




Fertility, pregnancy and lactation in women with systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that predominantly affects women of childbearing age. As the prevalence of SLE rises, and advances since the 1960s have substantially improved survival and quality of life, the number of women with SLE who become pregnant is steadily increasing. Although pregnancy is feasible for most patients with well-controlled SLE, pregnancy remains challenging for both women with SLE and clinicians because the risk of maternal complications and adverse fetal outcomes is higher than that in the general population. Moreover, the increased risk of pregnancy complications persists in subsequent pregnancies in women with SLE, whereas in healthy women this risk decreases owing to the development of maternal–fetal immune tolerance. During pregnancy and the postpartum period, women remain at risk of disease flares and other complications, particularly those with active disease at conception, a history of lupus nephritis, antiphospholipid syndrome or recent medication withdrawal. Important knowledge gaps persist regarding the mechanisms underlying these complications and the safety of treatment during conception, pregnancy and lactation. Preconception counselling, assessment of risk factors for adverse outcomes, pregnancy planning, timely medication adjustment and multidisciplinary management are essential to improve the maternal and fetal outcomes in women with SLE.

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Key points

- In women with systemic lupus erythematosus (SLE), pregnancy is associated with higher risks of maternal complications and adverse fetal outcomes than in women in the general population.
- Fertility in women with SLE might be reduced owing to disease activity, renal failure, cyclophosphamide exposure, age-related decline in ovarian reserve and lifestyle factors.
- Achieving ≥ 6 –12 months of inactive SLE on pregnancy-compatible medication before conception reduces the risks of disease flare and pregnancy complications.
- Preconception counselling, pregnancy planning, adjustment of medication, multidisciplinary management and shared decision-making are central to achieving safe pregnancies in women with SLE.
- Elucidating the pathogenesis of pregnancy complications in women with SLE is crucial for improving maternal and fetal outcomes.
- Important gaps persist regarding the safety of antirheumatic medication use during conception, pregnancy and lactation, and so further research is required.

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease, characterized by episodes of disease activity and disease remission. The disease predominantly affects women of childbearing age, and pregnancy represents a major challenge for both women with SLE and clinicians, as SLE can adversely affect the pregnancy course and outcomes, and pregnancy itself can exacerbate disease activity. Despite improvements in the management of pregnant women with SLE over the past three decades – and a documented decline in adverse pregnancy outcomes between 2003 and 2022 in a Swedish nationwide study¹ – pregnancy in women with SLE continues to carry a higher risk of maternal complications and adverse fetal outcomes compared with the general population^{2,3}. Moreover, the increased risk of pregnancy complications persists in subsequent pregnancies in women with SLE, in contrast to a declining trend in healthy women⁴. In addition, patients are at risk of SLE flares throughout pregnancy and the postpartum period⁵.

Despite the increasing number of pregnant women with SLE⁶, studies over the past three decades have shown that patients with SLE have fewer children than women in the general population^{7–10}, and fewer children than originally planned¹¹. A Finnish nationwide study found higher rates of childlessness among both women and men with SLE (9.3% and 4.7%, respectively) compared with the rates in the general population¹⁰. Reduced family sizes in individuals with SLE can be attributed to the cumulative effects of previous adverse pregnancy outcomes, chronic disease, medication required to control the disease, treatment-related gonadotoxicity, reduced libido, sexual dysfunction and psychological factors, including concerns about the ability to parent and fears of transmission of the disease to offspring owing to hereditary factors^{12–14}. The physical and psychological impacts of SLE affect reproductive health in both men and women^{15–18}.

In this Review, we provide an overview of current insights into fertility in women with SLE, the bidirectional relationship between SLE and pregnancy and the pathophysiology of pregnancy complications in women with SLE. We also summarize contemporary standards of clinical care for women during the periconception period, pregnancy and lactation, and outline key priorities for future research.

Fertility

Since 2016, several guidelines have been published to support the clinical management of patients with SLE, including the British Society for Rheumatology (BSR) guidelines^{19–21}, the European Alliance of Associations for Rheumatology (EULAR) recommendations for family planning, assisted reproduction and pregnancy in women with SLE and/or antiphospholipid syndrome (APS)²², the American College of Rheumatology (ACR) guidelines on reproductive health in rheumatic diseases, including SLE²³, and updated EULAR recommendations for the use of antirheumatic drugs during reproduction and pregnancy²⁴. These guidelines address key aspects of fertility including the impact of SLE and its treatments, assisted reproductive techniques and contraception – topics explored in detail in this section.

Impact of SLE

Fertility is defined as the natural ability to conceive, and SLE does not seem to impair the function of the fallopian tubes²². Nevertheless, a systematic review of 1,272 women with SLE and 555 healthy individuals showed reduced concentrations of anti-Müllerian hormone (a marker for ovarian reserve) in women with SLE, especially those previously exposed to cyclophosphamide²⁵. Active autoimmune disease and renal failure independently contribute to impaired fertility^{26,27}. Age-related decline in ovarian reserve, comorbid conditions and lifestyle factors such as smoking and obesity affect women with SLE in the same way as in the general population, underscoring the importance of early counselling on family planning and reproduction during the reproductive years.

Influence of medication

The productive effects of conventional synthetic DMARDs (csDMARDs) differ by the drug, safety profile, reversibility and timing of discontinuation (Table 1). Biologic DMARDs (bDMARDs), such as belimumab and rituximab, generally have a compatible safety profile, whereas evidence on targeted synthetic DMARDs and small molecules remains limited²⁴. Use of TNF inhibitors in SLE varies widely, influenced by concerns about their potential to induce anti-double-stranded DNA antibodies²⁸.

Prior exposure to cyclophosphamide or other alkylating agents is linked to reduced ovarian reserve and an increased risk of premature ovarian failure, particularly in patients who receive cumulative cyclophosphamide doses exceeding 7.5–10 g or who are older than 30 years at the time of first exposure^{29,30}. The Euro-Lupus low-dose cyclophosphamide regimen (six fortnightly pulses at a fixed dose of 500 mg) is therefore generally preferred in women with SLE, as its much lower cumulative exposure confers only a low risk of infertility in women younger than 30 years^{31,32}.

Fertility preservation using gonadotropin-releasing hormone analogues should be considered in women prior to treatment with alkylating agents²². Against this background of well-established gonadotoxicity associated with alkylating agents, the potential reproductive effects of more commonly used agents, including NSAIDs, have also been explored. Although a prospective study in 2,573 women suggested that NSAIDs might adversely affect ovulation and implantation³³, the overall evidence on NSAID-related impairment of fertility is limited

Table 1 | Safety of antirheumatic drugs preconception, during pregnancy and during lactation

Drug	Before conception	During pregnancy	During lactation
Drugs widely used before conception, during pregnancy and during lactation			
Hydroxychloroquine	Compatible	Compatible	Compatible
Chloroquine	Compatible	Compatible	Compatible
Azathioprine	Compatible	Compatible	Compatible
Cyclosporine	Compatible	Compatible	Compatible
Tacrolimus	Compatible	Compatible	Compatible
Colchicine	Compatible	Compatible	Compatible
Prednisone and prednisolone	Compatible (aim for ≤ 5 mg/day ^a)	Compatible (aim for ≤ 5 mg/day ^a)	Compatible (aim for ≤ 5 mg/day ^a)
Drugs used only in selected circumstances^b			
NSAIDs (ibuprofen as first choice; only intermittent use)	Compatible (stop if conception is difficult)	Compatible (stop at 20 weeks of gestation)	Compatible
IVIG	Compatible	Compatible ^c	Compatible
Belimumab	Compatible	Compatible ^c	Compatible
Rituximab	Compatible	Compatible ^c	Compatible
TNF inhibitors	Compatible	Compatible	Compatible
Anifrolumab	Not compatible ^d	Not compatible ^{d,e}	Compatible
Drugs contraindicated during pregnancy (teratogenic or harmful)			
Cyclophosphamide	Not compatible ^f (stop 3 months before conception)	Not compatible ^{f,g}	Not compatible ^f
Methotrexate	Not compatible ^f (stop 1–3 months before conception)	Not compatible ^f	Not compatible ^{f,h}
Mycophenolate mofetil	Not compatible ^f (stop ≥ 6 weeks before conception)	Not compatible ^{f,g}	Not compatible ^f
Leflunomide	Not compatible ^d (cholestyramine washout if needed)	Not compatible ^d	Not compatible ^d
Voclosporin	Not compatible ^d	Not compatible ^d	Not compatible ^d

Data from refs. 22,23. IVIG, intravenous immunoglobulin. ^aUse only if possible without provoking a disease flare. ^bOnly use when necessary, such as during disease flares or uncontrolled disease, failure, if other (pregnancy-compatible) options are contraindicated, or to reduce the need for higher than optimal prednisolone doses. ^cCan be used during pregnancy if needed to effectively control maternal disease. ^dNot compatible because of insufficient evidence to establish safety. ^eShould be used during pregnancy only if no pregnancy-compatible medication can effectively control maternal disease. ^fNot compatible because of proven harm or teratogenicity. ^gIn severe, refractory maternal disease during pregnancy, IVIG, or (in the second and third trimester) cyclophosphamide or mycophenolate mofetil can be considered. ^hMethotrexate ≤ 25 mg weekly can be considered during lactation if no safer alternative can be used. ⁱCholestyramine washout is recommended only if leflunomide discontinued < 3.5 months before conception.

and does not require stopping NSAIDs when attempting to conceive. Nevertheless, NSAID withdrawal might be considered if conception takes longer than expected^{23,24}.

