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Society for Maternal-Fetal Medicine Consult Series #64: Systemic lupus erythematosus in pregnancy

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The American College of Obstetricians and Gynecologists (ACOG) endorses this document.

Systemic lupus erythematosus (SLE) is a chronic, multisystem, inflammatory autoimmune disease characterized by relapses (commonly called "flares") and remission. Many organs may be involved, and although the manifestations are highly variable, the kidneys, joints, and skin are commonly affected. Immunologic abnormalities, including the production of antinuclear antibodies, are also characteristic of the disease. Maternal morbidity and mortality are substantially increased in patients with systemic lupus erythematosus, and an initial diagnosis of systemic lupus erythematosus during pregnancy is associated with increased morbidity. Common complications of systemic lupus erythematosus include nephritis, hematologic complications such as thrombocytopenia, and a variety of neurologic abnormalities. The purpose of this document is to examine potential pregnancy complications and to provide recommendations on treatment and management of systemic lupus erythematosus during pregnancy. The following are the Society for Maternal-Fetal Medicine recommendations: (1) we recommend low-dose aspirin beginning at 12 weeks of gestation until delivery in patients with systemic lupus erythematosus to decrease the occurrence of preeclampsia (GRADE 1B); (2) we recommend that all patients with systemic lupus erythematosus, other than those with quiescent disease, either continue or initiate hydroxychloroquine (HCQ) in pregnancy (GRADE 1B); (3) we suggest that for all other patients with quiescent disease activity who are not taking HCQ or other medications, it is reasonable to engage in shared decision-making regarding whether to initiate new therapy with this medication in consultation with the patient's rheumatologist (GRADE 2B); (4) we recommend that prolonged use (>48 hours) of nonsteroidal antiinflammatory drugs (NSAIDs) generally be avoided during pregnancy (GRADE 1A); (5) we recommend that COX-2 inhibitors and full-dose aspirin be avoided during pregnancy (GRADE 1B); (6) we recommend discontinuing methotrexate 1-3 months and mycophenolate mofetil/mycophenolic acid at least 6 weeks before attempting pregnancy (GRADE 1A); (7) we suggest the decision to initiate, continue, or discontinue biologics in pregnancy be made in collaboration with a rheumatologist and be individualized to the patient (GRADE 2C); (8) we suggest treatment with a combination of prophylactic unfractionated or low-molecular-weight heparin and low-dose aspirin for patients without a previous thrombotic event who meet obstetrical criteria for antiphospholipid syndrome (APS) (GRADE 2B); (9) we recommend therapeutic unfractionated or low-molecular-weight heparin for patients with a history of thrombosis and antiphospholipid (aPL) antibodies (GRADE 1B); (10) we suggest treatment with low-dose aspirin alone in patients with systemic lupus erythematosus and antiphospholipid antibodies without clinical events meeting criteria for antiphospholipid syndrome (GRADE 2C); (11) we recommend that steroids not be routinely used for the treatment of fetal heart block due to anti-Sjögren's-syndrome-related antigen A or B (anti-SSA/SSB) antibodies given their unproven benefit and the known risks for both the pregnant patient and fetus (GRADE 1C); (12) we recommend that serial fetal echocardiograms for assessment of the PR interval not be routinely performed in patients with anti-SSA/SSB antibodies outside of a clinical trial setting (GRADE 1B); (13) we recommend that patients with systemic lupus erythematosus undergo prepregnancy counseling with both maternal–fetal medicine and rheumatology specialists that includes a discussion regarding maternal and fetal risks (GRADE 1C); (14) we recommend that pregnancy be generally discouraged in patients with severe maternal risk, including patients with active nephritis; severe pulmonary, cardiac, renal, or neurologic disease; recent stroke; or pulmonary hypertension (GRADE 1C); (15) we recommend antenatal testing and serial growth scans in pregnant patients with systemic lupus erythematosus because of the increased risk of fetal growth restriction (FGR) and stillbirth (GRADE 1B); and (16) we recommend adherence to the Centers for Disease Control and Prevention medical eligibility criteria for contraceptive use in patients with systemic lupus erythematosus (GRADE 1B).

Key words: lupus, nephritis, systemic lupus erythematosus, thrombocytopenia

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem, inflammatory autoimmune disease characterized by relapses (commonly called "flares") and remission. Many organs may be involved and although the manifestations are highly variable, the kidneys, joints, and skin are commonly affected. Immunologic abnormalities, including the production of antinuclear antibodies (ANA), are also characteristic of the disease. The prevalence of SLE is estimated to be approximately 28 to 150 per 100,000 individuals.[1] SLE is several times more prevalent in females than males,[2] and because it often affects young adults, pregnancy is common among affected individuals. In the United States, there are approximately 3300 deliveries per year in people with SLE.[3,4] Optimal care of a pregnant patient with SLE involves consultation and co-management with a rheumatologist.

The pathophysiology of SLE is complex and incompletely understood. The condition involves breakdown in the tolerance of both T and B cells to self-antigens, and abnormalities in immunologic processes involving both innate and adaptive immunity.[5] Anticardiolipin (aCL) antibodies are detected in 40% of patients with SLE, although the development of antiphospholipid syndrome (APS) is less common.[6]

SLE seems to be a disorder with some underlying genetic component, an observation based in part on twin studies. In addition, 15% of patients with SLE have a first-degree relative with the condition.[7,8] Although numerous genes have been implicated, the genetics of SLE are complex.[9] Environmental and hormonal factors also play a role in the disease process, and increased levels of estrogen have been implicated.[10]

What are the diagnostic criteria for systemic lupus erythematosus?

SLE is a syndrome, and the diagnosis requires the presence of characteristic clinical features and confirmatory laboratory studies. Major organs affected include the kidneys, brain, lungs, heart, skin, and joints, and the most common symptoms of SLE are fatigue, fever, arthralgias, myalgias, weight loss, and rash (Table 1).[11] When a new diagnosis of SLE is suspected in pregnancy, many symptoms of SLE are difficult to distinguish from normal pregnancy complaints.

The broad range of clinical manifestations and lack of pathognomonic features or laboratory tests make the diagnosis of SLE challenging. Currently, the diagnosis is often made on the basis of classification criteria developed by the European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR)[12] (Figure) or the Systemic Lupus International Collaborating Clinics (SLICC) (Table 2).[13] These criteria were developed for research purposes but are often used as diagnostic criteria for clinical management. The sensitivity of the SLICC criteria for making the diagnosis of SLE is 97% vs 96% for the ACR criteria, and the specificity of SLICC is 84% vs 93% for ACR.[12,13]

TABLE 1
Frequency of clinical symptoms in patients with systemic lupus erythematosus

Clinical symptoms	Frequency (%)
Fatigue	80–100
Fever	80–100
Arthritis	80–95
Myalgias	70
Weight loss	60
Photosensitivity	60
Malar rash	50
Nephritis	50
Pleurisy	50
Lymphadenopathy	50
Pericarditis	30
Neuropsychiatric	20–30

Reference: Djekidel and Silver.[11]

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The mainstay of laboratory testing for diagnosis of SLE is the assessment of ANA. Although useful in diagnosis, a positive ANA test result is not specific for SLE. In contrast, antibodies against double-stranded DNA (anti-dsDNA) are relatively specific for SLE.[14,15] In addition, complement levels, erythrocyte sedimentation rate and/or c-reactive protein levels, and urine protein-to-creatinine ratio, although not diagnostic, can be useful in supporting the diagnosis.

Antibodies against ribonuclear proteins, such as anti-Sjögren's-syndrome-related antigen A (SSA) (anti-Ro) and anti-Sjögren's-syndrome-related antigen B (SSB) (anti-La), are present in a minority of patients with SLE. These antibodies are associated with neonatal lupus erythematosus (NLE) and are important in assessing fetal and neonatal risks.[16] Antiphospholipid (aPL) antibodies, including lupus anticoagulants (LAC), aCL antibodies, and anti-beta-2-glycoprotein-I (anti-β2 GPI) antibodies can be used to establish the diagnosis of APS.[17]

In addition to diagnostic testing, some tests are useful to follow disease activity. Decreases in complement activation (C3 and C4) and elevations in double-stranded DNA levels are useful as markers and may indicate a flare.

What maternal complications are associated with systemic lupus erythematosus during pregnancy?

