



Indian Rheumatology Association

ISSN 0973-3698

Supplement 2 2016

*Indian Journal of*

# RHEUMATOLOGY

[www.indianjrheumatol.com](http://www.indianjrheumatol.com)

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Fertility and Pregnancy in Autoimmune Rheumatic Diseases

# Fertility and Pregnancy in Systemic Lupus Erythematosus

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Received: July, 2016

Accepted: October, 2016

Published: November, 2016

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## Abstract

Systemic Lupus Erythematosus (SLE) is a chronic multisystem autoimmune disease with a heterogeneous pattern of clinical and serological manifestations. The predilection for women, particularly of childbearing age, combined with improved survival has led to increasing numbers of women with lupus considering pregnancy. Management of pregnancy in SLE however, requires careful planning and close medical and obstetric monitoring to ensure optimal outcomes. This review, discusses possible causes of subfertility, issues regarding contraception and family planning as well as management of lupus during pregnancy and outcomes in pregnant women with SLE.

**Key Words:** *Fertility, SLE, parity, pregnancy*

## Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease with a heterogeneous pattern of clinical and serological manifestations. Pathogenesis of this disease involves a complex interaction between gene susceptibility, hormonal influences, and certain environmental triggers which induce autoantibody production, formation of immune complexes, activation of T-lymphocytes, dysregulation of apoptosis, and production of proinflammatory cytokines.<sup>[1]</sup> It has an overall incidence of 4.9–5.5 and prevalence of 72.8–97 in recent UK and US population estimates with a 6–10-fold female predominance.<sup>[2,3]</sup>

The predilection for women, particularly of childbearing age, combined with improved survival has led to increasing numbers of women with lupus considering pregnancy. Management of pregnancy in SLE, however, requires careful planning and close medical and obstetric monitoring to ensure optimal outcomes. In this review, we shall address possible causes of subfertility, issues regarding contraception and family planning, as well as management of lupus during pregnancy, and outcomes in pregnant women with SLE.

## Fertility and Parity may be Reduced in Women with Systemic Lupus Erythematosus

Reduced parity has been documented in patients with SLE. A study of women with SLE ( $n = 119$ ) found that

they viewed their disease as a barrier to childbearing<sup>[4]</sup> and a multicenter study found that 42% of women with SLE ( $n = 339$ ) diagnosed before 50 years of age had never been pregnant.<sup>[5]</sup> The reasons for this reduced parity in SLE are complex, and potential causes of infertility have been investigated. Interestingly, a higher incidence of SLE (~1%) has been identified among infertile women in the general population than would be expected given the incidence of SLE in adult women.<sup>[6]</sup> The precise incidence however of infertility in SLE is uncertain, and a number of potential factors have been identified and are summarized in Table 1.

Age is an important factor in all women as ovarian reserve and oocyte quality diminishes over time. Maternal age has been steadily increasing in recent years in economically developed societies with many women now deferring pregnancy until the end of their fourth decade, and this phenomenon may be exacerbated in patients with SLE to allow for a period of disease remission and drug washout preconception.<sup>[7]</sup>

Menstrual disturbances are common in women with lupus and associated with increased disease activity. This finding is likely to reflect the adverse effects of any active inflammatory disease process on menstruation but has also been linked with the production of anticorpus luteum antibodies and corresponding high levels of follicle stimulating hormone.<sup>[8]</sup> Drugs used to treat

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| <b>DOI:</b><br>10.4103/0973-3698.194546   |   |

**How to cite this article:** Jones A, Giles I. Fertility and pregnancy in systemic lupus erythematosus. *Indian J Rheumatol* 2016;11:128-34.