Assisted reproductive techniques

Assisted reproductive techniques are generally safe in women with well-controlled SLE^{22,34,35}, provided that management includes multidisciplinary assessment and thrombotic risk stratification owing to the use of oestrogen-containing agents with prothrombotic potential. Indications for assisted reproductive techniques are the same as for women without chronic diseases. Because twin and higher-order multiple pregnancies are associated with adverse outcomes – most notably preterm birth³⁶, a complication that is already more frequent in women with SLE² – ovarian stimulation should be carried out with caution, and single-embryo transfer should be routinely recommended, as supported by prior literature³⁷. The use of adjusted ovarian stimulation protocols aimed at minimizing peak oestrogen levels might further improve safety and reduce complications in women with rheumatic diseases, including SLE and APS^{38–40}. Furthermore, prophylactic

anticoagulation therapy with low-molecular-weight heparin (LMWH) or heparin should be considered in asymptomatic antiphospholipid antibody (aPL)-positive women and is recommended in women with obstetric APS undergoing assisted reproductive techniques, in line with the ACR guidelines and EULAR recommendations^{22,23}.

Contraception

Effective contraception – tailored to the patient's comorbidities and individual thrombosis risk, and balanced against the risks of an unplanned pregnancy – remains essential, and should be actively discussed with all women with SLE of childbearing age to prevent unplanned pregnancy and to enable optimization of disease control and medication regimens before conception^{22,23}. Thrombosis risk is mainly associated with the presence of aPLs or APS^{22,23}, although consideration of factors such as hypertension, obesity and smoking is also warranted.

Both copper and progesterone-containing intrauterine devices are safe options in women with SLE in the absence of gynaecological contraindications^{22,23}. As copper intrauterine devices are more likely

to be associated with increased menstrual bleeding⁴¹, progesterone-containing intrauterine devices are often preferred; importantly, intrauterine devices, including progesterone-containing devices, are not associated with an increased risk of venous thromboembolism (VTE) or arterial thromboembolism⁴².

Use of oestrogen-containing contraceptives is associated with a twofold to threefold increased risk of VTE compared with non-use in the general population, and this risk seems to be further amplified in women with SLE, particularly in aPL-positive women⁴³. Therefore, women with an increased thrombotic risk are advised against using oestrogen-containing contraceptives^{22,23,44}. However, combined hormonal contraceptives can be considered in women with inactive disease and absence of aPLs⁴⁵. By contrast, women with SLE who are persistently aPL-positive, regardless of whether they fulfil criteria for APS, should avoid combined contraceptives²². For these women, progesterone-only contraception pills are an alternative option⁴². Although limited data are available, the use of depot medroxyprogesterone acetate in aPL-positive women should be avoided as use of this agent is associated with an increased risk of thrombosis in the general population, unlike progesterone-only pills and progesterone-containing intrauterine devices^{23,46}. In practice, women with SLE and a low thrombotic risk and inactive disease can use combined hormonal contraceptives or any intrauterine device. In those with higher thrombotic risk or persistent aPL positivity, progesterone-only options or progesterone-containing intrauterine devices are generally more suitable; the latter is especially useful in women with SLE who are receiving anticoagulation therapy because this method minimizes menstrual blood loss while maintaining highly effective contraception.

The impact of pregnancy on SLE

Pregnancy in women with SLE involves a finely regulated interplay between maternal immune adaptations and underlying autoimmune activity. Over the past three to five decades, substantial progress has been made in characterizing the frequency and spectrum of disease flares during pregnancy and the postpartum period, as well as factors that predispose to these events.

Disease flares during pregnancy

SLE flares occur in approximately 2.5–35% of pregnancies, most frequently during the second and third trimesters or in the early postpartum period^{4,47,48}. The spectrum of flares ranges from mild mucocutaneous or musculoskeletal manifestations to severe renal, haematological or neuropsychiatric involvement. Whether flare risk is increased during pregnancy and the postpartum period remains debated, as studies on this topic have yielded conflicting results, possibly owing to differences in study design, inclusion criteria, flare definitions and pregnancy management^{49,50}. Evidence from the Hopkins Pregnancy Cohort, which included 1,349 women with SLE and 398 pregnancies in 304 women⁵, showed higher flare rates during pregnancy than in non-pregnancy periods, and an additional increase during the first 3 months after birth. Notably, the increased risk of flares occurred exclusively among women not taking hydroxychloroquine, aligning with prior observational data showing that continuous hydroxychloroquine use before conception and throughout pregnancy reduces the risk of flares during gestation and the early postpartum period^{51,52}.

Risk factors for disease flares

Hydroxychloroquine is recommended as baseline therapy in all pregnant women with SLE to help maintain disease control^{5,51}. Discontinuation

of hydroxychloroquine^{5,51}, active disease at conception^{52–55}, and a history of active or previous lupus nephritis^{47,56,57} are major risk factors for flare during pregnancy and the postpartum period. High disease activity at conception or within the 6 months preceding conception, as well as serologically active disease in the first trimester (characterized by hypocomplementaemia or failure to increase to supranormal complement levels) are also associated with an increased risk of flare during pregnancy^{52–55,58}.

Past lupus nephritis has been identified as a risk factor for both renal and non-renal flares in prospective studies^{47,56}. Moreover, renal flare risk also varies substantially with disease activity: in one cohort of women with lupus nephritis, the renal relapse rate was 72% among those with an unplanned pregnancy or who were not in complete remission, compared with 11.3% among women who had achieved complete renal remission at conception⁵⁷. Furthermore, a systematic review published in 2025 showed that younger age is associated with an increased risk of disease flares during pregnancy⁵⁹, and in another study primigravida was linked to a higher risk of both renal and non-renal flares⁶⁰.

In summary, maintaining low disease activity, continuing treatment with hydroxychloroquine and achieving complete remission of prior lupus nephritis are major factors in preventing disease flares during pregnancy and the postpartum period.

The impact of SLE on pregnancy

Despite improvements in the management of pregnancies in women with SLE, these pregnancies remain associated with higher risks of both maternal and fetal complications compared with pregnancies in the general population^{1,61}. Moreover, complications arising during pregnancy in women with SLE not only endanger the health of the mother and child during pregnancy, but are also linked to an increased risk of several health complications later in life for both mother and child^{62,63}. In the following section, we first outline the pregnancy complications associated with SLE, and then provide an overview of current knowledge regarding the pathophysiology of these complications in SLE.

Pregnancy complications and adverse outcomes

Several studies have shown that women with SLE have higher rates of obstetric complications than women in the general population, including pregnancy loss, fetal death, (pre-)eclampsia, fetal growth restriction (FGR), low birthweight and preterm birth^{1,64,65}. Moreover, in a population-based study from the USA, maternal mortality was 20-fold higher among women with SLE⁶⁴. Despite a decrease in maternal and fetal mortality and obstetric complications over the past decades (with fetal loss falling from 43% in the 1960s to 17% in the early 2000s)^{61,66}, overall complication rates and the associated health-care costs remain higher than in pregnancies in women without SLE⁶⁷. Furthermore, the increased risk of hypertensive disorders of pregnancy (HDP), FGR, fetal death and premature birth persist across subsequent pregnancies in women with SLE, contrasting with the declining risk typically observed in healthy women⁴. When considering population-level temporal trends, a nationwide Swedish study examining the past two decades found that adverse pregnancy outcomes declined more markedly in nulliparous than in parous pregnancies in women with SLE, whereas the rates of adverse outcomes remained unchanged in the general population¹.

SLE-specific risk factors for adverse pregnancy outcomes include active disease prior to or at conception, lupus flares during pregnancy, hypertension, a history of lupus nephritis, severe organ failure (such as of the kidneys, heart or lungs), the presence of aPLs

or established APS, anti-Ro/SSA and/or anti-La/SSB antibodies and thrombocytopenia^{47,68–73}. A retrospective cohort study of 347 pregnancies in 332 Chinese women with SLE showed that women who fulfilled a combination of favourable preconception conditions (such as stable disease for at least 6 months, absence of active vital organ involvement, use of hydroxychloroquine, and glucocorticoid doses not exceeding the dose equivalent to prednisone 7.5 mg per day) had the highest chance of achieving a favourable pregnancy outcome⁷⁴. The results of this study support previous observations identifying factors associated with more favourable pregnancy outcomes and show that the likelihood of a favourable outcome increases when multiple favourable preconception conditions are present⁷⁴. The combination of favourable preconception factors in this retrospective Chinese study might also apply to patients of other ethnic backgrounds, but confirmation in future (preferably prospective) studies is needed.