Maternal morbidity and mortality are substantially increased in patients with SLE, and an initial diagnosis of SLE during

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FIGURE
2019 EULAR/ACR classification criteria for systemic lupus erythematosus

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Reference: Aringer et al.[12]

ACR, American College of Rheumatology; *anti-β2GP1*, anti-beta-2-glycoprotein-1; *anti-dsDNA*, anti—double-stranded DNA; *EULAR*, European Alliance of Associations for Rheumatology; *SLE*, systemic lupus erythematosus.

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pregnancy is associated with increased morbidity.[18] Common complications of SLE include nephritis, hematologic complications such as thrombocytopenia, and a variety of neurologic abnormalities. Some patients with SLE also have APS, which is associated with an increased risk of pregnancy loss and thrombosis.[19] In a large study in the United States including >16 million pregnancies, patients with SLE had a several-fold increased risk of thrombosis, thrombocytopenia, infection, multiorgan disease, and need for blood transfusion when compared with those without SLE. A 20-fold increase in maternal mortality was also reported.[4]

Pregnancy poses a theoretical risk for disease flares because of increased levels of estrogen, which are linked to an increased risk of SLE. In addition, stress and the effect of physical demands of pregnancy can increase the risk of

TABLE 2
Clinical and immunologic criteria used in the Systemic Lupus International Collaborating Clinics classification criteria

Four of 17 criteria, with at least 1 clinical and 1 immunologic criterion or biopsy-proven lupus nephritis in the presence of ANA or anti-dsDNA antibodies:

Clinical criteria
Acute cutaneous lupus
Chronic cutaneous lupus
Nonscarring alopecia
Oral or nasal ulcers
Synovitis involving ≥2 joints
Serositis
Renal: proteinuria >500 mg/24 h or red cell casts
Neurologic: seizures, psychosis, stroke
Hemolytic anemia
Leukopenia or lymphopenia
Thrombocytopenia
Immunologic criteria
ANA
Anti-dsDNA
Anti-Sm
Antiphospholipid antibodies
Low complement
Direct Coombs test in the absence of hemolytic anemia

Modified from: Petri et al.[13]

ANA, antinuclear antibody; *anti-dsDNA*, anti—double-stranded DNA; *Sm*, Smith.

Society for Maternal-Fetal Medicine. Systemic lupus erythematosus in pregnancy. Am J Obstet Gynecol 2023.

flares. However, it is not clear that the risk of flares is increased during pregnancy, and several well-designed studies have yielded conflicting results.[20]

Most flares during pregnancy are mild, typically consisting of arthritis and cutaneous manifestations, and easily treatable.[21,22] Fifteen percent to 30% of flares are severe,[23,24] and some can be life-threatening. Flares may occur during any trimester and in the postpartum period.[25] Risk factors for a flare occurring during pregnancy include active disease within the 6 months before pregnancy, severe underlying disease, active nephritis, and discontinuation of hydroxychloroquine (HCQ).[23,11]

Lupus nephritis

Lupus nephritis is one of the most serious complications of SLE, with significant implications for pregnancy. Active renal disease is defined as >1 g per day of proteinuria, or a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 in the nonpregnant state.[26] The kidneys are affected in one-third of patients at the time of SLE diagnosis; eventually, 50% of individuals with SLE will have kidney involvement.[27] Renal damage occurs because of inflammation associated with immune-complex deposition and complement activation. Laboratory features of lupus nephritis include increased levels of anti-dsDNA antibodies, decreased levels of complement, elevated serum creatinine, and the presence of urinary red-cell casts.[11] Decreased complement levels may be difficult to ascertain during pregnancy because complement levels increase during normal gestation. Relative decreases from baseline may be more informative than absolute levels.[24] Many clinicians obtain anti-dsDNA antibodies and complement levels at the start of pregnancy to assess baseline levels and disease activity.

Patients with preexisting renal disease have an approximately 16% chance of developing active nephritis during pregnancy.[28] Flares are also more likely in patients with active renal disease who become pregnant. As with most renal disorders, the risk of permanent renal damage is increased with a GFR <40 mL/min/1.73 m^2 and/or a serum creatinine level of approximately ≥1.5 mg/dL.[29]

It can be difficult to distinguish lupus nephritis from preeclampsia because both conditions are characterized by hypertension and proteinuria. The distinction is critical, especially if nephritis occurs in the late second or early third trimester because the treatment for these 2 conditions differs significantly; preeclampsia is best treated with delivery or close inpatient monitoring depending on gestational age, although lupus nephritis can be treated medically.[30] Several laboratory parameters have been proposed to distinguish lupus nephritis from preeclampsia (Table 3), although none are 100% accurate. Renal biopsy to assess for glomeruloendotheliosis may yield a definitive diagnosis and in one systematic review led to therapeutic changes in 66% of cases.[31] Although frequently deferred during pregnancy because of a theoretical risk for increased bleeding, renal biopsy should be considered in uncertain clinical situations when a diagnosis of lupus nephritis would delay the need for delivery and potentially prevent extreme prematurity.[31–34]

Hematologic complications

Hematologic abnormalities affect many patients with SLE; these include anemia, thrombocytopenia, and leukopenia. Approximately one-half of patients with SLE are anemic because of a variety of causes, including iron-deficiency anemia, anemia of chronic disease, and hemolytic anemia, which can be chronic or acute.[35] Leukopenia is common in patients with SLE and generally secondary to lymphopenia or neutropenia.[36] The finding of leukopenia may be related to disease activity (flare), infection, or drug toxicity from immunosuppressant medications. The significance of leukopenia in patients with SLE is controversial, although this may contribute to an increased risk of infection, depending on the severity and duration of the leukopenia.[8]

Thrombocytopenia affects approximately 25% of pregnancies with SLE and results from immune-mediated platelet destruction. Risk factors include previous thrombocytopenia, the presence of aPL antibodies, and increased

TABLE 3
Laboratory test results used to distinguish preeclampsia from a lupus flare

Test	Preeclampsia	SLE
Decreased complement levels	+	+++
Increased anti-dsDNA	−	+++
Antithrombin III deficiency	++	+/−
Microangiopathic hemolytic anemia	++	−
Coombs positive hemolytic anemia	−	++
Thrombocytopenia	++	++
Leukopenia	−	++
Urinary cellular casts/hematuria	−	+++
Increased serum creatinine	+/−	++
Hypocalciuria	++	+/−
Increased liver transaminases	++	+/−
Elevated uric acid	+	—

Reference: Djekidel and Silver.[11]

anti-dsDNA, anti—double-stranded DNA; *SLE*, systemic lupus erythematosus.

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TABLE 4
Diagnostic criteria for antiphospholipid syndrome[a]

Clinical criteria	
Vascular thromboses	One or more clinical episodes of arterial, venous, or small-vessel thrombosis
Obstetrical criteria	1) ≥1 unexplained death of a structurally normal fetus at ≥10 wk of gestation 2) ≥1 preterm birth of a structurally normal infant at <34 wk of gestation because of severe preeclampsia or sequelae of uteroplacental insufficiency 3) ≥3 unexplained consecutive spontaneous abortions at <10 wk of gestation
Laboratory criteria	
Lupus anticoagulant	On ≥2 occasions at least 12 wk apart
Anticardiolipin antibodies	IgG and/or IgM present at medium or high titer (ie, >40 GPL or MPL, or >the 99th percentile), on ≥2 occasions at least 12 wk apart
Anti-beta-2 glycoprotein I antibody	IgG and/or IgM in titer >the 99th percentile present on ≥2 occasions at least 12 wk apart

Reference: Miyakis et al.[17]

GPL, IgG phospholipid unit; *Ig*, immunoglobulin; *MPL*, IgM phospholipid unit.

[a] Diagnosis requires one of the clinical criteria and one of the laboratory criteria.

Society for Maternal-Fetal Medicine. Systemic lupus erythematosus in pregnancy. Am J Obstet Gynecol 2023.

disease activity.[11] It is important to consider other causes, although laboratory studies are not able to distinguish between gestational thrombocytopenia, thrombocytopenia owing to lupus flare, primary immune thrombocytopenia, and thrombocytopenia associated with APS. Treatment is based primarily on platelet count, although treatment for an SLE flare may be initiated earlier if thrombocytopenia is a feature.[37] Additional laboratory studies may help in the diagnosis of HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelet count) syndrome, which can cause thrombocytopenia and is managed very differently.

