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

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Abstract:

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. Maternal morbidity and mortality are substantially increased in patients with SLE, and an initial diagnosis of SLE during pregnancy is associated with increased morbidity. Common complications of SLE 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 SLE during pregnancy. The following are the SMFM recommendations: we recommend low-dose aspirin beginning at 12 weeks of gestation until delivery in patients with SLE to decrease the occurrence of preeclampsia (GRADE 1B); we recommend that all patients with SLE, other than those with quiescent disease, either continue or initiate HCQ in pregnancy (GRADE 1B); we suggest that for patients with quiescent disease, shared decision making is used to decide whether to initiate HCQ during pregnancy (GRADE 2B); we recommend that prolonged use (>48 hours) of NSAIDs should be avoided during pregnancy (GRADE 1A); we recommend that Cox-2 inhibitors and full dose aspirin should be avoided during pregnancy (GRADE 1B); we recommend discontinuing methotrexate and mycophenolate mofetil/mycophenolic acid at least three months
prior to attempting pregnancy (GRADE 1A); we suggest against initiating newer biologic medications with pregnancy unless alternatives with better safety profiles are ineffective (GRADE 2C); we suggest treatment with a combination of prophylactic unfractionated or low molecular weight heparin and low-dose aspirin for patients without a prior thrombotic event who meet obstetric 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); we suggest treatment with low-dose aspirin alone in patients with SLE and antiphospholipid antibodies without clinical events meeting criteria for APS (GRADE 2C); we recommend that steroids should 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); 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 (GRADE 1B); 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); we recommend that pregnancy should 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); we recommend antenatal testing and serial growth scans in pregnant patients with SLE due to the increased risk of FGR and stillbirth (GRADE 1B); and we recommend...
adherence to the Centers for Disease Control and Prevention (CDC) medical eligibility criteria for contraceptive use in patients with SLE (GRADE 1B).

Key Words: systemic lupus erythematosus, SLE, lupus, nephritis, thrombocytopenia
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 about 28 to 150 per 100,000 individuals. SLE is several times more prevalent in females than males, and since it often affects young adults, pregnancy is common among affected individuals. In the United States, there are about 3300 deliveries per year in people with SLE.

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, as well as abnormalities in immunological processes involving both innate and adaptive immunity. Anticardiolipin (aCL) antibodies are detected in 40% of patients with SLE, although the development of antiphospholipid syndrome is less common.

SLE appears 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. Although numerous genes have been implicated, the genetics of SLE are complex. Environmental and hormonal factors also play a role in the disease process, and increased levels of estrogen have been implicated.

What are the diagnostic criteria for SLE?
SLE is a syndrome, and the diagnosis requires the presence of characteristic clinical features as well as 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). 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 League Against Rheumatism (EULAR)/American College of Rheumatology (ACR)\(^\text{11}\) (Figure 1) or the Systemic Lupus International Collaborating Clinics (SLICC) (Table 2).\(^\text{12}\) 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% compared with 96% for the ACR criteria, and the specificity of SLICC is 84% compared with 93% for ACR.\(^\text{11, 12}\)

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.\(^\text{13, 14}\) In addition, complement levels, erythrocyte sedimentation rate (ESR) and/or c-reactive protein (CRP) levels, and urine protein-to-creatinine ratio, while 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.\textsuperscript{15} Antiphospholipid (aPL) antibodies, including lupus anticoagulant (LAC), aCL antibodies, and anti-beta 2-glycoprotein-I (anti-\(\beta_2\) GPI) antibodies can be used to establish the diagnosis of antiphospholipid syndrome (APS).\textsuperscript{16}

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 SLE during pregnancy?**

Maternal morbidity and mortality are substantially increased in patients with SLE, and an initial diagnosis of SLE during pregnancy is associated with increased morbidity.\textsuperscript{17} 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.\textsuperscript{18} In a large study in the United States, including over 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.\textsuperscript{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 a flare. However, it is
not clear that the risk of flares is increased during pregnancy, and several well-designed studies have yielded conflicting results.\textsuperscript{19} The majority of flares during pregnancy are mild, typically consisting of arthritis and cutaneous manifestations, and easily treatable.\textsuperscript{20,21} Fifteen to thirty percent of flares are severe,\textsuperscript{22,23} and some can be life threatening. Flares may occur during any trimester as well as in the postpartum period.\textsuperscript{24} Risk factors for a flare occurring during pregnancy include active disease within the 6 months prior to pregnancy, severe underlying disease, active nephritis, and discontinuation of hydroxychloroquine (HCQ).\textsuperscript{22,25} \textit{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\textsuperscript{2} in the non-pregnant state.\textsuperscript{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.\textsuperscript{27} Renal damage occurs due to 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.\textsuperscript{25} 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.\textsuperscript{23} Many clinicians obtain anti-dsDNA antibodies and complement levels at the start of pregnancy to assess for baseline levels and disease activity.
Patients with pre-existing renal disease have an approximately 16% chance of developing active nephritis during pregnancy. 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 if the GFR is <40 mL/min/1.73 m² and/or a serum creatinine of approximately ≥1.5 mg/dL.