Evidence on ethnic and racial disparities in adverse pregnancy outcomes in women with SLE remains scarce^{75,76} and existing studies do not provide definitive conclusions. In the PROMISSE cohort, Black women with SLE had higher rates of adverse pregnancy outcomes than white women; however, this difference was not statistically significant when adjusted for disease activity and socioeconomic status⁷⁵.

Pregnancy loss. Over the past six decades, the frequency of pregnancy loss in women with SLE has declined markedly. A US study found a decline in pregnancy loss rate from 43% in 1960–1965 to 17% in 2000–2003, a rate approaching that in the general US population (10–15%)⁶⁶. Key predictors of pregnancy loss in women with SLE include APS (especially in women with persistent lupus anticoagulant positivity), clinical and serological disease activity, hypertension, proteinuria and low platelet count^{3,77–79}. The highest risk occurs in women with concurrent high disease activity, low complement levels and elevated anti-dsDNA titres in the second trimester⁷⁷.

(Pre-)eclampsia. Pre-eclampsia is a pregnancy complication characterized by newly developed hypertension and proteinuria, as well as other organ involvement, after 20 weeks of gestation. In the general obstetric population, pre-eclampsia occurs in approximately 5% of pregnancies⁸⁰, but in women with SLE, the reported incidence rates are considerably higher, ranging from 6.1% to 25%^{4,52,64,81,82}. Beyond established general obstetric risk factors – including maternal age, obesity and diabetes mellitus – SLE-specific predictors of pre-eclampsia include history of lupus nephritis, active disease at or before conception, pre-existing hypertension, aPL positivity and thrombocytopenia^{3,47,49}.

Fetal growth restriction and small for gestational age infant. FGR is a pregnancy condition in which the fetus does not reach its biological growth potential owing to impaired placental function, and is diagnosed using both biometric and functional parameters⁸³. Fetuses with FGR are at increased risk of perinatal morbidity and mortality, as well as adverse long-term health outcomes⁸³. Small for gestational age infant refers to a birthweight below the tenth percentile, and includes both growth-restricted and constitutionally small but healthy infants. Population-based data indicate that FGR occurs more often in pregnancies in women with SLE than in the general obstetric population (5.3% versus 1.6%)⁸⁴. Independent risk factors for FGR in women with SLE include active disease at or before conception, lupus nephritis and aPL positivity^{49,85,86}. Conversely, hydroxychloroquine use during pregnancy has been associated with a reduced FGR rate compared with non-use⁸⁷.

In addition, the rate of small for gestational age infants is markedly higher in pregnancies in women with SLE than in age-matched and parity-matched women from the general population (25% versus 4.5%)⁸⁸.

Preterm birth. Preterm birth – defined as delivery before 37 weeks of gestation – is among the most frequent complications of pregnancy in women with SLE. A systematic review and meta-analysis of 8,157 pregnancies in women with SLE found a preterm birth rate of 31% (95% CI 0.14–0.50), markedly higher than the 6–10% observed in the general obstetric population⁷². Risk factors for preterm birth in women with SLE include active disease, past or active lupus nephritis and glucocorticoid therapy^{89,90}. Remarkably, preterm births in women with SLE show an almost equal distribution between spontaneous and medically indicated deliveries. Spontaneous preterm birth beginning with preterm prelabour rupture of membranes occurs twice as frequently in pregnant women with SLE than does spontaneous preterm birth in the general population (51% versus 25%)².

Neonatal lupus syndrome. Anti-Ro/SSA and/or anti-La/SSB autoantibodies are present in approximately 40% of women with SLE and can lead to fetal and neonatal manifestations through FcγR-mediated transplacental transfer of maternal IgG autoantibodies, which begins at 16 weeks of gestation⁹¹. The most severe and usually permanent manifestations involve the fetal heart. The risk of congenital heart block (CHB) in the fetus is 1–2% in women without previously affected offspring, but increases to 17% in women with a previous child with CHB^{92,93}, and usually develops during the second trimester, and rarely occurs after 26 weeks of gestation. The results of the STOP-BLOC study highlight high-titre anti-Ro antibodies as an important risk factor for CHB, but also emphasize the importance of yet-unidentified factors⁹⁴. CHB is associated with substantial mortality and morbidity; approximately 20% of affected fetuses do not survive, and among survivors, around two-thirds require permanent pacemaker implantation^{95,96}; a minority later develop dilated cardiomyopathy⁹⁷. Hydroxychloroquine use during pregnancy has been associated with a 50% reduction in recurrence rate of CHB in a subsequent pregnancy among anti-Ro/SSA-positive women with a previous baby with CHB, as shown in an open-label study of 54 pregnancies (7.4%; 90% CI 3.4–15.9%)⁹⁸. Neonatal lupus includes transient cutaneous lesions and, more rarely, hepatomegaly, elevated liver enzymes, splenomegaly, anaemia and thrombocytopenia⁹⁹.

Long-term consequences of pregnancy complications. Pregnancy complications in women with SLE not only endanger the health of the mother and child during pregnancy but can also confer long-term health consequences for both mother and child. In general, pregnancy can be regarded as a stress test for future cardiovascular risk: HDP are associated with an increased risk of subsequent cardiovascular disease, depending on gestational age and the severity of the HDP, and with a twofold to threefold increase in cardiovascular mortality¹⁰⁰. Data specifically addressing long-term cardiovascular risk after HDP in women with SLE are limited. In a population-based study from Sweden, women with SLE who experienced a HDP, including pre-eclampsia, had a twofold higher rate of major cardiovascular events (including myocardial infarction, stroke and heart failure) and a threefold higher rate of incident hypertension compared with women from the general population, after a median follow-up of 10.8 years⁶².

Preterm birth and low birthweight are leading causes of mortality in children under 5 years of age and are associated with an increased

risk of several health complications (including cognitive impairment and developmental delays), and development of cardiovascular and chronic kidney disease later in life⁶³. Given the approximately three-fold higher rate of preterm birth² and the at least twofold increased risk of low birthweight^{1,84} in women with SLE, these long-term risks are especially relevant to this population. In addition, children with cardiac manifestations of neonatal lupus might experience lifelong cardiac complications.

Pathophysiology of pregnancy complications in SLE

Although several risk factors for adverse pregnancy outcomes in SLE have been identified, they do not reliably predict which patients will develop complications. This limitation has led to growing interest in the biological mechanisms underlying pregnancy complications in SLE.

A healthy pregnancy depends on precisely regulated maternal immune responses. The maternal immune system works in concert with placental extravillous trophoblasts to remodel spiral arteries, ensure adequate placental blood flow and repair decidual tissue damage caused by implantation^{101–103}. The immune system must also establish maternal–fetal tolerance to prevent rejection of the semi-allogeneic fetus, through interactions with both extravillous trophoblasts and syncytiotrophoblasts at the maternal–fetal interface, and contributes to the initiation of labour at term^{102,103}. In SLE, the immune system is

dysregulated¹⁰⁴ and is therefore likely to disrupt these processes and contribute to pregnancy complications. Although the full mechanisms underlying SLE-related pregnancy complications remain to be elucidated, the presence of aPLs, increased activation of neutrophils and other immune cells and insufficient downregulation of type I interferon response are potential pathophysiological drivers, as detailed below and summarized in Fig. 1.

Autoantibodies – particularly aPLs – are among the most prominent molecular risk factors for pregnancy complications in women with SLE³. The prevailing hypothesis is that aPLs bind to trophoblasts, triggering complement factor C5a generation and neutrophil recruitment^{105,106}. Neutrophils can then promote placental damage through natural killer cell recruitment¹⁰⁷, release of reactive oxygen species¹⁰⁸, and formation of immunogenic neutrophil extracellular traps (NETs)¹⁰⁶, which are also thrombogenic and might contribute to the increased thrombosis risk in women with aPL-positive SLE and APS¹⁰⁶. Although much of this evidence comes from animal models, increased NET deposition in placentas from women with SLE supports the relevance of these mechanisms in humans^{107,109,110}. However, the role of complement in SLE-related pregnancy complications remains unclear: placentas from women with SLE show increased C3 and C4 deposition, whereas C5 levels are often decreased or unchanged^{109,111,112}.