Antiphospholipid syndrome

APS can occur as a primary condition, or in the setting of SLE or other autoimmune conditions. APS is characterized by the presence of persistent aPL antibodies (anti-β2 GPI, aCL antibody, and LAC) and a history of thromboembolic events or specific pregnancy complications, including death at ≥10 weeks of gestation of a structurally normal fetus, preterm birth at <34 weeks of gestation owing to severe preeclampsia or fetal growth restriction (FGR), or ≥3 consecutive unexplained fetal losses before 10 weeks of gestation (Table 4).[17]

Central nervous system and neurologic complications

Central nervous system (CNS) complications are rare but serious consequences of SLE. Neurologic manifestations may include headache, seizures, neuropathy, chorea, cerebritis, and mood disorders, including psychosis. CNS vasculitis is the most serious CNS disorder and occurs in 10% of patients with SLE.[38] The most frequent manifestation of neurologic SLE is diffuse cerebritis caused by autoantibodies. Symptoms tend to be nonlocalizing, and it is imperative to exclude causes other than SLE flare when individuals present with neurologic symptoms because this is generally a diagnosis of exclusion. Typical evaluation includes brain imaging and consideration of assessment of cerebrospinal fluid and electroencephalography. Neurologic manifestations of SLE most often present during the first 2 years after disease onset.[11]

Cutaneous lupus erythematosus

Cutaneous lupus erythematosus includes a number of skin diseases that are generally categorized into 3 subsets—acute, subacute, and chronic.[39] Cutaneous lupus erythematosus can occur independently or as a manifestation of SLE. If a patient has not been evaluated previously for SLE and there is clinical concern for systemic symptoms, an evaluation could be considered, especially for patients with the subacute cutaneous lupus erythematosus subset, which is more commonly associated with SLE and anti-SSA antibodies.[40] In the absence of systemic lupus, most patients with isolated cutaneous lupus have normal pregnancy outcomes and do not require further surveillance beyond testing for anti-SSA and anti-SSB antibodies.[41]

Other organ system involvement

SLE can affect many other organ systems, including bones and joints, lungs, skin, and heart. Joint involvement is one of the most common manifestations of SLE, and 69% to 95% of SLE patients experience arthralgias or arthritis.[42] The arthritis is typically migratory and symmetrical and affects multiple joints. Serositis, including pericardial serositis and pleural effusion, can be a recurring feature.[12,13] Other potential cardiac complications of SLE include pericarditis without effusion, myocarditis, valvular disease, and endocarditis.[43] Pulmonary complications are relatively frequent and include pleuritis, pneumonitis, interstitial lung disease, and rarely, pulmonary hypertension or pulmonary hemorrhage.[44] The most common skin findings are malar rash and discoid lesions, which are often photosensitive.[45]

Vascular symptoms common in lupus include Raynaud phenomenon and vasculitis, which can affect multiple organs. Thromboembolic disease is common and largely related to coexisting APS.

What adverse obstetrical outcomes are associated with systemic lupus erythematosus during pregnancy?

SLE is associated with an increased risk of many obstetrical complications primarily because of obstetrical conditions associated with placental insufficiency. Placentas in SLE pregnancies are typically smaller and often have vascular lesions such as decidual vasculopathy, thrombosis, and infarction.[46]

SLE with APS is associated with a 3-fold increased risk of pregnancy loss.[47] The greatest risk factors for pregnancy loss are the coexistence of aPL antibodies and active renal disease. Others include previous pregnancy loss and active disease at the time of conception.[47–50] The rate of pregnancy loss in women with well-controlled SLE without APS or these other risk factors ranges from 8% to 32%, which may not be substantially different from early pregnancy loss rates reported in the general obstetrical population.[47–50]

Preeclampsia occurs in approximately 15% to 35% of pregnant women with SLE.[3,21,51] Patients with the highest risk for preeclampsia are those with active disease at the time of conception, renal disease, chronic hypertension, high-dose prednisone use, or aPL antibodies.[3,21,51,52] **We recommend low-dose aspirin beginning at 12 weeks of gestation until delivery in patients with SLE to decrease the occurrence of preeclampsia[53,54] (GRADE 1B).**

FGR is common in SLE pregnancies. The risk ranges from 6% to 35%, although precise data are lacking. Risk factors are similar to those previously noted for preeclampsia. One study reported an increased risk of FGR in patients with mild disease, even after controlling for confounders such as hypertension and renal disease.[55]

SLE is also associated with an increased risk for preterm birth, which is likely due in part to the increase in preeclampsia and FGR. The rate of preterm birth (<37 weeks of gestation) is reported to range from 19% to as high as 49%.[56] Risk factors for preterm birth are similar to those associated with preeclampsia, pregnancy loss, and FGR, and include increased disease activity at the time of conception, nephritis, chronic hypertension, and aPL antibodies.[21]

What fetal and neonatal complications are associated with systemic lupus erythematosus during pregnancy?

NLE is a rare but serious complication of SLE. NLE complicates approximately 1 in 20,000 live births, and most but not all of the children affected are born to women with SLE. Manifestations of NLE include skin lesions, congenital heart block (CHB), anemia, hepatitis, and thrombocytopenia, with skin lesions occurring in approximately one-half of affected infants. Other complications (eg, aplastic anemia) are less common.[57]

NLE is caused by antibodies that bind to cytoplasmic ribonucleoproteins. Most of these antibodies are anti-SSA, although anti-SSB antibodies are often present. NLE can occur when these autoantibodies are present in patients without a diagnosed autoimmune disease; approximately 50% of these patients will eventually develop SLE.[58] Anti-SSA and anti-SSB antibodies are present in approximately 30% and 15% to 20% of women with SLE, respectively.[59] In a prospective cohort study of women with anti-SSA and anti-SSB antibodies (with or without SLE), only approximately 2% of infants developed CHB.[60] However, the recurrence risk of CHB in women with a previously affected infant and positive antibodies is 15% to 20%.[61,62] Reports of cases of twins discordant for NLE support the likelihood of multifactorial causation requiring genetic susceptibility and exposure to antibodies.[63]

Because NLE is caused by transplacental passage of autoantibodies, manifestations such as skin rash, anemia, thrombocytopenia, and hepatitis typically resolve over the first 3 to 6 months of life as maternal antibodies are cleared.[64] However, anti-SSA antibodies are tropic for myocardial tissue and the conduction system of the fetal heart, leading to inflammation with mononuclear cell infiltration, and subsequent fibrosis, scarring, and calcification. When inflammation occurs in the atrioventricular and sinoatrial nodes, it can lead to CHB,[65] which occurs in 50% of cases of NLE.[66] CHB typically manifests between 16 and 25 weeks of gestation as fetal bradycardia with a fetal heart rate of 60 to 80 beats per minute, and can lead to fetal hydrops and stillbirth.[57] Scarring of the fetal conduction system and diffuse fibroelastosis in the endocardium and myocardium may occur as a result of inflammation. In contrast to neonatal skin lesions and anemia, heart block and fibroelastosis are usually permanent.[59]

The prognosis for neonates with CHB is variable and related to the extent of fibroelastosis and the presence of fetal hydrops; 15% to 20% of children with NLE and CHB die within the first 3 years of life.[16,59] Among survivors, approximately 60% require a pacemaker within the first few

years of life[59]; most of the remainder will require pacing before adulthood.

What is the approach to medical management of systemic lupus erythematosus in pregnancy?