It can be difficult to distinguish lupus nephritis from preeclampsia, as both conditions are characterized by hypertension and proteinuria. The distinction is critical, especially if nephritis occurs in the late second or early third trimester, as the treatment for these two conditions differs significantly; preeclampsia is best treated with delivery or close inpatient monitoring depending on gestational age, although lupus nephritis can be treated medically. 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. Although frequently deferred during pregnancy because of a theoretic 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.

**Hematologic complications**

Hematologic abnormalities affect many patients with SLE; these include anemia, thrombocytopenia, and leukopenia. Approximately one half of patients with SLE are anemic due to a variety of causes, including iron deficiency anemia, anemia of chronic disease, and hemolytic anemia, which can be chronic or acute. Leukopenia is common
in patients with SLE and generally secondary to lymphopenia or neutropenia.\textsuperscript{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.\textsuperscript{8}

Thrombocytopenia affects approximately 25\% of pregnancies with SLE and results from immune-mediated platelet destruction. Risk factors include prior thrombocytopenia, the presence of aPL antibodies, and increased disease activity.\textsuperscript{25} It is important to consider other causes, although laboratory studies are not able to distinguish between gestational thrombocytopenia, thrombocytopenia due 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.\textsuperscript{37} Additional laboratory studies may help in the diagnosis of Hemolysis, Elevated Liver enzymes, Low Platelet count (HELLP), which can cause thrombocytopenia and are managed very differently.

\textit{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 antiphospholipid antibodies (anti-\(\beta\)2 GPI, aCL antibody, and LAC) and a history of thromboembolic events or specific pregnancy complications, including fetal death at or beyond 10 weeks of gestation of a structurally normal fetus, preterm birth less than 34 weeks of gestation due
to severe preeclampsia or fetal growth restriction, or three or more consecutive unexplained fetal losses before 10 weeks of gestation (Table 4).\textsuperscript{38}

\textbf{CNS 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.\textsuperscript{39} 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 as 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.\textsuperscript{25}

\textbf{Cutaneous lupus erythematosus}

Cutaneous lupus erythematosus includes a number of skin diseases that are generally categorized into three subsets, including acute cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, and chronic cutaneous lupus erythematosus.\textsuperscript{40} 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. 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.

Other organ system involvement

SLE can affect many other organ systems, including bone 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. The arthritis is typically migratory and symmetrical and affects multiple joints. Serositis, including pericardial serositis and pleural effusion, can be a recurring feature. Other potential cardiac complications of SLE include pericarditis without effusion, myocarditis, valvular disease, and endocarditis. Pulmonary complications are relatively frequent and include pleuritis, pneumonitis, interstitial lung disease, and, rarely, pulmonary hypertension or pulmonary hemorrhage. The most common skin findings are malar rash and discoid lesions, which are often photosensitive.

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

What adverse obstetric outcomes are associated with SLE during pregnancy?

SLE is associated with an increased risk of many obstetric complications primarily due to obstetric conditions associated with placental insufficiency. Placentas in
SLE pregnancies typically are smaller and often have vascular lesions such as decidual vasculopathy, thrombosis, and infarction.\textsuperscript{47} SLE with APS is associated with a threefold increased risk of pregnancy loss.\textsuperscript{48} The greatest risk factors for pregnancy loss are the co-existence of aPL antibodies and active renal disease. Others include prior pregnancy loss and active disease at the time of conception.\textsuperscript{48-51} 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 reported in the general obstetric population.\textsuperscript{48-51} Preeclampsia occurs in approximately 15\% to 35\% of pregnant women with SLE.\textsuperscript{3, 20, 52} 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.\textsuperscript{3, 20, 52, 53} We recommend low-dose aspirin beginning at 12 weeks of gestation until delivery in patients with SLE to decrease the occurrence of preeclampsia\textsuperscript{54, 55} (GRADE 1B).