The presence of elevated NET and increased C3 and C4 deposition in placentas from women with aPL-negative SLE and in women with

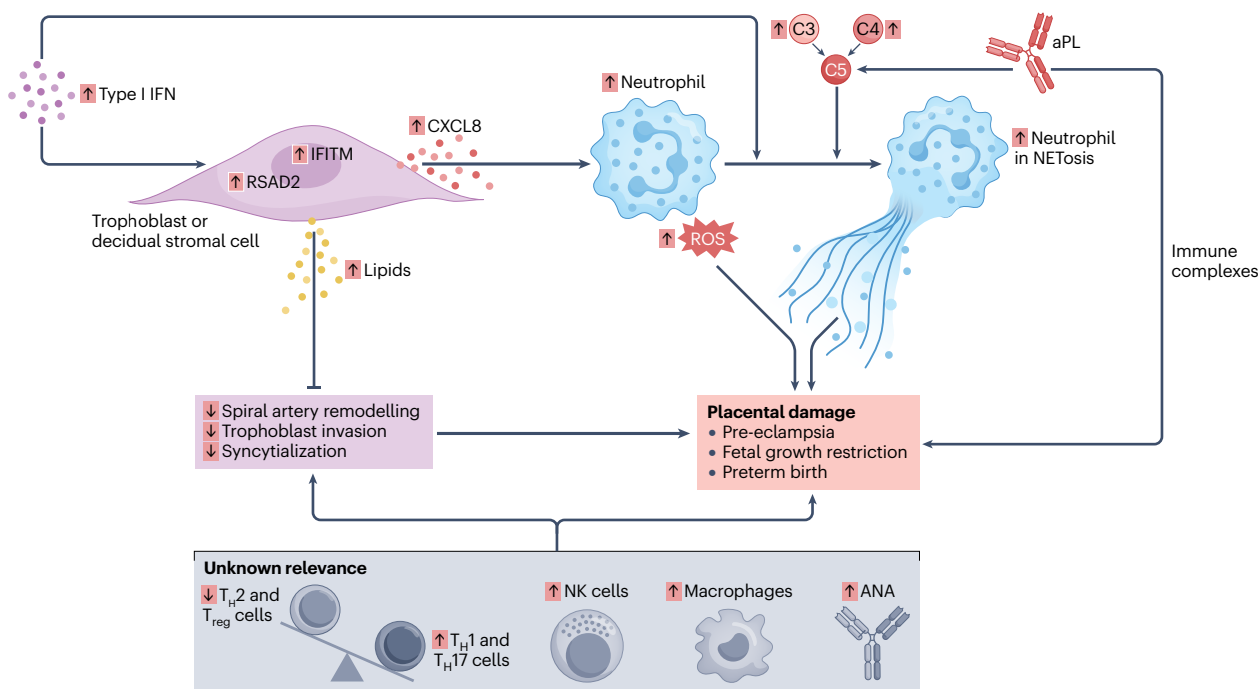


Fig. 1 | Immunological processes involved in placental dysfunction in SLE.

In pregnancies in women with systemic lupus erythematosus (SLE), type I interferon (IFN) activity is increased and induces the expression of radical S-adenosyl methionine domain-containing protein (RSAD2), interferon-inducible transmembrane protein (IFITM) and CXCL8 in trophoblasts and/or decidual stromal cells, which together contribute to placental damage and impaired placental development by promoting lipid accumulation (RSAD2), inhibiting cytotrophoblast fusion (via IFITM-mediated syncytialization) and recruiting neutrophils (CXCL8). Recruited neutrophils can release neutrophil extracellular traps (NETosis), triggered by type I IFN or by activated complement

(C3, C4 and C5) generated in response to antiphospholipid antibodies (aPL). Activated complement, together with aPLs, can also form immune complexes that further contribute to placental damage. Additional abnormalities reported in pregnancies in women with SLE, including altered T cell balance, increased natural killer (NK) cell and macrophage populations and deposition of antinuclear antibodies (ANA), might contribute to placental dysfunction, although their mechanistic roles remain unclear. C3, complement factor 3; C4, complement factor 4; C5, complement factor 5; ROS, reactive oxygen species; T_H cells; T helper cells; T_{reg} cell, regulatory T cell. Original figure created using BioRender.

pre-eclampsia without SLE or aPLs^{107,109,110}, indicates that neutrophil activation and complement dysregulation contribute more broadly to the pathogenesis of pregnancy complications. In SLE, this broader contribution is supported by associations between adverse pregnancy outcomes and higher circulating and intervillous neutrophil levels^{113–116}, together with reduced circulating C3 and C4, consistent with increased complement consumption³. Mechanistically, activation of C5a might initiate this inflammatory cascade even in the absence of antibody stimulation¹¹⁷, with aPLs serving as an additional trigger for placental injury and subsequent complications.

Another hallmark of SLE that might contribute to pregnancy complications is elevated type I interferon activity, measured by increased expression of type I interferon-stimulated genes (the so-called type I interferon signature). In healthy pregnancy, this signature is downregulated relative to the non-pregnant state, as indicated by longitudinal analysis of blood samples¹¹⁸. By contrast, women with SLE exhibit an elevated signature prior to conception that is less effectively downregulated during pregnancy, with the smallest reduction observed in those who later develop complications such as pre-eclampsia or FGR¹¹⁸. Type I interferons might contribute to placental dysfunction through several mechanisms. IFN α induces RSAD2 in trophoblasts, decidual stromal cells and macrophages, leading to lipid accumulation and impaired placental vascular development¹¹⁹. Type I interferons also induce upregulation of interferon-inducible transmembrane proteins (IFITMs), which inhibit cytotrophoblast fusion into syncytiotrophoblasts, a key process in placental development¹²⁰. Finally, IFN α stimulates CXCL8 production in decidual stromal cells, promoting neutrophil recruitment¹¹⁵. However, studies in patients with multiple sclerosis treated with IFN β have shown no changes in pre-term birth rate, birthweight or live birth rate^{121–123}, even though IFN β also induces RSAD2, IFITMs and CXCL8. Combined with the fact that 50–70% of patients with SLE have elevated type I interferon¹²⁴ but not all develop pregnancy complications, these data suggest that additional mechanisms contribute to the increased risk of such complications.

Beyond neutrophils and type I interferon, other immune alterations have been described in pregnant women with SLE, including high levels of cytokines (such as CXCL8 and IL-10)¹²⁵, an increase in circulating CCR5⁺CD16⁺ monocytes¹²⁶, and a reduced T helper 1 to T helper 2 immunological shift¹²⁷. Reported placental abnormalities in women with SLE include reduced monocytes and resting mast cells¹²⁸, altered long non-coding RNA expression¹²⁸, increased macrophage infiltration¹²⁹ and deposition of antinuclear antibodies¹¹¹. Findings regarding elevated natural killer cells in the placenta are inconsistent^{107,129}. Although understanding of the mechanisms underlying pregnancy complications in women with SLE continues to advance, further insight is needed to predict, prevent and treat these outcomes. Progress is limited by the fact that much mechanistic evidence was derived from animal models or small studies in humans that compared pregnancies in women with SLE with pregnancies in healthy women without stratifying by pregnancy outcomes, and by considerable methodological variability, factors that limit direct translation into risk prediction and treatment.

Preconception counselling

Preconception counselling is the cornerstone of reproductive health care and family planning for women with SLE and is required to evaluate and reduce risks of adverse pregnancy outcomes for each patient (Table 2). During this process, women should be informed about the importance of timing – specifically that pregnancy outcomes are optimized when conception occurs during a period of quiescent

disease – as well as the potential bidirectional effects of SLE and pregnancy. Counselling should also address the potential need for medication alterations before conception, throughout pregnancy and during breastfeeding^{22,23}.

Early, structured and multidisciplinary collaboration among rheumatologists, obstetricians, general practitioners, pharmacists and other allied health-care professionals is essential. Such coordination ensures consistent counselling messages, clear communication of treatment plans across teams and easy avenues for patients to seek clarification, particularly when they encounter conflicting messages. Providing patients with written, lay-friendly information that summarizes agreed recommendations allows patients to share consistent guidance with family members and external health-care providers. This written information equips patients to respond confidently if their treatment plan is questioned (for example, by pharmacists or other health-care professionals unfamiliar with SLE-specific pregnancy management).

Importance of preconception counselling

Although fertility and sexual health have historically been under-prioritized areas in the care of patients with rheumatic musculoskeletal diseases¹³⁰, updated EULAR recommendations and the 2020 ACR guidelines call for reproductive health to be addressed in clinical practice with “early and regular counselling” and with discussion of family planning “early and often”^{23,24}. Effective preconception counselling is the cornerstone of optimizing the reproductive journey for women with SLE. Such counselling relies on multidisciplinary collaboration, when needed, and is built on several key components: a comprehensive medical assessment of each individual patient, careful review and adjustment of medications, and evaluation of the individual risk profile associated with the specific SLE phenotype (Table 2).

Clinical review

The main priority of the clinical review is to ensure that women are receiving pregnancy-compatible medication before conception (Tables 1 and 2 and Box 1). Any necessary treatment changes should be made prior to pregnancy, as achieving remission on an optimal and pregnancy-safe regimen is essential to reducing the risks of flare, miscarriage and FGR²². Discontinuing or modification of pregnancy-compatible SLE medication should be strongly discouraged in women with SLE planning to conceive (even in those with low disease activity or in remission), because medication withdrawal is a common trigger for disease flares²².