Hydroxychloroquine

The ACR conditionally recommends initiating HCQ during pregnancy in women with SLE not already taking this medication.[19] This recommendation is based on data suggesting decreased disease activity, prednisone use, and frequency of adverse pregnancy outcomes, including preterm delivery, in people exposed to HCQ compared with people not exposed during pregnancy. However, most studies do not differentiate between people who stopped HCQ with pregnancy diagnosis and people not taking HCQ because their disease was quiescent. To date, no randomized controlled trials have compared initiating and not initiating HCQ in pregnant people with quiescent SLE. **We recommend that all patients with SLE, other than those with quiescent disease, either continue or initiate HCQ in pregnancy (GRADE 1B).** This includes patients who are taking low-dose prednisone or nonsteroidal antiinflammatory drugs (NSAIDs) for SLE-related pain because use of these medications suggests disease activity. Some investigators recommend that patients with quiescent disease activity who have anti-SSA, anti-SSB, or aPL antibodies consider initiating HCQ because some studies[67–70] suggest improved maternal and fetal outcomes in these specific populations. **We suggest that for all other patients with quiescent disease activity who are not taking HCQ or other medications, it is reasonable to engage in shared decision-making regarding whether to initiate new therapy with this medication in consultation with the patient's rheumatologist (GRADE 2B).**

Corticosteroids

Typically, corticosteroids are recommended when SLE is not controlled with HCQ alone. Corticosteroids that are not fluorinated (prednisone, hydrocortisone, or prednisolone) are largely inactivated by the placenta and are preferred.[24] Although some older studies suggested an association of steroid exposure with fetal orofacial clefts, recent evidence indicates that corticosteroids are not associated with fetal malformations.[71] However, the dosage should be minimized to reduce the risk of dose-dependent adverse effects such as hypertension, fluid retention, infection, avascular necrosis, and moon facies. Steroid use also increases the risk of gestational diabetes mellitus, preeclampsia, FGR, preterm premature rupture of membranes, and preterm birth.[72] Once disease activity is stable, the steroid dosage should be slowly tapered to the lowest effective dose.[11]

Other immunosuppressive agents

Severe flares that are refractory to HCQ and prednisone should be treated with additional immunosuppressive agents, in consultation with the patient's rheumatologist. Azathioprine has been used extensively during pregnancy. Adverse effects are rare, and human teratogenicity has not been reported.[72] Although this drug has been associated with an increased risk of FGR and pregnancy loss, the association is controversial.[73] In patients anticipating pregnancy who require ongoing immunosuppression, transitioning to azathioprine from potentially teratogenic medications (Table 5) several months before attempting to conceive can help ensure stable disease during pregnancy.

Cyclosporine is another option for lupus flares that are refractory to other medical therapies. It is particularly effective in the treatment of proliferative lupus nephritis.[74] Side effects of cyclosporine include headache, flu-like symptoms, rash, and rarely, hemolytic anemia. Tacrolimus, a calcineurin inhibitor, can be used to treat lupus nephritis and is reported to be more effective than cyclosporine in inducing remission.[75] Although case series have not shown teratogenic effects, neonatal hyperkalemia and renal dysfunction have been reported.[76] Finally, intravenous immune globulin (IVIg) may be useful specifically in cases of thrombocytopenia associated with SLE.[77] Cyclosporine, tacrolimus, and IVIg are not first-line therapies but can be considered for treatment of an active lupus flare or lupus nephritis that has not responded to corticosteroids, azathioprine, or HCQ. Lupus nephritis can be life-threatening, and the benefits of these effective drugs generally outweigh any potential risks.

Medications to avoid

Several medications used to treat SLE should be avoided during pregnancy (Table 5). NSAIDs are a mainstay of treatment for mild joint pain in nonpregnant individuals. Because of fetal effects such as renal insufficiency leading to oligohydramnios, necrotizing enterocolitis, premature closure of the ductus arteriosus, and pulmonary hypertension, **we recommend that prolonged use of NSAIDs (>48 hours) generally be avoided during pregnancy (GRADE 1A).** Because of a similar mechanism of action, **we recommend that COX-2 inhibitors and full-dose aspirin be avoided during pregnancy (GRADE 1B).** Acetaminophen is a safe, although less effective, alternative to NSAIDs and aspirin.[78] Mycophenolate and methotrexate are teratogens and are contraindicated.[19] **We recommend discontinuing methotrexate 1-3 months and mycophenolate mofetil/mycophenolic acid at least 6 weeks before attempting pregnancy (GRADE 1A).** Leflunomide is considered a teratogen and is therefore contraindicated, although data are mixed.[79] Pregnancy should be delayed 2 years after discontinuing leflunomide because of the long half-life and enterohepatic circulation.[80] Cholestyramine may be utilized to accelerate leflunomide elimination for pregnancy planning or in case of unanticipated pregnancy while taking leflunomide. Once the metabolite is no longer detected in the serum, the pregnancy risks are not elevated.[19]

Biologic agents

Over the past several years, new biologic agents have been used for a range of autoimmune disorders, including SLE.

TABLE 5
Medications used for treatment of lupus during pregnancy and lactation

Medications	Safety	Other concerns	Recommendations	Lactation
NSAIDs, ASA, COX-2 inhibitors	Can cause closure of fetal ductus when used during the third trimester.[11]	Oligohydramnios[78]	Generally avoid in third trimester; substitute acetaminophen.[78]	Safe to continue[19]
Hydroxychloroquine	No adverse fetal effects.[11]	Discontinuation is associated with increased risk of SLE flares.[11]	Continue during pregnancy and consider for all patients with SLE.[11]	Safe to continue[11]
Glucocorticoids	Some concerns for oral clefts in animals and some human studies. Recent data show no clear association with fetal malformations.[71]	Effective and minimal placental transfer. High doses are associated with significant maternal and obstetrical side effects.[24]	Use lowest effective dose. Avoid empirical use. Avoid fluorinated glucocorticoids that cross the placenta. Routine use of stress dose steroids not recommended at time of vaginal delivery; conditionally recommend at time of cesarean delivery.[19]	Safe to continue[19]
Azathioprine	Teratogenic in animals. Seems safe in humans.[11]		Reasonable to continue if stable on this medication at a dosage not exceeding 2 mg/kg per day. Consider adding if SLE not controlled on hydroxychloroquine and glucocorticoids.[11]	Safe to continue[19]
Cyclosporine A	Extensive experience with the use of cyclosporine in pregnant transplant patients. Not an animal teratogen. Seems safe in humans.[11]	Transient lowered platelets and white cells in infants have been reported.[11]	Reasonable option if disease refractory to other medications.[72]	Reasonable option with infant monitoring[72]
Tacrolimus	Neonatal hyperkalemia and renal dysfunction have been reported. Successful pregnancies reported.[11]		Effective for lupus nephritis. Benefit may outweigh risks in severe cases.[75]	Limited data suggest safety[11]
Certolizumab	No adverse fetal effects.[81]		Continue throughout pregnancy.	Safe to continue
Abatacept	Animal studies showed alterations in immune function. Inadequate pregnancy data.[84]		Avoid if other, safer alternatives can be used.	Inadequate data
Infliximab, Adalimumab, Golimumab, Rituximab, Belimumab	Inadequate pregnancy data.[82,83,85,86]		Management decisions should be individualized and made in collaboration with Rheumatology.	Inadequate data
Cyclophosphamide	Associated with cleft palate and skeletal abnormalities. Second- and third-trimester use associated with FGR and neonatal pancytopenia.[11]	Risk of premature ovarian failure.[11]	Effective for lupus nephritis.[87] Benefit may outweigh risks in severe cases.[88]	Contraindicated[19]

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TABLE 5
Medications used for treatment of lupus during pregnancy and lactation *(continued)*

Medications	Safety	Other concerns	Recommendations	Lactation
Mycophenolate mofetil	Associated with facial clefts and facial and ear abnormalities.[11]		Avoid in pregnancy.[11] Stop >6 weeks before attempting pregnancy	Contraindicated, limited data[11]
Methotrexate	Lethal to embryo; associated with multiple anomalies.[11]		Avoid in pregnancy. Stop 1-3 mo before attempting pregnancy.[11]	Contraindicated[19]
Leflunomide[a]	Teratogenic in animals.[80]	Elimination may take 2 y after dosing because of long half-life and enterohepatic circulation.[80]	Avoid in pregnancy. Cholestyramine "wash out" before pregnancy or in case of inadvertent exposure.[80]	Contraindicated[19]

ASA, acetylsalicylic acid; *FGR*, fetal growth restriction; *NSAIDs*, nonsteroidal antiinflammatory drugs; *SLE*, systemic lupus erythematosus; *TNFα*, tumor necrosis factor alpha; *VACTERL*, vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities.

[a] Not clinically available in the United States.

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Society for Maternal-Fetal Medicine. Systemic lupus erythematosus in pregnancy. Am J Obstet Gynecol 2023.