Fetal growth restriction (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.\textsuperscript{56} 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\%.\textsuperscript{57} 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 antiphospholipid antibodies.\textsuperscript{20}

**What fetal and neonatal complications are associated with SLE during pregnancy?**

NLE is a rare but serious complication of SLE. NLE complicates approximately one 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 (e.g., aplastic anemia) are less common.\textsuperscript{58}

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.\textsuperscript{59} Anti-SSA and anti-SSB antibodies are present in approximately 30\% and 15\% to 20\% of women with SLE, respectively.\textsuperscript{60} In a prospective cohort study of women with anti-SSA and anti-SSB antibodies (with or without SLE), only about 2\% of infants developed CHB.\textsuperscript{61}

However, the recurrence risk of CHB in women with a previously affected infant and positive antibodies is 15\% to 20\%.\textsuperscript{62,63} Reports of cases of twins discordant for NLE supports the likelihood of multifactorial causation requiring genetic susceptibility as well as exposure to antibodies.\textsuperscript{64}

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.\textsuperscript{65} 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 (AV) and sinoatrial (SA) nodes, it can lead to CHB, which occurs in 50% of cases of NLE. 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. Scarring of the fetal conduction system as well as 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 usually are permanent.

The prognosis for neonates with CHB is variable and related to the extent of fibroelastosis and the presence of fetal hydrops. Fifteen to twenty percent of children with NLE and CHB die within the first three years of life. Among survivors, approximately 60% require a pacemaker within the first few years of life; most of the remainder will require pacing prior to adulthood.

What is the approach to medical management of SLE in pregnancy?

**Hydroxychloroquine**

The ACR conditionally recommends initiating HCQ during pregnancy in women with SLE not already taking this medication. 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. Currently, no randomized controlled trials compare initiating versus 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). We suggest that for patients with quiescent disease, **shared decision making is used to decide whether to initiate HCQ during pregnancy (GRADE 2B).** This includes patients who are taking low-dose prednisone or using non-steroidal anti-inflammatory drugs (NSAIDs) for SLE-related pain as use of these medications suggests disease activity. Some investigators recommend that patients with quiescent disease activity who have anti-SSA or antiphospholipid antibodies consider initiating HCQ, as some studies\(^68-71\) suggest improved maternal and fetal outcomes in these specific populations. For all other patients with quiescent disease activity who are not taking medications including taking HCQ, it is reasonable to engage in shared decision-making regarding whether to initiate new therapy with this medication.

**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.\(^23\) 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.\(^72\) 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, preeclampsia, FGR, preterm premature rupture of membranes, and preterm birth. Once disease activity is stable, the steroid dosage should be slowly tapered to the lowest effective dose.

**Other immunosuppressive agents**

Severe flares that are refractory to HCQ and prednisone should be treated with additional immunosuppressive agents. Azathioprine has been used extensively during pregnancy. Adverse effects are rare, and human teratogenicity has not been reported. Although this drug has been associated with an increased risk of FGR and pregnancy loss, the association is controversial. Generally, the benefits are considered to outweigh the risks in cases of severe SLE flare.

Cyclosporine is another option for lupus flare that is refractory to other medical therapies. It is particularly effective in the treatment of proliferative lupus nephritis. 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 in inducing remission than cyclosporine. Although case series have not shown teratogenic effects, neonatal hyperkalemia and renal dysfunction have been reported. Finally, intravenous immune globulin (IVIg) may be useful specifically in cases of thrombocytopenia associated with SLE. 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 not be used during pregnancy (Table 5). NSAIDs are a mainstay of treatment for mild joint pain in nonpregnant individuals. Due to 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) should be avoided during pregnancy (GRADE 1A). Due to a similar mechanism of action, we recommend that Cox-2 inhibitors and full dose aspirin should be avoided during pregnancy (GRADE 1B). Acetaminophen is a safe, although less effective, alternative to NSAIDs and aspirin.\textsuperscript{79} Mycophenolate and methotrexate are teratogens and are contraindicated.\textsuperscript{18} We recommend discontinuing methotrexate and mycophenolate mofetil/mycophenolic acid at least three months prior to attempting pregnancy (GRADE 1A). Leflunomide is considered a teratogen and is therefore contraindicated, although data are mixed.\textsuperscript{80}

Biologic agents

Over the past several years, new biologic agents (Rituximab, Belimumab, Infliximab, Adalimumab, and Golimumab) have been used for a range of autoimmune disorders, including SLE. Data on perinatal outcomes with these medications are limited, although more evidence is emerging from cases of inadvertent early exposure during pregnancy and use of these medications in patients unresponsive to other therapies. Initial reports of
a suspected link between tumor necrosis factor-alpha (TNF-alpha) inhibitors and Vertebral defects, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal anomalies, and Limb abnormalities (VACTERL) association have not been confirmed in larger observational studies that included first trimester exposure.\textsuperscript{81}