Sustained remission for 6 to 12 months before conception remains a key determinant of favourable pregnancy outcomes¹³¹, particularly in women with a history of lupus nephritis⁶⁸ or involvement of other important organs^{3,23,24,132}. Conception should be avoided during periods of active disease or in the presence of severe organ dysfunction, including renal failure⁴⁹, pulmonary hypertension¹³² or recent cerebrovascular accident, owing to the increased risks of maternal flares and maternal and fetal complications^{23,24}.

Women with SLE are, on average, older at first conception than women in the general population, and this age trend is accompanied by higher BMI¹³³ as well as increased use of assisted reproductive techniques¹⁰. In this context, a comprehensive thrombosis risk assessment is more crucial than ever, given that VTE remains the leading direct cause of maternal death¹³⁴. Contemporary registry and cohort data indicate that women with rheumatic musculoskeletal diseases, including SLE, now conceive at a median age in the mid-30s, mirroring broader trends in high-income countries^{10,48,135}.

Table 2 | Counselling and management during all stages of pregnancy in women with SLE

	Before conception	During pregnancy	After birth and between pregnancies
Clinical review	Achieve and maintain remission for ≥ 6 –12 months on pregnancy-compatible medication; perform VTE assessment; address modifiable risk factors (such as smoking, depression and obesity)	Regular multidisciplinary monitoring; assess kidney function, blood pressure, urine protein and disease biomarkers; monitor fetal growth and placental blood flow; timely induction of labour, weighing all parameters	Monitor for flares (common in the first 3–6 months after delivery); use postpartum period for future pregnancy planning
Medication management	Discontinue teratogens (MMF, MTX and cyclophosphamide) per washout; initiate hydroxychloroquine (if not already prescribed); continue or transition to pregnancy-compatible immunosuppressants (azathioprine, cyclosporine or tacrolimus) and ensure remission; continue pregnancy-compatible biologic DMARDs if patient is in remission	Continue hydroxychloroquine; use DMARDs as needed to control the disease (see Table 1 and main text); use lowest effective glucocorticoid dose; initiate low-dose aspirin in the first trimester in women at increased risk of pre-eclampsia; add LMWH in high-risk patients as indicated; supplement calcium and vitamin D	Adjust medication as needed; most pregnancy-compatible drugs are safe during breastfeeding; re-establish VKA when indicated; continue bone health supplements if on long-term glucocorticoids or heparin, particularly when breastfeeding
Autoantibody assessment	Test for aPLs, anti-Ro/SSA and anti-La/SSB antibodies	If anti-Ro/SSA-positive and/or anti-La/SSB-positive, fetal echocardiography at 18–20 weeks and, if indicated, repeated fetal heart rate surveillance for CHB; if aPL-positive, follow thromboprophylaxis protocols; coordinate aspirin cessation with multidisciplinary team if epidural anaesthesia is planned	If aPL-positive, follow specific local postpartum thromboprophylaxis protocols
Contraception counselling	Avoid conception during active disease or ongoing severe organ dysfunction; provide effective contraception	NA	Discuss effective contraception to prevent unplanned pregnancy, especially with active disease or teratogenic drugs
Pregnancy follow-up and counselling	Provide information on pregnancy expectations; involve family and multidisciplinary team as appropriate	Provide ongoing counselling evolving risks and preferences	Counselling on the consequences of pregnancy outcome on subsequent pregnancy; discuss long-term cardiovascular risk

Data from refs. 22–24. aPLs, anti-phospholipid antibodies; CHB, congenital heart block; LMWH, low-molecular-weight heparin; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not appropriate; SLE, systemic lupus erythematosus; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Risk factors for adverse pregnancy outcomes in the general population, such as overweight and obesity, are also relevant for women with SLE. In women with SLE specifically, obesity compounds the effects of disease activity and is associated with a higher likelihood of adverse pregnancy outcomes¹³⁶. Evidence from a systematic review indicates that a prepregnancy BMI of >25 kg/m² confers an increased risk of fetal death and preterm birth (HR 3.58, 95% CI 1.45–8.83)¹³⁶. Cohort and population-based studies over the past two decades have shown greater use of assisted reproductive techniques among women with rheumatic musculoskeletal diseases, including SLE, than among women in the general population^{10,48}, reflecting higher infertility rates, older maternal age and evolving patient expectations.

Autoantibody assessment

Testing for aPLs, anti-Ro/SSA autoantibodies and anti-La/SSB autoantibodies is a critical component of preconception evaluation in women with SLE^{22,23}, as these autoantibodies directly inform risk stratification, perinatal management (including antepartum and postpartum thromboprophylaxis) and fetal monitoring strategies. aPLs (including the presence of lupus anticoagulant, anticardiolipin IgG or IgM antibodies and anti- β_2 -glycoprotein-I IgG or IgM antibodies) identify women with a specific risk profile that includes recurrent pregnancy loss before 10 weeks of gestation, pregnancy loss after 12 weeks and adverse pregnancy outcomes related to placental dysfunction, as well as maternal arterial and venous thrombosis typical of APS¹³⁷. Importantly, the clinical

relevance of low titre or IgA isotypes of classic aPLs, or of non-classic aPLs (such as antibodies against the phosphatidylserine–prothrombin complex) remains unclear. These situations necessitate careful assessment of other thrombosis risk factors, the patient’s broader clinical context and individual preferences. It is important to emphasize that the updated 2023 ACR–EULAR APS classification criteria are more complex, weighted criteria than the earlier 2006 APS criteria, yet these criteria are still not intended as diagnostic criteria¹³⁸.

Communication and planning

Effective communication and strategic planning are the cornerstones of optimal care for women with SLE who are contemplating pregnancy. Early and regular involvement²⁴ of the patient, the patient’s family and the multidisciplinary team, including rheumatologists, gynaecologists and other allied health-care professionals, ensures a foundation of shared decision-making. The process goes beyond discussing medical risks, medication adjustments, adherence and lifestyle advice, extending to an exploration of the patient’s reproductive goals, personal values and psychosocial context¹². Thorough counselling, ideally involving both family members and the multidisciplinary team, not only ensures that the patient is fully informed about the interplay between SLE and reproductive health but also allows the patient to express concerns and set realistic expectations¹². The importance of shared decision-making for providing optimal clinical care to pregnant women with SLE is illustrated by the two case vignettes presented in Box 1.

Management during pregnancy

Pregnancy in women with SLE is a high-risk period, with several potential complications that can influence both the outcome of pregnancy and the course of the disease. Therefore, careful multidisciplinary management and close monitoring throughout pregnancy, together with timely adjustment of medication, are of the utmost importance to reduce the risks of obstetric complications and disease flares.

Multidisciplinary management and pregnancy monitoring

Pregnancies in women with SLE are best managed within a specialized combined rheumatological–obstetric clinic throughout pregnancy and the postpartum period, following local protocols for high-risk pregnancies and shared-care protocols. The general schedule comprises regular clinic visits, with the frequency varying depending on SLE disease activity, organ involvement, autoantibody profile, comorbidities and the course of pregnancy^{22,23}. Close monitoring of blood pressure is vital for early detection of pre-eclampsia, and home blood pressure measurements should be encouraged in women with hypertension, a history of HDP, or past or present lupus nephritis¹³⁹.

Regular blood and urine investigations are necessary for monitoring disease activity and early detection of pregnancy complications^{22,23}. Haemoglobin levels and platelet counts can fall as a result of SLE-related immune haemolytic anaemia, thrombocytopenia or pre-eclampsia with haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome¹³⁹. Regular urine investigations are also essential for detecting proteinuria, which could be the earliest sign of pre-eclampsia or a renal flare.

Distinguishing pre-eclampsia from a renal lupus flare is often challenging because hypertension, oedema, proteinuria and impaired renal function can occur in both conditions (Box 2). Yet making this distinction is crucial, given the differences in management. Pre-eclampsia, by definition, arises only after 20 weeks of gestation and is characterized by a new-onset hypertension. The only effective treatment for pre-eclampsia is delivery of the fetus and placenta. Furthermore, pre-eclampsia and active lupus nephritis can co-occur, further complicating clinical assessment.

Routine ultrasonographic screening should be performed in all pregnant women with SLE²². Additional fetal echocardiographic surveillance is advised for those women who are anti-Ro/SSA-positive and/or anti-La/SSB-positive, commencing at 16–20 weeks of gestation and repeated at appropriate intervals up to 26 weeks of gestation. Enhanced monitoring is warranted in high-risk patients, specifically those with high-titre anti-Ro/SSA antibodies or a prior infant with neonatal lupus or CHB^{22,23}. In the third trimester, supplementary fetal growth assessments, including Doppler measurements, are advised for the early detection of placental insufficiency and/or FGR, in accordance with EULAR recommendations and the 2020 ACR guidelines^{22,23}.