These medications can be broadly categorized into tumor necrosis factor (TNF)-alpha inhibitors (certolizumab, infliximab, adalimumab, golimumab) and other biologics (rituximab, belimumab). Two medications recently approved by the FDA for lupus treatment include anifrolumab and voclosporin, which have minimal safety data in pregnancy. Certolizumab appears safe to use throughout pregnancy.[81] Data on perinatal outcomes with other medications are limited, but there do not appear to be consistent patterns of birth defects or associated serious adverse perinatal outcomes.[82,83] **We suggest the decision to initiate, continue, or discontinue biologics in pregnancy be made in collaboration with a rheumatologist and be individualized to the patient (GRADE 2C).**

Biologics such as the TNF-alpha class including infliximab, adalimumab, and golimumab cross the placenta and are found in cord blood at birth.[89] They can remain detectable in infants for up to 12 months, which also raises concern for potential effects on immune system development.[90] Some evidence suggests that this antibody exposure in utero may be associated with childhood infections.[91,92] There are no data demonstrating that stopping these medications in the third trimester reduces the potential risk of infections although this is sometimes practiced.[92] The reasons for stopping medications in the third trimester should be weighed against the risk of flares if medications are stopped. Small studies of children exposed in utero suggest that they have appropriate immune responses to vaccines.[93,94]

How should pregnant patients with systemic lupus erythematosus and specific complications be managed during pregnancy?

Antiphospholipid syndrome

For patients with SLE and clinical and laboratory criteria for APS, the goal for treatment during pregnancy is to improve maternal, fetal, and neonatal outcomes. Patients with SLE who meet clinical and laboratory criteria for APS should be treated with prophylactic anticoagulation during pregnancy and for 6 weeks postpartum.[19,95] For patients with APS who have had a previous thrombotic event, therapeutic anticoagulation throughout pregnancy and for 6 weeks postpartum is recommended to minimize the risk of maternal thromboembolism.[95] For patients with a history of stillbirth or recurrent pregnancy loss in the setting of SLE and APS, the American College of Obstetricians and Gynecologists has suggested that prophylactic heparin throughout pregnancy and 6 weeks postpartum should be considered.[95] Anticoagulation dosage may be individualized on the basis of a patient's specific history, previous response to anticoagulation, and any comorbid conditions. **We suggest treatment with a combination of prophylactic unfractionated or low-molecular-weight heparin and low-dose aspirin for patients without a previous thrombotic event who meet obstetrical criteria for APS (GRADE 2B). We recommend therapeutic unfractionated or low-molecular-weight heparin for patients with a history of thrombosis and aPL antibodies (GRADE 1B).**

Antiphospholipid antibodies without antiphospholipid syndrome

Up to 40% of patients with SLE have aPL antibodies, but only one-third develop clinical manifestations of APS[95]; aPL antibodies have also been observed to transiently appear during infections, after vaccinations, and in reaction to drugs.[95] Patients with aPL antibodies, especially LAC, who do not meet the clinical criteria for APS remain at risk for preeclampsia; however, the risk for other adverse pregnancy outcomes and optimal management remain unclear.[96,97] A meta-analysis of 5 studies with 154 pregnancies complicated by the presence of asymptomatic aPL antibodies with or without SLE found no difference in adverse pregnancy outcomes between pregnant participants who received prophylactic treatment (primarily aspirin) and those who did not. However, the small sample size and heterogeneity of included studies limit the conclusions.[98]

We suggest treatment with low-dose aspirin alone in patients with SLE and aPL antibodies without clinical events meeting criteria for APS (GRADE 2C).

Anti-Sjögren's-syndrome-related antigen A/antigen B antibodies

People with anti-SSA and anti-SSB antibodies with or without diagnosis of SLE or Sjögren's disease are at increased risk of delivering an infant with NLE because of the transplacental passage of these antibodies. The major manifestations of NLE are cutaneous or cardiac, although hematologic and hepatic manifestations also occur. In women with anti-SSA and to a lesser extent anti-SSB antibodies, the risk of complete heart block is approximately 2%.[99] This risk increases in subsequent pregnancies after a first affected birth.[60,100,101] Affected fetuses may develop first-, second-, or third-degree heart block, most commonly between 18 and 25 weeks of gestation.[102]

Given the morbidity associated with the cardiac manifestations of NLE, investigators have studied a number of potential preventative medications, therapeutic interventions, and screening modalities. These include HCQ, corticosteroids, IVIg, beta-agonists, serial fetal echocardiograms for measurement of the fetal PR interval, and daily home monitoring using handheld Doppler devices.[102–109] Largely on the basis of mechanism of injury, it has been proposed that treatment with HCQ throughout pregnancy might decrease the occurrence of CHB in at-risk fetuses.[105] In one observational study, 54 women with a previous affected pregnancy were treated with HCQ beginning at <10 weeks of gestation; 4 of the 54 (7.4%) pregnancies developed CHB, which the authors noted was lower than the historic recurrence rate of 18%.[105] However, data are limited by a lack of appropriately powered clinical trials, and the benefit of HCQ remains uncertain. Nevertheless, treatment with HCQ presents few risks, and may also have maternal benefits.

Another approach to prevention has been to screen patients with anti-SSA or anti-SSB antibodies with fetal

echocardiogram for first- or second-degree heart block, and if found, to initiate steroid treatment to prevent progression to complete heart block. Biologic evidence suggests that antiinflammatory medications such as steroids could reduce the inflammation and scarring caused by anti-SSA antibodies. In the PR Interval and Dexamethasone Evaluation (PRIDE) study, women with anti-SSA and anti-SSB antibodies were assessed with serial fetal echocardiograms until 24 weeks of gestation, and those with first- or second-degree heart block were treated with dexamethasone.[102,110] In some cases, steroid treatment seemed to reverse first-degree heart block, but some cases spontaneously reversed, and other cases progressed despite steroid treatment. Overall, prolongation of the PR interval was uncommon and did not precede more advanced block, whereas several cases of complete heart block occurred without a graded progression through first- or second-degree heart block.[102,110]

Retrospective data provide similar inconclusive results. A multicenter international study reported on 175 pregnancies with congenital second- or third-degree heart block; 67 (38%) were treated with corticosteroids, with no significant effect of such treatment on outcomes. Side effects were reported in 11 pregnancies (6%), mainly oligohydramnios, growth restriction, and constriction of the ductus arteriosus. One mother developed diabetes mellitus, adrenal insufficiency, and psychosis.[111]

More recently, data from a large registry reported on the efficacy of steroids with regard to progression, mortality, and need for pacemaker implantation in neonates with CHB.[112] The study compared 71 fetuses who received steroids within 1 week of detection of CHB with 85 fetuses who were not treated, and found that steroids did not significantly prevent the progression of disease, reduce mortality, or prevent pacemaker implantation. In a 2018 meta-analysis of retrospective studies by Ciardulli et al[103] that included 71 fetuses diagnosed with second-degree CHB and treated with corticosteroids, rate of progression from abnormal conduction to complete congenital atrioventricular block at birth in fetuses treated with steroids was 52% (95% CI 23-79%) compared to 73% (95% CI 39-94%) in untreated cases. The authors noted the low quality of these retrospective data, concluding that any benefit of steroid treatment remains unproven. In conclusion, evidence of efficacy of corticosteroids for prevention of progression or prevention of CHB is conflicting, and there is some concern that high-dose fluorinated corticosteroids may adversely affect maternal health as well as fetal growth and brain development.[113–116]

Investigators have also studied the addition of other interventions to corticosteroid treatment.[104,106] For example, Mawad et al[117] studied outcomes in a case series of 130 fetuses with NLE treated with dexamethasone, some of whom also received IVIG (N = 34) or beta-mimetics (N = 47). Two patients (1.5%) had side effects from dexamethasone with one developing acute psychosis. They compared their outcomes to summary outcomes from 5 prior studies of patients who had similar diagnoses but lower frequencies of these therapies. While better neonatal outcomes were reported in their series, assessment of causation is limited by the lack of a control group and the corresponding inability to adjust for potential confounding and patient heterogeneity. Another retrospective study[118] examined outcomes of 127 pregnant individuals who were anti-Ro/SSA positive, 98 (77%) of whom received dexamethasone and other therapies and 29 (23%) of whom did not. There was no difference in the primary composite outcome or multiple secondary outcomes, although death or transplant after fetal diagnosis was higher in the untreated group (32% vs. 11.5%, $p<0.01$). While intriguing, specific treatment recommendations are difficult to justify given the heterogeneous patient population, different management strategies utilized, and multiple outcomes with no difference. Neither study directly addressed the independent effect of IVIG or beta mimetics on outcomes.

