last 6 months