Prevention of obstetric complications

Treatment with hydroxychloroquine, low-dose aspirin and adjunctive folic acid, vitamin D and calcium supplementation is strongly recommended during pregnancy for all women with SLE to reduce the risk of pregnancy complications^{22–24,140}. In addition, antenatal and

Box 1 | Case vignettes illustrating shared decision-making

Case vignette 1: medication safety in pregnancy planning

A 28-year-old nulliparous woman with stable systemic lupus erythematosus (SLE) for 2 months wishes to conceive. She has no history of lupus nephritis, organ involvement or antiphospholipid antibodies.

- The clinician recommends postponing conception until 6–12 months of quiescent disease, emphasizing the importance of continuing hydroxychloroquine owing to established safety and beneficial effects on disease control and pregnancy outcomes. The woman, however, is anxious about fetal medication exposure and expresses a preference to stop all therapy before conceiving.
- Through shared discussions, the clinician explains that active SLE poses greater risks to both parent and fetus than the recommended medications, and they review guideline-based evidence together. They agree on a plan to maintain hydroxychloroquine, begin low-dose aspirin in early pregnancy, delay conception until stable disease is achieved, and arrange multidisciplinary monitoring to optimize outcomes.

Case vignette 2: pregnancy planning in a high-risk patient

A 28-year-old nulliparous woman with SLE and prior lupus nephritis seeks preconception counselling. A previous pregnancy was complicated by severe pre-eclampsia with fetal growth restriction at 25 weeks, despite multidisciplinary management, ongoing treatment with hydroxychloroquine and azathioprine, and initiation of low-dose aspirin at 10 weeks of gestation, culminating in fetal death. At that

time, lupus nephritis had not reached complete remission, and a postpartum non-renal flare followed.

- The woman now wishes to pursue another pregnancy and demonstrates understanding of the prior complications. Her disease has been stable for 6 months on hydroxychloroquine, low-dose prednisone and azathioprine, with minimal proteinuria, stable renal function and well-controlled blood pressure.
- Her clinician outlines the high recurrence risk of severe complications — pre-eclampsia, preterm birth and fetal loss — drawing on guidelines and registry data, while acknowledging the woman's grief, hopes and values.
- Should she choose to proceed, the plan would include ≥ 12 months of stable remission, optimization of renal and cardiovascular health, low-dose aspirin, close monitoring of blood pressure and serology (including complement levels) and care within a highly specialized, multidisciplinary team. The limitations of preventive strategies are discussed openly, with emphasis on ongoing emotional and psychological support

These composite vignettes illustrate the complexity and high stakes of reproductive decision-making in women with SLE and the differences in risk perception of the woman. Shared decision-making integrates the best available evidence with individual preferences, fears, values and priorities. Open communication, collaborative planning and mutual respect underpin tailored management strategies

Box 2 | Distinguishing renal lupus flare from hypertension-related pregnancy disorder

Features common to both conditions

- Medical history and clinical manifestations:
 - Hypertension
 - Oedema
- Laboratory investigations:
 - Decline in renal function
 - Proteinuria
 - Reduced platelet count

Features more suggestive of a renal lupus flare

- Medical history and clinical manifestations:
 - History of lupus nephritis (especially if not in complete remission at conception)
 - Other clinical signs of active systemic lupus erythematosus
- Laboratory investigations:
 - Active urine sediment
 - Decline in complement component 3 (C3) and/or C4 levels (or a failure of complement levels to rise as expected during pregnancy)
 - Increase in anti-double-stranded DNA antibody titre

Features more suggestive of a hypertension-related pregnancy disorder

- Medical history and clinical manifestations:
 - History of antiphospholipid syndrome
 - No history of lupus nephritis
 - Absence of other clinical signs of active systemic lupus erythematosus
 - Headache or visual complaints
 - Right upper-quadrant abdominal pain
- Laboratory investigations:
 - Normal urinary sediment
 - No decline in C3 and/or C4 levels
 - No increase in anti-dsDNA titre
 - Elevated liver enzymes

Data from refs. 50,139.

postpartum thromboprophylaxis should be considered and discussed with all pregnant women with SLE^{22,23}.

Hydroxychloroquine. Hydroxychloroquine use is strongly advised before conception, during pregnancy and during lactation, according to EULAR, ACR and BSR guidelines^{23,24,140}, owing to its well-established role in reducing flare risk and improving pregnancy outcomes. Continued use during pregnancy is associated with a reduced risk of pre-eclampsia and FGR¹⁴¹ as well as a favourable effect on the risk of preterm birth¹⁴². In addition, a prospective open-label study demonstrated that hydroxychloroquine use during pregnancy reduces the recurrence of CHB in a subsequent pregnancy in anti-Ro/SSA-positive women who have previously given birth to an infant with CHB⁹⁸. Experts broadly agree that the risk–benefit profile of hydroxychloroquine in pregnancy in SLE strongly supports its use¹⁴³.

Low-dose aspirin. Low-dose aspirin is a cornerstone of preterm pre-eclampsia prevention and is generally recommended for all pregnant women at increased risk of HDP following an individualized risk–benefit assessment^{144,145}. In women with SLE, the use of low-dose aspirin during pregnancy is similarly recommended^{22,23}, given the markedly increased risk of HDP and other pregnancy-related complications. Low-dose aspirin reduces platelet aggregation and vasoconstriction, which are important contributors to the pathogenesis of pre-eclampsia and FGR²³. Evidence from randomized controlled trials¹⁴⁴ and meta-analyses¹⁴⁵ in high-risk obstetric populations (including women with autoimmune diseases) have shown that daily low-dose aspirin, when initiated before 16 weeks of gestation, considerably reduces the risk of preterm pre-eclampsia and related complications¹⁴⁴. This benefit is also considered applicable to women with SLE by many experts in the field, particularly women with SLE with additional risk factors such as hypertension, prior lupus nephritis or the presence of aPLs or APS, who are at increased risk of pre-eclampsia.

Heparin. Pregnancy is a procoagulant state associated with an increased risk of VTE, a risk that is particularly important to consider in women with predisposing conditions such as SLE with or without aPLs. Compared with pregnant women in the general population, pregnant women with SLE have a higher incidence of VTE (7.2 versus 62 per 10,000 pregnancies)¹⁴⁶. A retrospective analysis of the National Inpatient Sample database, including 8,040 pregnancies in women with SLE, showed markedly increased rates of deep vein thrombosis (42 per 10,000 in SLE pregnancies versus 5.34 per 10,000 in the general pregnant population) and pulmonary embolism (adjusted OR 9.76, 95% CI 6.13–15.55)¹⁴⁶.

Antenatal and postpartum thromboprophylaxis must therefore be considered and discussed with all patients with SLE²³. Evidence quantifying the contribution of SLE disease activity to VTE risk in pregnancy remains limited. One study¹⁴⁷ based on a secondary analysis of a prospective registry involving 55 pregnancies in 49 patients with SLE, evaluated the Royal College of Obstetricians and Gynaecologists VTE risk model alongside SLE activity defined by the Definition Of Remission In SLE (DORIS) remission criteria¹⁴⁸ to guide postpartum VTE prophylaxis. The findings suggest that not all patients with SLE automatically require postpartum VTE prophylaxis, but rather only those with active SLE or additional non-SLE VTE risk factors. The study also highlighted underuse of recommended prophylaxis even among individuals with elevated risk scores, underscoring the need for refined, individualized risk assessment rather than a blanket thromboprophylaxis approach in all pregnancies in women with SLE¹⁴⁷. In the absence of data from larger, prospective studies, antenatal and postpartum VTE prophylaxis should be guided by an individualized risk assessment that incorporates each patient's full risk factor profile. For the postpartum prophylaxis, additional peripartum risk factors, such as a caesarean delivery, postpartum haemorrhage, pre-eclampsia and proteinuria, should also be considered. Heparins remain the mainstay of antenatal and postpartum thromboprophylaxis and are widely recommended in clinical guidelines owing to their well-established safety profile in pregnancy^{23,140}. For individuals who require long-term anticoagulation outside pregnancy (for example, patients with thrombotic APS), switching from vitamin K antagonists to LMWH should be discussed prior to pregnancy, as vitamin K antagonists are contraindicated during pregnancy²⁴. The usual practice is to advise switching from vitamin K antagonists to LMWH upon confirmation of pregnancy.

Adjunctive treatment. Any woman planning to conceive should take 400 µg of folic acid daily to reduce the risk of fetal neural tube defects, ideally beginning 3 months before conception and continuing through the first trimester²². Additionally, all pregnant and lactating women with SLE should receive 1,000 IU of vitamin D supplementation daily, as higher dosages have been associated with greater reduction in pre-eclampsia risk¹⁴⁹, and vitamin D deficiency is common in women with SLE¹⁵⁰. Furthermore, since 2014, daily 1,000 mg of calcium supplementation has been recommended in pregnancy, based on evidence from the general obstetric population demonstrating reduced risks of pre-eclampsia and preterm birth compared with placebo¹⁵¹. An updated Cochrane systematic review, however, reported little to no difference in pre-eclampsia risk between calcium users and non-users in the general obstetric population (relative risk 0.83, 95% CI 0.67–1.04; six randomized controlled trials, 15,304 women)¹⁵². This finding should not be interpreted as a reason to discontinue calcium supplementation in women with SLE, for several reasons. Beyond increased physiological calcium requirements during pregnancy, supplementation is widely recommended because of the high prevalence of insufficient dietary calcium intake^{153,154}, the increased burden of osteoporosis and osteopenia¹⁵⁰, and the frequent use of glucocorticoids and heparin, both of which adversely affect bone metabolism.