Investigators have suggested that the lack of improved outcomes from corticosteroid and IVIG administration could be due to inability to intervene soon enough in the development of complete CHB.[109] The ongoing prospective AVB study (STOP BLOQ [Surveillance and Treatment to Prevent Fetal Atrioventricular Block Likely to Occur Quickly]; ClinicalTrials.gov: NCT04474223) risk stratifies pregnancies by anti-Ro/SSA antibody titer, employs thrice-daily home Doppler monitoring to detect rhythm disturbances in high-titer pregnancies, and investigates the efficacy of fetal echocardiogram followed by rapid initiation of steroid and IVIG treatment on fetal incomplete AVB to restore normal rhythm or prevent AVB progression. A second study, (SLOW HEART REGISTRY of Fetal Immune-mediated High Degree Heart Block: ClinicalTrials.gov: NCT04559425) prospectively compares morbidity and mortality between treated and untreated fetuses through the first 2 years of life and will provide needed outcome data.

Given these data, the utility of screening for or treating heart block remains unproven because early-stage heart block does not predictably progress to more advanced heart block, and interventions have not been shown to prevent progression or improve outcomes. **We recommend that steroids not be routinely used for the treatment of fetal heart block due to anti-SSA/SSB antibodies given their unproven benefit and the known risks for both the pregnant patient and fetus (GRADE 1C).** Furthermore, given the lack of an effective intervention, and the criteria that screening tests are only useful if effective interventions exist, the rationale for screening for early-stage fetal heart block in patients with anti-SSA/SSB antibodies is uncertain. **Accordingly, we recommend that serial fetal echocardiograms for assessment of the PR interval not be routinely performed in patients with anti-SSA or anti-SSB antibodies outside of a clinical trial setting (GRADE 1B).** We acknowledge that this monitoring has been recommended by other organizations[19,119,120] and that many patients undergo such screening, but believe that

serial fetal echocardiograms for assessment of the PR interval cannot be recommended until more evidence of benefit is available.

Doppler assessment of fetal heart rate during routine prenatal visits can be used to screen for fetal complete heart block. Once complete fetal heart block develops, management is expectant, with weekly ultrasound examinations recommended to assess for hydrops. Fetuses typically tolerate a ventricular rate of >55 beats per minute. Some authors have advocated maternal beta-agonist therapy when the fetal heart rate is less than 50 to 55 beats per minute to increase the fetal heart rate and theoretically increase the fetal stroke volume.[107,121] However, data are limited on the utility of this approach.

Fetuses with complete heart block should be delivered in a tertiary-care center with pediatric cardiology availability. In cases of complete fetal heart block, cesarean delivery is usually performed because interpretation of external fetal monitoring during labor in this setting is challenging. It is possible, however, to monitor fetal well-being by following the atrial rate using a Doppler device or with serial biophysical profile assessments.[122]

Mild systemic lupus erythematosus flares

A patient's personal history of flares can be helpful in distinguishing a flare from common pregnancy symptoms. Clinical and laboratory evaluation of a possible SLE flare in pregnancy includes a physical exam, complete blood count, anti-dsDNA titer, and measurement of complement levels. If the patient is not currently taking HCQ, 200 mg twice daily should be prescribed. If necessary, the dosage can be increased to 400 mg twice daily. If the patient does not respond and is not taking glucocorticoids, institution of 15 to 20 mg of prednisone daily is recommended. In patients already taking glucocorticoids, the dosage should be increased to 20 to 30 mg/d (Table 6).

Severe systemic lupus erythematosus flares

In patients presenting with symptoms suggesting a more severe flare, the clinical and laboratory evaluation described above is also recommended. Laboratory testing for preeclampsia, including urine protein–creatinine ratio or 24-hour urine assessment for protein and creatinine, uric acid, and liver function tests may also be useful because the signs and symptoms of SLE flares and preeclampsia overlap and are important to distinguish given that management differs (Table 3). Glucocorticoid dosage should be increased to 1.0 to 1.5 mg/kg, then tapered after clinical improvement. If necessary, cyclosporine or azathioprine can be added to avoid ongoing high doses of glucocorticoids. Hospitalization is generally appropriate in this setting.

Rheumatology consultation is recommended for patients with a severe flare, especially with renal or CNS involvement, for which intravenous glucocorticoids are recommended and other immunosuppressive agents may be required (Table 6).

What is the appropriate obstetrical management for pregnant patients with systemic lupus erythematosus?

Prepregnancy counseling

We recommend that patients with SLE undergo prepregnancy counseling with both maternal–fetal medicine and rheumatology specialists that includes a discussion regarding maternal and fetal risks (GRADE 1C). Patients should be informed that even successful pregnancies are often complicated by preeclampsia, FGR, and preterm birth.[124] In addition, some patients will experience flares during pregnancy, and medical options are more limited than in nonpregnant individuals. If delaying pregnancy is advisable to optimize medical therapy or improve disease control, appropriate contraception should be discussed and encouraged.

Prepregnancy counseling also allows for clinical and laboratory assessment of disease status and maternal and fetal risks, and adjustment of maternal therapeutic regimens. Factors that affect counseling include the patient's SLE history, specifically the presence or absence of lupus nephritis, CNS involvement, thromboembolism, and APS; the patient's obstetrical history, particularly any history of neonatal lupus in previous children; and disease status. Laboratory information can be useful in clarifying risks for a future pregnancy, but laboratory results in an asymptomatic patient are not likely to be useful if baseline values are already known. Testing for anti-SSA and anti-SSB antibodies in patients without a previous infant with NLE is controversial. Results may facilitate counseling, but the positive predictive value of testing for NLE in this population is low. In addition, it is unclear whether CHB can be prevented with antenatal management.[125]

When possible, pregnancy should be deferred until the disease has been in remission for at least 6 months.[126] **We recommend that pregnancy be generally discouraged in patients with severe maternal risk, including patients with active nephritis; severe pulmonary, cardiac, renal, or neurologic disease; recent stroke; or pulmonary hypertension (GRADE 1C).**[55] Patients who become pregnant with these conditions, among others, may need abortion care because of life-threatening maternal risk.

The patient's medical regimen may require modifications such as discontinuing NSAIDs and full-dose aspirin and minimizing corticosteroid dosages.[19] HCQ should be continued because it is safe in pregnancy and abrupt cessation may induce a flare.[127] Immunosuppressive agents with the potential for adverse or teratogenic fetal effects, including cyclophosphamide, methotrexate, mycophenolate, and leflunomide, should be discontinued before attempting pregnancy.[20] Azathioprine and cyclosporine are acceptable immunosuppressive agents during pregnancy.[20] Patients requiring anticoagulant therapy should be switched from warfarin to low-molecular-weight heparin before or as soon as pregnancy is recognized (Table 6).

TABLE 6
Prenatal care of patients with systemic lupus erythematosus

A. Prepregnancy counseling

1. Discuss potential pregnancy complications including preeclampsia, preterm birth, pregnancy loss, fetal death, FGR, and neonatal lupus.
2. Discontinue NSAIDs and cytotoxic agents.
3. Continue hydroxychloroquine and minimize doses of steroids.
4. Delay pregnancy until disease has been quiescent for 6 mo.
5. Avoid pregnancy in case of active disease, active nephritis, pulmonary hypertension, other severe end-organ damage, recent thrombosis.
6. Recommend folic acid supplementation.
7. Provide or confirm effective contraception if delaying pregnancy is recommended.