Rituximab is a monoclonal antibody that depletes B cells and initially showed promise for treatment of lupus nephritis, although subsequent randomized trials have not demonstrated significant benefit.\textsuperscript{82} No teratogenic effect has been reported, but B cells have been shown to be low in offspring.\textsuperscript{83} Belimumab, a monoclonal antibody against soluble B lymphocyte stimulator, has been shown to benefit patients with both SLE and lupus nephritis in clinical trials and has been approved by the U.S. Food and Drug Administration (FDA) for both SLE and lupus nephritis treatment.\textsuperscript{84} Other biologics are under development, but given the lack of safety data in pregnancy, these newer biologic medications should generally not be used unless alternatives with better safety profiles are ineffective and patients are counseled regarding potential unknown risks. We suggest against initiating newer biologic medications with pregnancy unless alternatives with better safety profiles are ineffective (GRADE 2C). For pregnant individuals with quiescent disease already taking newer biologic medications, shared decision-making to assess whether the risks of continuing these medications outweigh the risks of stopping them is recommended.

Biologics such as the TNF-alpha class including infliximab, adalimumab, and golimumab cross the placenta and are found in cord blood at birth.\textsuperscript{85} They can remain detectable in infants for up to 12 months, which also raises concern for potential effects on immune system development.\textsuperscript{86} Some evidence suggests that monoclonal antibody
exposure in utero may be associated with childhood infections. Small studies of children exposed in utero suggest that they have appropriate immune responses to vaccines. There are no data demonstrating that stopping these medications in the third trimester reduces the potential risk of infections although this is sometime practiced. The risk of stopping medications in the third trimester should be weighed against the risk of flare if medications are stopped.

How should pregnant patients with SLE 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. For patients with APS who have had a prior thrombotic event, therapeutic anticoagulation throughout pregnancy and for 6 weeks postpartum is recommended to minimize the risk of maternal thromboembolism. 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 (ACOG) has suggested that prophylactic heparin throughout pregnancy and 6 weeks postpartum should be considered. Anticoagulation dosage may be individualized based on 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 prior
thrombotic event who meet obstetric 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 APS**

Up to 40% of patients with SLE have aPL antibodies but only one third develop clinical manifestations of APS. aPL antibodies have also been observed to transiently appear during infections, after vaccinations, and in reaction to drugs. 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 remains unclear. A meta-analysis of five studies with 154 pregnancies complicated by the presence of asymptomatic aPL antibodies with or without SLE found no difference in adverse pregnancy outcomes between the pregnancies who received prophylactic treatment (primarily aspirin) and those without prophylaxis. However, the small sample size and heterogeneity of included studies limit the conclusions. We suggest treatment with low-dose aspirin alone in patients with SLE and antiphospholipid antibodies without clinical events meeting criteria for APS (GRADE 2C).

**Anti-SSA/SSB antibodies**

People with anti-SSA and anti-SSB antibodies are at increased risk of delivering an infant with neonatal lupus (NLE) due to transplacental passage of these antibodies in people who may or may not carry the diagnosis of SLE or Sjögren’s disease. 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 about 2%. This risk increases in subsequent pregnancies after a first affected birth. Affected fetuses may develop first-, second-, or third-degree heart block, most commonly between 18 to 25 weeks of gestation.

Given the morbidity associated with the cardiac manifestations of NLE, investigators have studied a number of potential preventative or therapeutic interventions, including HCQ, corticosteroids, IVIg, beta-agonists, and serial fetal echocardiograms for measurement of the fetal PR interval. Based largely on mechanism of injury, it has been proposed that treatment with HCQ throughout pregnancy might decrease the occurrence of CHB in at-risk fetuses. In one observational study, 54 women with a prior affected pregnancy were treated with HCQ beginning at <10 weeks of gestation. In all, 4 of 54 (7.4%) pregnancies developed CHB, which the authors noted was lower than the historical recurrence rate of 18%. 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 have maternal benefits as well.

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 anti-inflammatory 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.\textsuperscript{98, 104}

In some cases, steroid treatment appeared 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 while several cases of complete heart block occurred without a graded progression through first- or second-degree heart block.\textsuperscript{98, 104}

Another multicenter international retrospective study reported on 175 pregnancies with congenital second- or third-degree heart block. In all, 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.\textsuperscript{105}

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.\textsuperscript{106} The study compared 71 fetuses who received steroids within one week of detection 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 meta-analysis by Ciardulli et al., including 5 studies and 71 fetuses, rate of progression to congenital atrioventricular block at birth in fetuses treated with steroids was 52\% compared to 73\% in untreated cases. However, the authors note the low quality of this retrospective data and concluded that any benefit of steroid treatment
remains unproven. In conclusion, the efficacy of corticosteroids for prevention of progression or prevention of CHB has not been demonstrated, it is well documented that high-dose fluorinated corticosteroids may adversely affect fetal growth and brain development. IVIg also has been investigated for prenatal treatment of fetal heart block. However, several trials have similarly demonstrated no benefit from treatment with IVIg.