Prevention of disease flares

Maintaining stable, low disease activity and continuing hydroxychloroquine and other pregnancy-compatible DMARDs throughout pregnancy are essential for preventing disease flares. In particular, hydroxychloroquine adherence seems particularly important; a pharmacokinetic study in pregnant women with SLE demonstrated higher odds of preterm birth among women with non-adherent hydroxychloroquine concentrations, compared with those among women maintaining therapeutic concentrations, even after adjusting for lupus nephritis and race (OR 11.2, 95% CI 2.3–54.2; $p = 0.003$)¹⁵⁵.

Additionally, timely adjustment of immunosuppressive therapy is essential for individuals who require ongoing treatment during pregnancy. Several drugs used in the management of SLE are compatible with the periconception period and throughout pregnancy, whereas others are contraindicated (Table 1). Ensuring effective treatment of the disease during pregnancy can be challenging. If necessary, switching to pregnancy-compatible immunosuppressive drugs should be performed 4 to 6 months before conception, as such changes can trigger disease flares. This interval also allows for the recommended 6–12 months of sustained disease remission on stable therapy prior to conception, necessitating an adequate observation period after any treatment adjustment²². Women receiving long-term low-dose glucocorticoids should not abruptly discontinue therapy, owing to the risk of disease flare and stress-induced adrenal crisis, and the potential need for stress-dose glucocorticoids during labour should be discussed with the obstetric team (see the section ‘Glucocorticoids’).

Safety of antirheumatic medication use during pregnancy

Over the past 5 years, ACR and BSR guidelines and updated EULAR recommendations on the use of antirheumatic drugs during pregnancy and lactation have provided important guidance for health-care professionals and patients^{21,23,24}. In line with preconception counselling and these recommendations, emphasis should be placed on continuing pregnancy-compatible medication to maintain disease control throughout pregnancy. Table 1 provides an overview of pregnancy-compatible drugs that are considered safe and are widely used during pregnancy,

alongside those that are contraindicated because of known teratogenicity or insufficient safety data, and outlines the implications of exposure. Further detail on individual therapeutic agents can be found in the published international guidelines and recommendations^{21,23,24}.

Conventional synthetic DMARDs. No csDMARDs are formally licensed for use during pregnancy in women with SLE. Health-care professionals and patients therefore rely on guidance from major societies to inform csDMARD use during pregnancy and lactation. These guidelines are developed according to rigorous standards based on systematic reviews of the literature^{21,23,24,140}. Data from a global survey of 414 health-care professionals indicate that such guidance is widely used in daily clinical practice, underscoring the importance of these documents as essential clinical references¹⁵⁶. As evidence on the safety of DMARD use in pregnancy and lactation continues to expand – primarily through observational studies – shared decision-making remains crucial when discussing medication choices.

NSAIDs. According to BSR and updated EULAR recommendations^{21,24}, NSAIDs should only be used intermittently during pregnancy and discontinued after 28 weeks of gestation to avoid adverse fetal effects. The FDA advises caution with NSAID use even after 20 weeks of gestation, as these agents might cause rare but serious kidney problems in the fetus, leading to complications caused by low levels of amniotic fluid¹⁵⁷. Cyclooxygenase-2 inhibitors should be avoided owing to insufficient data on safety in pregnancy.

Glucocorticoids. Non-fluorinated glucocorticoids, including prednisone, prednisolone, hydrocortisone and methylprednisolone, are considered compatible with pregnancy²⁴. Doses should be titrated to the lowest effective level to minimize maternal complications such as hypertension, infection and gestational diabetes mellitus²³. Although glucocorticoid therapy can precipitate gestational diabetes mellitus in any pregnancy, particular attention to this risk warranted in SLE, as glucocorticoids are frequently used to maintain disease control. A systematic review and meta-analysis of five studies involving 3,432 pregnancies in women with SLE and 248 gestational diabetes mellitus events demonstrated a notable association between pregnancy and gestational diabetes mellitus in women with SLE¹⁵⁸. Moreover, high-dose or prolonged glucocorticoid use are associated with increased risks of premature birth¹⁵⁹, and some studies have linked glucocorticoid use to increased risk of premature rupture of membranes, although evidence is mixed¹⁶⁰. In women with SLE treated with the equivalent of ≥5 mg prednisolone daily for longer than about 3 weeks, as well as those on long-term lower doses after tapering from higher doses, the need for stress dose therapy before labour should be discussed within the multidisciplinary team, including endocrine expertise.

Fluorinated glucocorticoids, such as dexamethasone and betamethasone, readily cross the placenta and should be reserved primarily for accelerating fetal lung maturation in the setting of impending preterm birth. Fluorinated glucocorticoids have been used with the aim of reversing CHB, albeit in the absence of evidence to support the practice¹⁶¹.

Biologic DMARDs. Historically, the use of bDMARDs during conception and pregnancy was approached with considerable caution, given the evidence available at the time, often leading to withdrawal of therapy and potential harm owing to increased disease activity¹⁶². However, cumulative data and expert reviews now support the selective

use of certain bDMARDs, where clinically indicated, to mitigate the risks of active disease and support a successful pregnancy^{21,23,24,52,162}. bDMARDs cross the placenta through active transfer only after placental expression of neonatal Fc receptors begins around 16 weeks of gestation, after which active transplacental transport increases progressively towards term¹⁶³.

Although TNF-inhibiting agents are not standard first-line therapy for SLE, these drugs are used in some regions in selected patients – either to maintain disease control or to manage coexisting inflammatory diseases¹⁶⁴ – and are considered compatible throughout pregnancy. B cell-targeted therapies such as rituximab, belimumab and the more recently approved interferon-blocking agent anifrolumab are used in severe or refractory SLE when conventional DMARDs are insufficient or contraindicated^{24,162}. Studies have shown minimal to no increased risk of congenital malformations, low birthweight or other major adverse outcomes in infants exposed antenatally to belimumab, rituximab or TNF-inhibiting agents, when these therapies are used judiciously for maternal benefit^{21,23,24}. Administration of B cell-targeted agents after 20 weeks of gestation can lead to transient neonatal B cell depletion, although this effect has not been associated with serious infections, and B cells typically normalize within 6 months^{165–167}. Regarding infant vaccination, the 2024 updated EULAR guidelines recommend avoiding live infant vaccines (such as the BCG vaccine) during the first 6 months of life in infants born to women who received B cell-depleting therapy in the second or third trimester or TNF-inhibiting agents that undergo active transplacental transfer during the second half of pregnancy²⁴.

Lactation

Breastfeeding is an important aspect of postpartum care for both parent and infant, and several SLE-specific considerations deserve attention. In general, breastfeeding should be encouraged in all women with SLE.

General aspects of breastfeeding

Breast milk is widely regarded as the optimal source of infant nutrition, providing protection against infections and dental malocclusion, supporting cognitive development, and probably reducing the risk of overweight and diabetes in later life¹⁶⁸. For the mother, breastfeeding offers several long-term health benefits including protection against breast cancer and potentially also against ovarian cancer and type 2 diabetes¹⁶⁸. Moreover, breastfeeding is an important bonding component for mother and baby. However, no data are currently available on the long-term effects of breastfeeding on the mother, specifically in women with SLE.

Specific aspects of lactation in women with SLE

Breastfeeding initiation rate and duration are lower in women with SLE than in women without SLE^{169,170}. A qualitative study showed that attitudes on breastfeeding vary widely and are strongly shaped by personal preferences and lived experience¹⁷¹. Specifically, support from health-care professionals in reassuring patients that breastfeeding is safe with their medication is important¹⁷¹. Also important is the need to support whatever decision the woman makes¹⁷¹. Breastfeeding can be physically and emotionally demanding, and some women, especially those with a chronic illness such as SLE, might feel they lack the stamina to breastfeed, worry about insufficient milk or feel more confident using formula¹⁷¹. These concerns must be respected, as women can experience stress from being responsible for their child's health¹⁷¹.

Mixed feeding, combining breastfeeding with formula supplementation, should also be recognized as a pragmatic and acceptable option, offering flexibility for those women with SLE in whom exclusive breastfeeding is challenging – whether due to medication regimens, maternal fatigue or other disease-related factors.