**Table 1: Factors which may contribute to reduced fertility in lupus patients**

|  |
|--|
| Age - Delays to allow for disease remission and drug washout |
| Menstrual disturbances - Associated with disease activity    |
| Drugs - Direct effect on ovarian function (CYC)              |
| Renal failure  |
| Antiphospholipid syndrome - Unproven link with infertility   |
| Psychosocial   |
| CYC: Cyclophosphamide  |

lupus have also been linked with infertility. In particular, cyclophosphamide (CYC) is gonadotoxic and the risk of ovarian failure associated with this drug is increased by patient age, cumulative CYC dose and with oral compared with intermittent intravenous CYC.<sup>[9]</sup> Other drugs that have been linked with infertility include: Cyclooxygenase (COX)-2 inhibitors that have been associated with luteinized unruptured follicle syndrome, and high-dose corticosteroids have been associated with menstrual disturbances and reduced libido.<sup>[10]</sup> It is important to note, however, that while the safety of COX-2 inhibitors has not been established in pregnancy, corticosteroids are routinely used to treat SLE in pregnancy.

Patients with chronic renal failure secondary to lupus nephritis may develop infertility through hypothalamic-pituitary dysfunction, which manifests as a menstrual irregularity and anovulatory cycles. Patients with renal failure and those on dialysis tend to have raised prolactin which reduces the production of gonadotropin-releasing hormone from the hypothalamus.<sup>[10]</sup>

Up to 40% of patients with SLE test positive for antiphospholipid antibody (aPL) and around half of these patients have antiphospholipid syndrome (APS).<sup>[11]</sup> This disease is characterized by the association of vascular thromboses and/or various forms of pregnancy morbidity.<sup>[12]</sup> There is an established link between aPL and fetal loss in patients with APS, with various studies reporting direct effects of aPL on trophoblastic and/or endometrial cells that can impair placental implantation and formation, reviewed in.<sup>[13]</sup> A more direct link, however, between aPL and infertility remains controversial and assessment for aPL is not indicated in women undergoing *in vitro* fertilization on the basis of existing data from prospective studies.<sup>[14]</sup>

Psychosocial influences are important in fertility. SLE is associated with fatigue and depression and subsequent loss of libido/sexual function in women.<sup>[15]</sup> Therefore, an apparent reduction in fertility may actually reflect reduced frequency of sexual intercourse.

### Pregnancy Planning and Contraception

Preconception assessment and counseling are a vital component of pregnancy planning in patients with SLE to evaluate for specific risks in relation to pregnancy.

Poor pregnancy outcomes in patients with SLE can be predicted by the level of lupus disease activity at conception and during pregnancy, a history of lupus nephritis, the presence of maternal anti-Ro/La antibodies, APS, and maternal hypertension.<sup>[16]</sup> Patients are encouraged to time a pregnancy to begin during a period of disease remission. A recent retrospective study of 183 pregnancies in 143 patients with SLE has shown that 4 months<sup>[17]</sup> rather than the previously reported 6 months<sup>[18]</sup> of SLE quiescence significantly improved pregnancy outcomes.

Preconception assessment must, therefore, address: Disease activity, to ensure conception occurs during disease remission; disease burden and presence of organ involvement, such as lupus nephritis; the presence of aPL and anti-Ro antibodies; medication regime, to ensure avoidance of any drugs that are incompatible with pregnancy; and other comorbidities. Advanced recognition of these factors will enable the doctor and patient to make informed decisions regarding the risk and timing of pregnancy with appropriate changes in therapy to minimize the chances of an adverse pregnancy outcome.

There are very few absolute contraindications to pregnancy in patients with SLE, and these include pulmonary hypertension, moderate to severe renal impairment, severe restrictive lung disease, advanced heart failure, and previous severe hypertensive disorders of pregnancy despite therapy.<sup>[19]</sup> The presence of any of these complications should lead to a discussion with the patient of the unacceptably high risk to both mother and fetus and advice to avoid pregnancy.

Given the potential risk for disease flare and adverse pregnancy outcomes in women with SLE, it is important that effective contraception is used until a time when these women can safely consider pregnancy. It is equally important that the appropriate form of contraception is selected. Family planning discussions, however, are often neglected during routine consultations. A US study found that 51 of 86 (59%) women with SLE at risk for unplanned pregnancy (defined as premenopausal women <45 years of age who were sexually active with men) reported no contraceptive counseling in the past year and inconsistent contraceptive use, despite frequent use of potentially teratogenic medications.<sup>[20]</sup> Furthermore, the most reported use of contraception in this study was barrier methods which have a high failure rate.