Given these data, the utility of screening for or treating of first-degree heart block remains unproven as early-stage heart block does not predictably progress to more advanced heart block, and interventions do not reliably prevent progression. We recommend that steroids should 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, there is no benefit to screening for early-stage fetal heart block. 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 (GRADE 1B). We acknowledge that this monitoring has been recommended by other organizations and that many patients undergo such screening. However, given the lack of proven efficacy as well as the risks associated with proposed interventions, routine 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 greater than 55 beats per minute. Some authors have advocated maternal beta-agonist therapy when the fetal heart rate is less than 50–55 beats per minute to increase the fetal heart rate and theoretically increase the fetal stroke volume.\textsuperscript{103,112} However, data are limited as to 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 as 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.\textsuperscript{113}

**Mild SLE 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 include a physical exam, complete blood count (CBC), 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 15–20 mg of prednisone daily is recommended. In patients already taking glucocorticoids, the dosage should be increased to 20–30 mg/d (Table 6).

**Severe SLE 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 as the signs and symptoms of SLE flare and preeclampsia overlap and are important to distinguish as management differs (Table 3). Glucocorticoid dosage should be increased to 1.0–1.5 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 patients with renal or CNS involvement, intravenous glucocorticoids are recommended, and other immunosuppressive agents may be required (Table 6).

What is the appropriate obstetric management for pregnant patients with SLE?

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. 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.

Pregnancy 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 obstetric history, particularly any history of a prior child with neonatal lupus; 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 prior 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.\textsuperscript{115}

When possible, pregnancy should be deferred until the disease has been in remission for at least 6 months.\textsuperscript{116} We recommend that pregnancy should 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).\textsuperscript{56} Patients who become pregnant with these conditions, among others, may need abortion care due to life-threatening maternal risk.

The patient’s medical regimen may require modifications such as discontinuing NSAIDs and full-dose aspirin and minimizing corticosteroid dosages.\textsuperscript{18} HCQ should be continued since it is safe in pregnancy and abrupt cessation may induce a flare.\textsuperscript{117}
Immunosuppressive agents with the potential for adverse or teratogenic fetal effects, including cyclophosphamide, methotrexate, mycophenolate, and leflunomide, should be discontinued three months prior to pregnancy.\textsuperscript{19} Azathioprine and cyclosporine are acceptable immunosuppressive agents during pregnancy.\textsuperscript{19} Patients requiring anticoagulant therapy should be changed from warfarin to low molecular weight heparin prior to or as soon as pregnancy is recognized (Table 6).

\textbf{Pregnancy management}

Obstetric 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,\textsuperscript{19} the utility of this testing remains unproven. Testing is recommended if signs or symptoms suggest the possibility of a flare as 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 obstetric 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.\textsuperscript{118}

\textbf{We recommend antenatal testing and serial growth scans in pregnant patients with SLE due to 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 32–34 weeks of gestation. For pregnant patients with complicated SLE (eg, active lupus nephritis, recent lupus flare, antiphospholipid 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 upon diagnosis or at a gestational age when delivery would be undertaken for abnormal testing.\textsuperscript{119}

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.

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 14–45 with SLE, including 398 pregnancies in 304 patients. The authors reported an increased rate of flare with a hazard ratio (HR) of 1.59 (95% confidence interval [CI], 1.27–1.96) in pregnancy compared to nonpregnant/nonpostpartum periods. This effect was modified by HCQ use, with the HR of flares in pregnancy compared to non-pregnant/non-postpartum 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.\textsuperscript{24}
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. 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. Long-acting reversible contraception methods are appropriate for many patients with SLE. Intrauterine contraceptive devices (IUD) are safe and effective choices; the levonorgestrel IUD is associated with a decrease in menstrual blood loss, which is a benefit for patients taking anticoagulant therapy. Implants containing etonogestrel
may also be a good option for patients with SLE, but because the effect on bone density and thrombosis is uncertain, use of the implant should not be first choice for patients on long term corticosteroids or with APS.