The evidence on the effects of medication exposure on breast milk remains limited for most drugs. Nevertheless, only a small number of medications are now considered absolutely contraindicated during breastfeeding^{23,24}. Accurate counselling requires an assessment of the extent to which each drug is transferred into breast milk. Several factors influence infant exposure, including the route of administration, dosage, duration of use, half-life and timing of administration in relation to breastfeeding, as well as the volume of breast milk consumed by the infant¹⁷².

Women with SLE have an increased likelihood of giving birth to a premature² or growth-restricted⁸⁴ infant compared with women from the general population. For these babies, breast milk is particularly important. However, the risk of medication exposure through breast milk could be higher because drug elimination might be slower, increasing the potential for accumulation. In these situations, the risks and benefits should be carefully evaluated and discussed with the neonatologist²⁴.

Safety of antirheumatic medication use during lactation

For many drugs, direct evidence regarding the effects of maternal drug use during breastfeeding remains limited. Nevertheless, pharmacological principles allow reasonable estimation of infant exposure and associated risk, and these assessments are now incorporated in updated evidence-based BSR, EULAR and ACR guidelines^{21,23,24,140}. Most drugs commonly used to treat SLE are considered compatible with breastfeeding²⁴ (Table 1). These drugs are either not transferred – or only minimally transferred – into breast milk, or sufficient evidence supports their safety in breastfed infants. For mothers receiving intravenous methylprednisolone pulse therapy, a breastfeeding delay of approximately 2–4 h after administration is recommended to minimize infant exposure²⁴.

bDMARDs are considered safe for use during lactation^{21,23,24}. Owing to the large molecular size of these agents, which impedes passive diffusion through the intercellular space between mammary cells into breast milk¹⁷³, no or only minimal transfer of bDMARDs into breast milk is expected¹⁷⁴. Moreover, any bDMARD in breast milk is unlikely to be absorbed in active form after oral administration owing to digestion in the infant's gastrointestinal tract^{23,24}. Methotrexate at doses of ≤ 25 mg weekly might be considered during lactation when no suitable alternative is available, given the very low concentrations detected in breast milk and the absence of reported harm²⁴.

Drugs that should be avoided during breastfeeding owing to insufficient safety data include cyclophosphamide, mycophenolate mofetil, leflunomide, voclosporin, etoricoxib and targeted synthetic DMARDs, such as Janus kinase inhibitors^{21,24}. The decisions around breastfeeding in women with SLE involve careful counselling, before and after birth, taking into account the mother's desire to breastfeed, physical condition, medication safety and the necessity of continuing a particular medication or switching to an available alternative.

Future research directions

To improve the course and outcomes of pregnancy in women with SLE, future research should prioritize closing key knowledge gaps in two major areas: the pathogenesis of pregnancy complications in SLE

and the effects of immunosuppressive medications during pregnancy and lactation (Box 3).

To better predict and prevent the occurrence of adverse outcomes of pregnancy in women with SLE, elucidating the pathogenesis of pregnancy complications in SLE is crucial. Most current translational studies are underpowered to distinguish between complicated and uncomplicated pregnancies in women with SLE and often focus on differences in between pregnancies in women with SLE and pregnancies in healthy women, where the type I interferon signature predominates¹⁷⁵. Robust progress will therefore depend on larger, prospective, multi-ethnic cohort studies and registries ideally linked to high-quality biobanking to enable direct comparisons between pregnancies in women with SLE with and without complications. Further research should also address additional immune processes that are central to normal pregnancy, including maternal–fetal tolerance and the initiation of parturition. Mechanistic studies are required to determine whether placental abnormalities are a cause or consequence of adverse outcomes and how these processes intersect with SLE-related immune dysregulation. With advances in organoid models of placental development, the field is now poised to move beyond observational studies towards functional experiments that could provide deeper mechanistic insights into pregnancy complications in SLE.

In addition, several key research questions regarding the use of immunosuppressive medications during pregnancy and lactation in women with SLE remain unresolved. Progress in this area will require prospective pregnancy registries and, where feasible, pragmatic trials or comparative-effectiveness studies to move beyond the limitations of small, largely underpowered, retrospective analyses and to address specific safety signals identified in preliminary reports. Research in this field should not only seek to close knowledge gaps regarding the safety of currently used immunosuppressive medications in SLE and newly developed therapeutic agents during pregnancy and lactation, but also evaluate the efficacy of drugs in improving pregnancy outcomes. Clinical trials involving patients at high risk of adverse pregnancy outcomes are urgently needed¹⁷⁶. Securing approval for, and conducting, clinical trials in pregnant women with SLE remains a major challenge, but is of great importance to patients, and therefore deserves joint efforts from health-care professionals, regulatory authorities and other stakeholders.

Further research is also needed on the risk of infections, the response to vaccinations and the long-term development of children exposed in utero to antirheumatic drugs. Several additional questions, although not unique to SLE, remain highly relevant for women with SLE and other autoimmune diseases, including the optimization of assisted reproductive techniques, contraception strategies in the context of thrombosis risk and models of multidisciplinary preconception counselling and pregnancy care. These broader issues lend themselves well to disease-agnostic registries and implementation studies that can compare different service configurations and care pathways. Moreover, large multiethnic, multinational studies are needed to clarify whether socioeconomic, ethnic or other structural disparities contribute to differences in pregnancy outcomes among women with SLE.

Finally, the practical obstacles to conducting high-quality research in pregnant women with SLE must be acknowledged and addressed. These include ethical and regulatory constraints, liability concerns, the routine exclusion of pregnant women from clinical trials and the logistical complexity and cost of long-term mother–child follow-up. Progress will require collaborative research networks that bring together rheumatologists, obstetricians, neonatologists, paediatricians and patient

Box 3 | Future research agenda

Pathogenesis of pregnancy complications

- Identify early pregnancy biomarkers that predict later complications through prospective, multiethnic registries and harmonized biobanks, overcoming the limitations of small, retrospective, single-centre studies.
- Clarify how maternal–fetal immune tolerance fails in systemic lupus erythematosus (SLE) and contributes to adverse pregnancy outcomes.
- Investigate the effects of therapeutic agents on biological processes at the maternal–fetal interface using placental organoid models, examining both established and emerging therapies.
- Elucidate the mechanisms of spontaneous preterm birth in SLE.
- Determine how ethnic, socioeconomic and other structural disparities shape pregnancy outcomes.
- Assess, in large multiethnic cohorts, the impact of parity on flare risk and pregnancy outcomes.
- Evaluate the feasibility of a treat-to-target approach aimed at remission or low disease activity in women with SLE planning pregnancy or already pregnant.

Antirheumatic medication during pregnancy and lactation

- Define the safety profiles of antirheumatic drugs with limited or no pregnancy and lactation data.
- Conduct clinical trials in high-risk individuals, including women with persistent antiphospholipid antibodies.
- Study the safety of newly developed SLE therapies during pregnancy and lactation, and their efficacy in improving pregnancy outcomes.
- Characterize drug transfer by measuring medication levels in maternal blood, breast milk and infant blood in both term and preterm infants during lactation.
- Investigate infection risk, vaccine responses and long-term development in children exposed in utero to antirheumatic therapies, particularly biologic DMARDs administered after 20 weeks of gestation.
- Advance care model and implementation research, including optimization of multidisciplinary preconception and pregnancy pathways, and address barriers (such as ethical and regulatory constraints, exclusion of pregnant women from clinical trials and costs and logistics of long-term follow-up). Collaborative networks and dedicated funding mechanisms will be essential.

partners, alongside harmonized data standards and dedicated funding mechanisms that explicitly support pregnancy research. Such coordinated efforts will be essential to close the critical knowledge gaps outlined throughout this Review.

Conclusions

Pregnancy outcomes in women with SLE have substantially improved over the past four decades; however, the risks of maternal complications and adverse fetal outcomes remain substantially higher than in the general population. Optimizing care therefore requires a comprehensive approach that begins well before conception and extends throughout pregnancy and the postpartum period. Preconception

counselling, careful pregnancy planning, systematic assessment of risk factors, timely adjustment of medication and coordinated multidisciplinary management all have central roles in minimizing the likelihood of disease flares and pregnancy complications. Impaired fertility in women with SLE, associated with disease activity, renal failure, medication exposure, age-related decline in ovarian reserve and lifestyle factors, underscores the importance of early counselling about family planning during the reproductive years. Lactation rates in women with SLE are reduced owing to safety concerns, disease flares, physical limitations and mental challenges, illustrating the need to integrate multidisciplinary care and breastfeeding support into postpartum care. Continued research and sustained collaboration between patients and multidisciplinary teams is essential to further improve outcomes for families affected by SLE.

Published online: 07 April 2026

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Acknowledgements

I.E.M.B. and W.D. acknowledge the European Reference Network on Rare and Complex Connective Tissue Diseases (ERN ReCONNET) for granting membership to the Department of Rheumatology and Clinical Immunology at our center.

Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

Additional information

Peer review information *Nature Reviews Rheumatology* thanks Laura Andreoli, who co-reviewed with Frederico Rajão Martin; Caroline Gordon; and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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