B. Initial evaluation and management of SLE during pregnancy

1. Obtain specific history regarding course of SLE and history of lupus nephritis, thrombosis, or CNS complications.
2. Obtain obstetrical history including history of preeclampsia, FGR, stillbirth, or congenital heart block.
3. Discuss potential pregnancy complications including preeclampsia, preterm labor, pregnancy loss, fetal death, FGR, and neonatal lupus.
4. Advise of significant maternal and fetal risks in case of active disease, active nephritis, pulmonary hypertension, other severe end-organ damage, or recent thrombosis.
5. Assess SLE disease status using standardized, validated tool (eg, SLEDAI).
6. Screen for hypertension.
7. Review previous or obtain laboratory assessment of:
   a. Renal function with urinalysis, urine protein—creatinine ratio, serum creatinine
   b. Complete blood count
   c. Antiphospholipid antibody syndrome (lupus anticoagulant, IgG and IgM anticardiolipin antibodies, and IgG and IgM anti-beta-2-glycoprotein-I antibodies)
   d. Anti-dsDNA and complement levels
   e. Anti-Ro/SSA and -La/SSB
8. Adjust medications
   a. Discontinue NSAIDs and cytotoxic agents.
   b. Continue hydroxychloroquine.
   c. Minimize doses of steroids.
   d. Recommend folic acid supplementation.
   e. Recommend low-dose aspirin.
9. Establish communication with patient's rheumatologist.

C. Antenatal care

1. Assess SLE status and screen for hypertension at each prenatal visit.
2. Test anti-dsDNA and complement levels in case of any signs or symptoms of flare.
3. Perform serial blood counts with history of leukopenia, thrombocytopenia, or anemia.
4. Perform serial evaluation of serum creatinine and proteinuria with history of nephritis.
5. Perform ultrasound assessment of fetal growth (eg, at 28 wk and 32—34 wk of gestation).
6. Initiate antenatal surveillance (eg, weekly beginning at 32 wk of gestation through delivery for uncomplicated SLE; individualize for complicated SLE).
7. Deliver between 39 and 40 wk of gestation, and earlier if FGR or other comorbidities exist.

D. Management of SLE exacerbation

1. Mild to moderate exacerbations
   a. If the patient is taking glucocorticoids, increase the dosage to at least 20 to 30 mg/d.
   b. If the patient is not taking glucocorticoids, start 15- to 20-mg prednisone daily. Alternatively, intravenous methylprednisolone (1000 mg daily) for 3 days may avoid the need for daily maintenance doses of steroids.
   c. If the patient is not taking hydroxychloroquine, initiate 200 mg twice daily.
2. Severe exacerbations without renal or CNS manifestations
   a. Rheumatology consultation and consider hospitalization.
   b. Glucocorticoid treatment 1.0 to 1.5 mg/kg. Expect clinical improvement in 5 to 10 d.
   c. Taper the glucocorticoids once the patient demonstrates clinical improvement.
   d. If the patient cannot be tapered off high doses of glucocorticoids, consider starting cyclosporine or azathioprine.
3. Severe exacerbations with renal or CNS involvement
   a. Hospitalization and rheumatology consultation.
   b. Maintain patient on 1.0 to 1.5 mg/kg of oral prednisone.
   c. When the patient responds, taper the glucocorticoid.
   d. For unresponsive patients, consider immunosuppressive agents and/or plasmapheresis.

References: Djekidel and Silver,[11] and American College of Obstetricians and Gynecologists.[123]

Anti-dsDNA, anti—double-stranded DNA; *Anti-La/SSB*, anti-Sjögren's-syndrome-related antigen B; *Anti-Ro/SSA*, anti-Sjögren's-syndrome-related antigen A; *CNS*, central nervous system; *FGR*, fetal growth restriction; *Ig*, immunoglobulin; *NSAID*, nonsteroidal antiinflammatory drug; *SLE*, systemic lupus erythematosus; *SLEDAI*, Systemic Lupus Erythematosus Activity Index.

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TABLE 7
US Medical Eligibility Criteria for contraceptive use in patients with systemic lupus erythematosus

	Contraceptive method							
	Cu-IUD				DMPA			
Condition	Initiation	Continuation	LNG-IUD	Implants	Initiation	Continuation	POPs	CHCs
Positive (or unknown) antiphospholipid antibodies	1[a,b]	1[a,b]	3[a,b]	3[a,b]	3[a,b]	3[a,b]	3[a,b]	4[a,b]
Severe thrombocytopenia	3[a,c]	2[a,c]	2[a,c]	2[a,d]	3[a,d]	2[a,d]	2[a,d]	2[a]
Immunosuppressive therapy	2[a]	1[a]	2[a]	2[a]	2[a]	2[a]	2[a]	2[a]
None of the above	1[a]	1[a]	2[a]	2[a]	2[a]	2[a]	2[a]	2[a]

Categories for classifying intrauterine devices and hormonal contraceptives: 1=a condition for which there is no restriction for the use of the contraceptive method; 2=a condition for which the advantages of using the method generally outweigh the theoretical or proven risks; 3=a condition for which the theoretical or proven risks usually outweigh the advantages of using the method; 4=a condition that represents an unacceptable health risk if the contraceptive method is used.

Data from:[129]. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65:1–104.

CHC, combined hormonal contraceptive (including pill, patch, and ring); *Cu-IUD*, copper-containing intrauterine device; *DMPA*, depot medroxyprogesterone acetate; *LNG-IUD*, levonorgestrel-releasing intrauterine device; *POP*, progestin-only pill.

[a] Clarification: persons with systemic lupus erythematosus (SLE) are at increased risk for ischemic heart disease, stroke, and venous thromboembolism. Categories assigned to such conditions in US MEC should be the same for women with SLE who have these conditions. For all subconditions of SLE, classifications are based on the assumption that no other risk factors for cardiovascular disease are present; these classifications must be modified in the presence of such risk factors. Many women with SLE can be considered good candidates for most contraceptive methods, including hormonal contraceptives;; [b] Evidence: antiphospholipid antibodies are associated with a higher risk for both arterial and venous thrombosis;; [c] Comment: severe thrombocytopenia increases the risk for bleeding. The category should be assessed according to the severity of thrombocytopenia and its clinical manifestations. In women with very severe thrombocytopenia who are at risk for spontaneous bleeding, consultation with a specialist and certain pretreatments might be warranted. Evidence: the LNG-IUD might be a useful treatment for menorrhagia in women with severe thrombocytopenia;; [d] Comment: severe thrombocytopenia increases the risk for bleeding. POPs might be useful in treating menorrhagia in women with severe thrombocytopenia. However, given the increased or erratic bleeding that might be observed on initiation of DMPA and its irreversibility for 11 to 13 weeks after administration, initiation of this method in women with severe thrombocytopenia should be done with caution.

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Pregnancy management

Obstetrical management of patients with SLE is outlined in Table 6. Baseline laboratory testing early in pregnancy is similar to that advised for preconception counseling. Although some experts recommend serial assessment of autoantibodies, complement levels, complete blood count, and serum chemistry,[20] the utility of this testing remains unproven. Testing is recommended if signs or symptoms suggest the possibility of a flare because clinical and laboratory evidence of a flare can be used to adjust treatment.

Consultation with a rheumatologist and maternal–fetal medicine subspecialist throughout pregnancy is recommended, especially for patients with active and severe disease. Those with severe disease or a history of obstetrical complications may benefit from more frequent evaluation. Use of a standardized, validated tool, such as the Systemic Lupus Erythematosus Activity Index (SLEDAI), has been reported to be helpful for assessing disease activity in the general population and during pregnancy.[128]

We recommend antenatal testing and serial growth scans in pregnant patients with SLE because of the increased risk of FGR and stillbirth (GRADE 1B). Although there is no evidence to support an optimal approach, weekly antenatal fetal surveillance may be considered by 32 weeks of gestation, and ultrasonography to assess interval growth is commonly performed monthly or at least at 28 and 32 to 34 weeks of gestation. For pregnant patients with complicated SLE (eg, active lupus nephritis, recent lupus flare, aPL antibodies with previous fetal loss, anti-SSA or anti-SSB antibodies, or thrombosis), the gestational age at initiation of and frequency of antenatal fetal surveillance should be individualized in consultation with maternal–fetal medicine and may be considered on diagnosis or at a gestational age when delivery would be undertaken for abnormal testing.[123]

Timing, mode, and management of delivery in pregnant patients with complicated SLE should be individualized. With uncomplicated SLE, early term delivery is not indicated but delivery can be considered at term (39 weeks of gestation). Complications such as preeclampsia or FGR, or comorbidities such as APS, chronic hypertension, renal disease, or active SLE may modify delivery timing and management, and may necessitate earlier delivery. For patients who required prolonged use of corticosteroids during the pregnancy, stress dose steroids are indicated for cesarean delivery but should be individualized for vaginal delivery.