Estrogen-containing oral contraceptives pose a theoretical risk for SLE flare. However, the safety of estrogen-containing oral contraceptives has been shown in two randomized trials,\textsuperscript{124,125} although women with prior thrombosis as well as active and severe SLE were excluded from these studies. Estrogen-containing oral contraceptives are contraindicated in patients with prior thrombosis or aPL antibodies. It is important to consider the interaction of medical therapy for SLE with contraceptives, as mycophenolate, cyclosporine, and warfarin may all decrease the effectiveness of oral contraceptives.

Progesterone-only oral contraceptives are safe but less effective in preventing pregnancy than estrogen-containing pills. 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 use of DMPA. This may be a particular concern in patients taking corticosteroids. Barrier methods are safe but are the least effective contraceptive choices (Table 7). We recommend adherence to the Centers for Disease Control and Prevention (CDC) 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 obstetric 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 complication is an important part of prenatal care. Ideally, people are counseled prior to pregnancy to optimize timing of pregnancy as well as pregnancy outcomes. Appropriate and effective contraception is an essential part of comprehensive care for patients with SLE.

**Summary of Recommendations**

<table>
<thead>
<tr>
<th>Number</th>
<th>Recommendations</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>We recommend low-dose aspirin beginning at 12 weeks of gestation until delivery in patients with SLE to decrease the occurrence of preeclampsia.</td>
<td>1B</td>
</tr>
<tr>
<td>2</td>
<td>We recommend that all patients with SLE, other than those with quiescent disease, either continue or initiate HCQ in pregnancy.</td>
<td>1B</td>
</tr>
<tr>
<td>3</td>
<td>We suggest that for patients with quiescent disease, shared decision making is used to decide whether to initiate HCQ during pregnancy.</td>
<td>2B</td>
</tr>
<tr>
<td>4</td>
<td>We recommend that prolonged use (&gt;48 hours) of NSAIDs should be avoided during pregnancy.</td>
<td>1A</td>
</tr>
<tr>
<td>5</td>
<td>We recommend that Cox-2 inhibitors and full dose aspirin should be avoided during pregnancy.</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td>Statement</td>
<td>Level</td>
</tr>
<tr>
<td>---</td>
<td>---------------------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>6</td>
<td>We recommend discontinuing methotrexate and mycophenolate mofetil/mycophenolic acid at least three months prior to attempting pregnancy.</td>
<td>1A</td>
</tr>
<tr>
<td>7</td>
<td>We suggest against initiating newer biologic medications with pregnancy unless alternatives with better safety profiles are ineffective.</td>
<td>2C</td>
</tr>
<tr>
<td>8</td>
<td>We suggest treatment with a combination of prophylactic unfractionated or low molecular weight heparin and low-dose aspirin for patients without a prior thrombotic event who meet obstetric criteria for APS.</td>
<td>2B</td>
</tr>
<tr>
<td>9</td>
<td>We recommend therapeutic unfractionated or low molecular weight heparin for patients with a history of thrombosis and aPL antibodies.</td>
<td>1B</td>
</tr>
<tr>
<td>10</td>
<td>We suggest treatment with low-dose aspirin alone in patients with SLE and antiphospholipid antibodies without clinical events meeting criteria for APS.</td>
<td>2C</td>
</tr>
<tr>
<td>11</td>
<td>We recommend that steroids should 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.</td>
<td>1C</td>
</tr>
<tr>
<td>12</td>
<td>We recommend that serial fetal echocardiograms for assessment of the PR interval not be routinely</td>
<td>1B</td>
</tr>
</tbody>
</table>
performed in patients with anti-SSA or anti-SSB antibodies.

| 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 should 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 due to the increased risk of FGR and stillbirth. | 1B |
| 16 | We recommend adherence to the Centers for Disease Control and Prevention (CDC) medical eligibility criteria for contraceptive use in patients with SLE. | 1B |
### Society for Maternal-Fetal Medicine Grading System: Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

**Recommendations**

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Clarity of Risk and Benefit</th>
<th>Quality of Supporting Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A. Strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risks and burdens, or vice versa.</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>1B. Strong recommendation, moderate-quality evidence</td>
<td>Benefits clearly outweigh risks and burdens, or vice versa.</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>1C. Strong recommendation, low-quality evidence</td>
<td>Benefits appear to outweigh risks and burdens, or vice versa.</td>
<td>Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.</td>
<td>Strong recommendation that applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.</td>
</tr>
<tr>
<td>2A. Weak recommendation, high-quality evidence</td>
<td>Benefits closely balanced with risks and burdens.</td>
<td>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.</td>
<td>Weak recommendation; best action may differ depending on circumstances or patients or societal values.</td>
</tr>
<tr>
<td>2B. Weak recommendation, moderate-quality evidence</td>
<td>Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens.</td>
<td>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.</td>
<td>Weak recommendation; alternative approaches likely to be better for some patients under some circumstances.</td>
</tr>
<tr>
<td>Recommendation</td>
<td>Reasoning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2C. Weak recommendation, low-quality evidence</td>
<td>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, other alternatives may be equally reasonable.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best practice</td>
<td>Recommendation in which either (i) 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 (ii) recommendation to the contrary would be unethical.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Guyatt GH, et al., 2008
Table 1. Frequency of clinical symptoms in patients with SLE