Small cohort and case studies have shown that hormonal contraceptive agents increase the risk of SLE disease flares.<sup>[21,22]</sup> Two large, randomized, clinical trials, however, have not identified a significant impact of contraceptive agents on SLE disease activity. In particular, oral contraceptives did not increase the risk of flares in premenopausal women with SLE whose disease was stable.<sup>[23]</sup> Furthermore, disease activity remained mild and

stable among women with SLE irrespective of whether they received combined oral contraceptives, a progestin-only pill or copper intrauterine device.<sup>[24]</sup> Patients with severe disease, however, were excluded from these trials.

An important consideration is the elevated risk of thrombosis with estrogen-containing contraceptives<sup>[25]</sup> making them unsuitable for patients with SLE and APS. In patients with SLE who are aPL positive but lack APS, a stratification of risk with specialist advice if necessary is recommended. In particular, patients with persistence of aPL positivity, high titer aPL, presence of lupus anticoagulant (LA) positivity, triple positivity for anticardiolipin (aCL), anti- $\beta$ 2glycoprotein I (a $\beta$ 2GPI), and LA, as well as IgG aPL, have a greater risk for future thrombotic events<sup>[26]</sup> and estrogen-containing contraceptives are best avoided in these patients.

The use of an intrauterine contraceptive device is a suitable alternative, particularly in patients with increased thrombotic risk. Although concomitant immunosuppressive therapy, raises theoretical concerns of an increased infection risk with these devices, no specific recommendation exists as to what degree of immunosuppression imparts a meaningful risk of infection in patients with SLE.<sup>[27]</sup>

### Adverse Outcomes in Pregnancy

Advances in disease management, prepregnancy counseling, and monitoring during pregnancy have led to a significant improvement in pregnancy outcomes in SLE. The rate of pregnancy loss has decreased from 43% in 1960–65 to 17% in 2000–03, which approximates that of the general US population.<sup>[28]</sup> Despite these improvements, however, pregnancy in SLE still carries a high risk of complications as shown in Table 2. Interrogation of the US national database of 16.7 million deliveries (2000–03) identified 13,555 deliveries in women with SLE and found an increased risk of maternal death, preeclampsia, preterm labor, thrombosis, infection, and hematological complications during SLE compared with non-SLE pregnancies.<sup>[29]</sup> Notably, however, women with SLE in this study were older and had significantly higher rates of comorbidities than women in non-SLE pregnancies.

Women with SLE are at particular risk of developing adverse pregnancy outcomes related to placental disease. For

instance, they have a much higher risk (23%) of developing hypertensive disorders in pregnancy and (5%) intrauterine growth restriction (IUGR) compared with (7.8% hypertension and 1.6% IUGR) in otherwise healthy controls.<sup>[29,30]</sup>

A significant hypertensive complication in SLE pregnancies is preeclampsia, a syndrome of pregnancy defined by the onset of hypertension and proteinuria after 20 weeks of gestation. In the general population, predisposing factors for preeclampsia include advanced maternal age, previous personal or family history of preeclampsia, preexisting hypertension, diabetes, or obesity. In SLE, specific risk factors are a history of lupus nephritis, presence of aPLs, declining complement levels, and thrombocytopenia.<sup>[31]</sup> These factors may also increase the risk of fetal loss and other adverse pregnancy outcomes as well-being negative predictors for fetal survival.<sup>[19]</sup>

### ***Pregnancy complications of anti-Ro and anti-La antibodies***

Active transplacental transfer of maternal IgG takes place through neonatal fragment of crystallizable component/ Fc receptors (FcRn), present on the syncytiotrophoblast, from 16 weeks of pregnancy onward. The active placental transfer of maternal anti-Ro and/or anti-La antibodies can cause congenital heart block or neonatal lupus syndromes. The risk of congenital heart block in an anti-Ro/La-positive mother is low at 2% but rises to 15%–20% in a mother with a previously affected pregnancy.<sup>[32]</sup> Cardiac manifestations including conduction defects, structural abnormalities, cardiomyopathy, and congestive cardiac failure are often permanent and can contribute to the fetal loss. The most common cardiac manifestation, however, is congenital heart block and given the timing of placental transfer of maternal anti-Ro/La antibodies, it is important to begin screening for this condition with fetal cardiac ultrasound scan at 16–20 gestation, with repeat at 28 weeks if the initial 20-week scan was normal.<sup>[33]</sup> Fetal cardiac ultrasound auscultation with each clinic visit is advised and if there is evidence of progressive heart block and cardiac failure in the fetus, then a decision needs to be taken for optimal timing for a planned delivery of a viable fetus or termination of the pregnancy. No interventions have been shown to reverse established heart block.<sup>[34]</sup> The use of hydroxychloroquine (HCQ), however, during pregnancy has been shown to significantly reduce the risk of recurrence of cardiac neonatal lupus in the offspring of anti-Ro/La-positive women.<sup>[35]</sup> Neonatal cutaneous lupus is more common than heart block and presents as a florid cutaneous rash that fades over the first 6 months of life with conservative management.