Postpartum management

As with other autoimmune diseases, the incidence of relapse or flare of SLE symptoms is increased in the postpartum period. One cohort study reported on 1349 patients aged 14 to 45 years with SLE, including 398 pregnancies in 304 patients. The authors reported an increased rate of flares, with a hazard ratio (HR) of 1.59 (95% confidence interval [CI], 1.27–1.96) in pregnancy compared with nonpregnant/nonpostpartum periods. This effect was modified by HCQ use, with the HR of flares in pregnancy vs nonpregnant/nonpostpartum periods estimated to be 1.83 (95% CI, 1.34–2.45) for patients with no HCQ use and 1.26 (95% CI, 0.88–1.69) for patients with HCQ use.[25]

Summary of recommendations

Number	Recommendations	GRADE
1	We recommend low-dose aspirin beginning at 12 wk of gestation until delivery in patients with SLE to decrease the occurrence of preeclampsia.	1B
2	We recommend that all patients with SLE, other than those with quiescent disease, either continue or initiate HCQ in pregnancy.	1B
3	We suggest that for all other patients with quiescent disease activity who are not taking HCQ or other medications, it is reasonable to engage in shared decision-making regarding whether to initiate new therapy with this medication in consultation with the patient's rheumatologist.	2B
4	We recommend that prolonged use (>48 h) of NSAIDs generally be avoided during pregnancy.	1A
5	We recommend that COX-2 inhibitors and full-dose aspirin be avoided during pregnancy.	1B
6	We recommend discontinuing methotrexate 1-3 months and mycophenolate mofetil/mycophenolic acid at least 6 weeks before attempting pregnancy.	1A
7	We suggest the decision to initiate, continue, or discontinue biologics in pregnancy be made in collaboration with a rheumatologist and be individualized to the patient.	2C
8	We suggest treatment with a combination of prophylactic unfractionated or low-molecular-weight heparin and low-dose aspirin for patients without a previous thrombotic event who meet obstetrical criteria for APS.	2B
9	We recommend therapeutic unfractionated or low-molecular-weight heparin for patients with a history of thrombosis and aPL antibodies.	1B
10	We suggest treatment with low-dose aspirin alone in patients with SLE and aPL antibodies without clinical events meeting criteria for APS.	2C
11	We recommend that steroids not be routinely used for the treatment of fetal heart block due to anti-SSA/SSB antibodies given their unproven benefit and the known risks for both the pregnant patient and fetus.	1C
12	We recommend that serial fetal echocardiograms for assessment of the PR interval not be routinely performed in patients with anti-SSA or anti-SSB antibodies outside of a clinical trial setting.	1B
13	We recommend that patients with SLE undergo prepregnancy counseling with both maternal—fetal medicine and rheumatology specialists that includes a discussion regarding maternal and fetal risks.	1C
14	We recommend that pregnancy be generally discouraged in patients with severe maternal risk, including patients with active nephritis; severe pulmonary, cardiac, renal, or neurologic disease; recent stroke; or pulmonary hypertension.	1C
15	We recommend antenatal testing and serial growth scans in pregnant patients with SLE because of the increased risk of FGR and stillbirth.	1B
16	We recommend adherence to the Centers for Disease Control and Prevention medical eligibility criteria for contraceptive use in patients with SLE.	1B

aPL, antiphospholipid; *APS*, antiphospholipid syndrome; *FGR*, fetal growth restriction; *HCQ*, hydroxychloroquine; *NSAID*, nonsteroidal antiinflammatory drug; *SLE*; systemic lupus erythematosus; *SSA*, anti-Sjögren's-syndrome-related antigen A; *SSB*, anti-Sjögren's-syndrome-related antigen B.

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Prophylactic changes in medications are not recommended, but patients should be informed of the potential for worsening symptoms and evaluated more frequently as needed. NSAIDs can be used postpartum for mild joint pain. Patients who require lifelong anticoagulation can be transitioned back to warfarin after delivery. Those that do not require lifelong anticoagulation are generally continued on low-molecular-weight heparin for 6 weeks after delivery.

Breastfeeding should be encouraged, with consideration of each person's medications. NSAIDS, HCQ, and corticosteroids are considered compatible with breastfeeding by the American Academy of Pediatrics.[130] There are limited data regarding safety of lactation with many other medications used for SLE, and decisions to breastfeed while taking these medications are often shared between the patient and their clinician (Table 5). Ongoing follow-up with a rheumatologist should be encouraged. An appropriate, acceptable, and effective contraception method should be recommended.

Contraception

Given the considerable maternal and fetal risks of pregnancy, the use of appropriate contraception in patients with SLE is paramount (Table 7). In particular, people taking potentially teratogenic medications should avoid pregnancy. It has been reported that many patients with SLE at risk for pregnancy do not use effective contraception.[131,132]

Long-acting reversible contraception methods are appropriate for many patients with SLE. Intrauterine contraceptive devices (IUDs) are safe and effective choices; the

Society for Maternal-Fetal Medicine grading system: Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[136,a]

Grade of recommendation	Clarity of risk and benefit	Quality of supporting evidence	Implications
1A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa.	Consistent evidence from well-performed, randomized controlled trials, or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Strong recommendation that can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation that applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
1C. Strong recommendation, low-quality evidence	Benefits seem to outweigh risks and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Strong recommendation that applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.
2A. Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens.	Consistent evidence from well-performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.	Weak recommendation; best action may differ depending on circumstances or patients or societal values.
2B. Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an effect on confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances.
2C. Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation; alternatives may be equally reasonable.
Best practice	Recommendation in which either: (1) there is an enormous amount of indirect evidence that clearly justifies strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize), or (2) recommendation to the contrary would be unethical.		

[a] Adapted from Guyatt et al.[137]

Society for Maternal-Fetal Medicine. Systemic lupus erythematosus in pregnancy. Am J Obstet Gynecol 2023.

levonorgestrel IUD is associated with a decrease in menstrual blood loss, which is a benefit for patients taking anticoagulant therapy.[133,134] Implants containing etonogestrel may also be a good option for patients with SLE, but because the effect on bone density and thrombosis is uncertain, the use of such implants should not be the first choice for patients on long-term corticosteroids or with APS.

Estrogen-containing oral contraceptives pose a theoretical risk for SLE flares. However, the safety of estrogen-containing oral contraceptives has been shown in 2 randomized trials,[134,135] although women with previous thrombosis and active and severe SLE were excluded from these studies. Estrogen-containing oral contraceptives are contraindicated in patients with previous thrombosis or aPL antibodies. It is important to consider the interaction of medical therapy for SLE with contraceptives because mycophenolate, cyclosporine, and warfarin may all decrease the effectiveness of oral contraceptives.

Progesterone-only oral contraceptives are safe but less effective than estrogen-containing pills in preventing pregnancy. Intramuscular and implantable progestins such as depot medroxyprogesterone acetate (DMPA) injections are safe and reasonably effective, but there is a theoretical risk of osteopenia with the long-term use of DMPA. This may be a particular concern in patients taking corticosteroids. Barrier methods are safe but are the least effective contraceptive option (Table 7). **We recommend adherence to the Centers for Disease Control and Prevention medical eligibility criteria for contraceptive use in patients with SLE (GRADE 1B).**

Conclusion

SLE is a chronic, multisystem disease that carries significant risk of adverse maternal, fetal, and obstetrical outcomes. Patients with SLE should be cared for by clinicians with expertise in managing the condition, and multidisciplinary care may be required. Medical therapy requires adjustment in pregnancy to avoid medications associated with potential untoward fetal effects. Surveillance for evidence of flare and for maternal or fetal complications is an important part of prenatal care. Ideally, people should be counseled before pregnancy to optimize timing of pregnancy and pregnancy outcomes. Appropriate and effective contraception is an essential part of comprehensive care for patients with SLE.

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The SMFM recognizes that obstetrical patients have diverse gender identities and is striving to use gender-inclusive language in all of its publications. The SMFM will be using terms such as "pregnant person/persons" or "pregnant individual/individuals" instead of "pregnant woman/women" and will use the singular pronoun "they." When describing study populations used in research, the SMFM will use the gender terminology reported by the study investigators.

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