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>80-100</td>
</tr>
<tr>
<td>Fever</td>
<td>80-100</td>
</tr>
<tr>
<td>Arthritis</td>
<td>80-95</td>
</tr>
<tr>
<td>Myalgia</td>
<td>70</td>
</tr>
<tr>
<td>Weight loss</td>
<td>60</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>60</td>
</tr>
<tr>
<td>Malar rash</td>
<td>50</td>
</tr>
<tr>
<td>Nephritis</td>
<td>50</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>50</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>50</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>30</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>20-30</td>
</tr>
</tbody>
</table>

Figure 1. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus.

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

4 of 17 criteria, with at least one clinical and one 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 two or more joints
Serositis
Renal: proteinuria >500 mg/24 hrs 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

ANA, antinuclear antibody; Anti-dsDNA, anti-double stranded DNA; LE, lupus erythematosus; RPR, rapid plasma regain.

Table 3. Laboratory tests used to distinguish preeclampsia from a lupus flare

<table>
<thead>
<tr>
<th>Test</th>
<th>Preeclampsia</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased complement levels</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Increased anti-dsDNA</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Microangiopathic hemolytic anemia</td>
<td>++</td>
<td>−</td>
</tr>
<tr>
<td>Coombs positive hemolytic anemia</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>Urinary cellular casts/hematuria</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td>Increased serum creatinine</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Hypocalciuria</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Increased liver transaminases</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Elevated uric acid</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

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

1Diagnosis requires one of the clinical criteria and one of the laboratory criteria.

Table 5. Medications used for treatment of lupus during pregnancy and lactation

<table>
<thead>
<tr>
<th>Medications</th>
<th>Safety</th>
<th>Other concerns</th>
<th>Recommendations</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs, ASA, Cox-2 inhibitors</td>
<td>Can cause closure of fetal ductus.¹</td>
<td>Oligohydramnios²</td>
<td>Avoid in third trimester; substitute acetaminophen²</td>
<td>Safe to continue³</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>No adverse fetal effects.¹</td>
<td>Discontinuation is associated with increased risk of SLE flare.¹</td>
<td>Continue during pregnancy and consider for all patients with SLE.¹</td>
<td>Safe to continue.¹</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Some concerns for oral clefts in animals and some human studies. Recent data show no clear association with fetal malformations. ⁴</td>
<td>Effective and minimal placental transfer. High doses are associated with significant maternal and obstetric side effects.⁵</td>
<td>Use lowest effective dose. Avoid empiric use. Avoid fluorinated glucocorticoids which cross the placenta. Stress dose steroids not recommended at time of vaginal delivery; conditionally recommend at time of cesarean delivery.³</td>
<td>Safe to continue³</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Teratogenic in animals. Appears safe in humans.¹</td>
<td></td>
<td>Reasonable to continue if stable on this medication at a daily dose not exceeding 2 mg/kg per day. Consider adding if SLE not controlled on hydroxychloroquine and glucocorticoids.¹</td>
<td>Safe to continue³</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>Extensive experience with the use of cyclosporine in pregnant transplant patients. Not an animal teratogen. Appears safe in humans.¹</td>
<td>Transient lowered platelets and white cells in infants have been reported.¹</td>
<td>Reasonable option if disease refractory to other medications.⁶</td>
<td>Reasonable option with infant monitoring ⁶</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Neonatal hyperkalemia and renal dysfunction have been reported. Successful</td>
<td></td>
<td>Effective for lupus nephritis. Benefit may outweigh risks in severe cases.⁷</td>
<td>Limited data suggests safety.¹</td>
</tr>
<tr>
<td><strong>TNFα Inhibitors</strong></td>
<td>Early reports of VACTERL not confirmed in larger studies. Limited data on continuation during pregnancy.</td>
<td>Avoid if other, safer alternatives can be used.</td>
<td>Inadequate data</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td><strong>Rituximab</strong></td>
<td>Can cause B cell depletion, which has been reported in humans. Inadequate data in pregnancy.</td>
<td>Avoid during pregnancy and avoid pregnancy for 12 months after exposure.</td>
<td>Inadequate data</td>
<td></td>
</tr>
<tr>
<td><strong>Abatacept</strong></td>
<td>Animal studies showed alterations in immune function. Inadequate pregnancy data.</td>
<td>Avoid if other, safer alternatives can be used.</td>
<td>Inadequate data</td>
<td></td>
</tr>
<tr>
<td><strong>Belimumab</strong></td>
<td>Limited data but not a teratogen in animals. No controlled data in humans.</td>
<td>Avoid if other, safer alternatives can be used.</td>
<td>Inadequate data</td>
<td></td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>Associated with cleft palate and skeletal abnormalities. Second and third trimester use associated with FGR and neonatal pancytopenia.</td>
<td>Risk of premature ovarian failure.</td>
<td>Effective for lupus nephritis. Benefit may outweigh risks in severe cases.</td>
<td>Contraindicated</td>
</tr>
<tr>
<td><strong>Mycophenolate Mofetil</strong></td>
<td>Associated with facial clefts and facial and ear abnormalities.</td>
<td></td>
<td></td>
<td>Contraindicated, limited data</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>Embryolethal; associated with multiple anomalies.</td>
<td>Avoid in pregnancy.</td>
<td></td>
<td>Contraindicated</td>
</tr>
<tr>
<td><strong>Leflunomide</strong>*</td>
<td>Teratogenic in animals.</td>
<td>Elimination may take 2 years after dosing due to long half-life and</td>
<td>Avoid in pregnancy. Cholestyramine “wash out” prior to pregnancy or if inadvertent exposure.</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>
enterohepatic circulation.\textsuperscript{14} 