### ***Pregnancy complications of antiphospholipid antibodies***

The presence of aPL in pregnancy is associated with a significant risk of recurrent fetal loss, preeclampsia,

**Table 2: Adverse pregnancy outcomes associated with lupus**

|                                 |
|---------------------------------|
| Preeclampsia                    |
| Preterm labor                   |
| Thrombosis                      |
| Infection                       |
| Hematological complications     |
| Intrauterine growth restriction |

placental insufficiency, IUGR, and preterm delivery.<sup>[29,30,36]</sup> Further details of how patients with aPL are managed in pregnancy are given in an accompanying article "Pregnancy in antiphospholipid syndrome" on pages S117-S121 in this issue.

### **Predictors of adverse pregnancy outcomes in systemic lupus erythematosus pregnancy**

Various single-center cohort studies in SLE have identified several novel predictors of poor pregnancy outcomes, such as mid-gestational biomarkers, including ferritin, estradiol, and uric acid in a prospective study of  $n = 40$  SLE pregnancies<sup>[37]</sup> and uterine artery Doppler findings in a retrospective study of  $n = 65$  SLE pregnancies.<sup>[38]</sup> The largest study of adverse pregnancy outcomes in SLE is the Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and SLE (PROMISSE) study. This prospective multicenter study has assessed the frequency of adverse pregnancy outcomes and clinical and laboratory variables that predict them, in women with aPL and/or (inactive, mild, or moderate) SLE at conception. To date, this study has reported that LA—rather than aCL or a $\beta$ 2GPI-positivity is the primary predictor of adverse pregnancy outcomes in two independent groups of patients recruited at different time intervals,  $n = 144$  aPL-positive patients recruited between 2003 and 2011<sup>[39]</sup> and  $n = 44$  aPL-positive patients recruited between 2011 and 2015.<sup>[40]</sup> It has also shown that in  $n = 385$  pregnant patients with inactive or stable mild/moderate SLE, severe flares are infrequent and in the absence of specific risk factors (LA positive, use of antihypertensive medications, nonwhite or Hispanic mother) pregnancy outcomes are favorable.<sup>[41]</sup> Although this knowledge is very useful when counseling patients considering lupus pregnancy, there are certain limitations of the PROMISSE study such as the timing of patient enrollment that precludes ascertainment of first-trimester loss, exclusion of patients with lupus nephritis, and/or severe SLE disease activity. Therefore, further studies to include patients with more severe SLE are required.

### **Disease Flares during Pregnancy**

There are conflicting results of the impact of pregnancy on SLE activity, with some studies reporting no increased risk of SLE flares during pregnancy compared with controls<sup>[42-44]</sup> while others found pregnancy to be associated with increased SLE flares rate compared with control.<sup>[45-47]</sup> Overall, many studies have identified between 35% and 70% of all pregnancies in patients with SLE to have some form of measurable disease activity of which 15%–30% have a moderate to severe flare during pregnancy.<sup>[48]</sup> These discrepant findings are likely to reflect differences in definitions of SLE flares, assessment of disease activity, and selection of control group. In particular, there are certain physiological changes which occur in pregnancy that can

be hard to differentiate from a lupus flare including an increase in proteinuria and hypertension which could lead to overestimation of lupus flares.

There is consensus, however, that the risk for SLE flare during pregnancy is increased in patients with active disease within 4–6 months of pregnancy,<sup>[17,18]</sup> active disease at conception,<sup>[44,49]</sup> a history of highly active disease in the years prior to pregnancy, and discontinuation of HCQ.<sup>[18,50]</sup>

### **Management during Pregnancy**

Given the complex nature of SLE and its relationship with pregnancy, management of these patients should involve a multidisciplinary approach that considers prepregnancy counseling; therapy received prior to, during, and after pregnancy; early recognition of both obstetric and medical complications relating to the underlying disease; prenatal fetal development; and postnatal management of the patient and infant. Ideally, patients should be managed by clinicians with specialized expertise in early recognition and treatment of complications of pregnancy, to allow appropriate risk assessment/stratification of the patient, and provision of an individualized plan for antenatal and postnatal management of such high-risk pregnancies.<sup>[51]</sup>

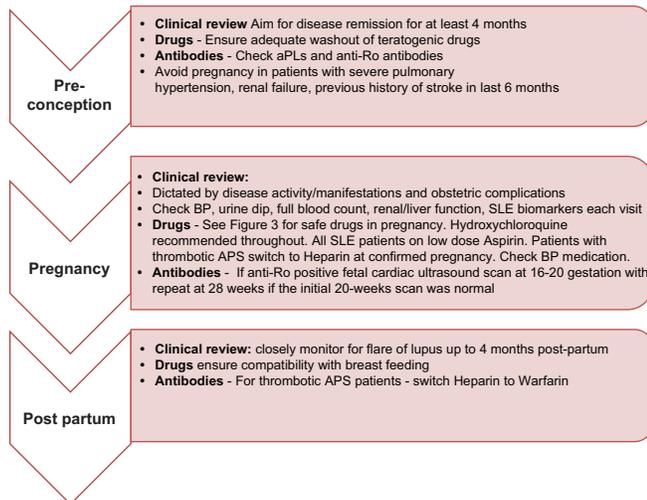
Treatment of SLE during pregnancy is guided by the degree and severity of organ involvement, similar to the nonpregnant state. Given the direct relationship between active SLE and adverse pregnancy outcomes, adequate control of disease activity in pregnancy is paramount. Various anti-inflammatory, immunosuppressive, and/or biologic drugs may be required to control SLE disease activity outside of pregnancy. The use of many of these drugs in pregnancy, however, is contraindicated because exposure increases the risk of congenital malformations and spontaneous abortion. Recent, British Society of Rheumatology (BSR) and European League Against Rheumatism publications have issued evidence-based recommendations on prescribing antirheumatic drugs in pregnancy and breastfeeding.<sup>[52,53]</sup> These documents systematically review all current evidence on the use of various antirheumatic drugs before/during pregnancy and breastfeeding in patients with rheumatic disease. They provide invaluable guidance for all health-care professionals to allow prescribing in SLE of drugs compatible with pregnancy to ensure maintenance of remission or treatment of disease flare. Certain drugs that are safe to use in SLE pregnancy are shown in Table 3.

The main principles of management of SLE before, during, and after pregnancy are outlined in Figure 1. Prepartum, it is important to ensure a period of low/no disease activity for more than 4 months preconception. Stop medications that are harmful in pregnancy, such as mycophenolate mofetil (MMF) and CYC. Screen for the presence of anti-Ro/La and aPL and stratify risk according to the degree of organ involvement. In addition, it is important to

**Table 3: Drugs safe to use in systemic lupus erythematosus pregnancy**

| Drug  | Recommendations  |
|---|--|
| NSAIDs  | Use with caution in the first trimester - Possible low risk of miscarriage and congenital malformation. Avoid in last trimester - Associated with premature close of ductus arteriosus |
| Corticosteroids                                     | Prednisolone and methylprednisolone have ≤10% placental transfer and are safe in all trimesters and breastfeeding  |
| Hydroxychloroquine                                  | Safe throughout pregnancy and breastfeeding  |
| Azathioprine  | Safe throughout pregnancy - Limit dose to 2 mg/kg/day  |
| Calcineurin inhibitors (cyclosporin and tacrolimus) | Safe throughout pregnancy  |

NSAIDs: Nonsteroidal anti-inflammatory drugs



**Figure 1: Management of pregnancy in lupus**

reassure patients that HCQ is safe throughout pregnancy and breastfeeding<sup>[52,53]</sup> and withdrawal of this drug may actually be harmful since that has been associated with a flare of SLE in pregnancy.<sup>[38,39]</sup> Therefore, HCQ should be continued in all pregnant women with SLE. A prospective study<sup>[54]</sup> has confirmed that patients with quiescent renal lupus can be safely transitioned from MMF to azathioprine pre-conception and this drug is then safe to continue throughout pregnancy and breastfeeding.<sup>[52]</sup>

At conception, all patients with SLE should be commenced on low-dose aspirin since it has been shown to reduce the risk of preeclampsia in non-SLE high-risk pregnancies.<sup>[55]</sup> In patients with renal disease and/or hypertension, other medications which may need to be altered at this time include angiotensin converting enzyme inhibitors that are associated with a specific pattern of fetal malformation and should be switched to alternative antihypertensive drugs, such as amlodipine that are compatible with

pregnancy.<sup>[56]</sup> Immunosuppressive drugs that may safely be used through pregnancy also include ciclosporin and tacrolimus. In addition, corticosteroids (prednisolone, prednisone, and methylprednisolone) are metabolized in the placenta, so 10% or less of the active drug reaches the fetus; thus they are compatible with pregnancy and breastfeeding.<sup>[52]</sup> Typically, disease flares are managed in pregnancy by reducing dose regimes of oral prednisolone or intravenous pulse therapy with methylprednisolone to minimize adverse effects of corticosteroids on blood glucose, blood pressure, and bone density. It is important to ensure calcium supplementation in all women with SLE in pregnancy, particularly when taking corticosteroids although Vitamin D supplementation is best preserved for women at most risk of Vitamin D deficiency and rickets.<sup>[57]</sup>

When dealing with patients with a possible disease flare in pregnancy, it is important to distinguish between preeclampsia and lupus nephritis flares as the management of these two conditions is different. This distinction can be difficult as both may present with increasing proteinuria, deteriorating renal function, hypertension, and thrombocytopenia. The traditional biomarkers of SLE activity are less helpful since C3 and C4 serum levels normally rise steadily during pregnancy and in patients with preeclampsia;<sup>[41]</sup> hence, a drop in C3 and C4 coupled with a rising anti-dsDNA titer is likely to be associated with a disease flare in patient with SLE and proteinuria. The presence of active urinary sediments and signs of other disease activity including arthritis, cutaneous vasculitis, ulcers, and lymphadenopathy also point toward a lupus flare. Prednisolone will generally worsen preeclampsia but improve renal lupus. Interestingly, one SLE cohort study found that most patients with a relapse of nephritis in pregnancy were not hypertensive, in contrast to SLE complicated by preeclampsia patients.<sup>[16]</sup> Ultimately, a renal biopsy may be required to differentiate, however, the risk associated with this procedure often precludes its use in advanced pregnancy. Ultimately, delivery of a viable fetus may be the only definitive treatment.

Biologic therapy in SLE is centered upon B-cell blockade with rituximab (RTX) or belimumab (BEL). Currently, however, there is insufficient evidence to recommend their use in pregnancy. Therefore, despite limited evidence that RTX is not teratogenic and only second/third-trimester exposure is associated with neonatal B-cell depletion, the BSR guideline concludes that RTX should be stopped 6 months before conception although unintentional RTX exposure early in the first trimester is unlikely to be harmful.<sup>[52]</sup> Similarly, although limited data from BEL exposed pregnancies have not identified any harmful effects, the BSR guideline does not recommend BEL in pregnancy or breastfeeding, but unintentional exposure early in the first trimester is unlikely to be harmful.<sup>[52]</sup>

## Conclusion

Management of patients with SLE before, during, and after pregnancy is complicated by several factors including an increased burden of pregnancy morbidity, complex relationship with disease activity, and the presence of preexisting comorbidities requiring multiple medications that may be incompatible with pregnancy. Appropriate risk assessment/stratification, however, of each patient and provision of an individualized plan for antenatal and postnatal management will provide an optimal chance of a successful pregnancy outcome.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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