*Not clinically available in the U.S.

ASA, acetylsalicylic acid; \textit{FGR}, fetal growth restriction; \textit{NSAIDs}, non-steroidal anti-inflammatory drugs; \textit{SLE}, systemic lupus erythematosus; \textit{TNFα}, tumor necrosis factor alpha; \textit{VACTERL}, vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities.

References:
2. FDA NSAID warning
3. ACR guidelines
4. Skuladottir 2014
5. Clowse 2007
6. Ostenson 2006
7. Hannah 2016
8. Diav Citrin
9. Chakravarty 2011
10. FDA Abatacept
11. FDA Belimumab
12. Mok 2016
13. EULAR recs
14. FDA leflunomide
Table 6. Care of patients with SLE

### 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 months.
5. Avoid pregnancy if 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 obstetric history including history of preeclampsia, FGR, stillbirth, or congenital heart block.
3. Discuss potential pregnancy complications including preeclampsia, preterm labor, pregnancy loss, fetal death, fetal growth restriction, and neonatal lupus.
4. Advise of significant maternal and fetal risks if 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 prior 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 if 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 weeks and 32–34 weeks of gestation).
6. Initiate antenatal surveillance (eg, weekly beginning at 32 weeks of gestation through delivery for uncomplicated SLE; individualize for complicated SLE).
7. Deliver between 39–40 weeks of gestation, 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 20–30 mg/day.
   b. If the patient is not taking glucocorticoids, start 15–20 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 1.0–1.5 mg/kg. Expect clinical improvement in 5–10 days.
   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. Initiate intravenous glucocorticoid treatment, 10–30 mg/kg/d of methylprednisolone for 3-6 days.
   c. Maintain patient on 1.0–1.5 mg/kg of oral prednisone.
   d. When the patient responds, taper the glucocorticoid.
   e. For unresponsive patients, consider immunosuppressive agents and/or plasmapheresis.

Anti-dsDNA, anti-double stranded DNA; Anti-SSA, Anti-Sjögren's-syndrome-related antigen A; Anti-SSB, Anti-Sjögren's-syndrome-related antigen B; CNS, central nervous system; FGR, fetal growth restriction; NSAIDs, non-steroidal anti-inflammatory drugs; NST, non-stress test; SLE, systemic lupus erythematosus.

### Table 7. U.S. Medical Eligibility Criteria (U.S. MEC) for contraceptive use in patients with systemic lupus erythematosus (SLE).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cu-IUD Initiation</th>
<th>Cu-IUD Continuation</th>
<th>LNG-IUD Initiation</th>
<th>LNG-IUD Continuation</th>
<th>Implants Initiation</th>
<th>Implants Continuation</th>
<th>DMPA Initiation</th>
<th>DMPA Continuation</th>
<th>POPs Initiation</th>
<th>POPs Continuation</th>
<th>CHCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (or unknown) antiphospholipid antibodies</td>
<td>1*†</td>
<td>1*†</td>
<td>3*‡</td>
<td>3*‡</td>
<td>3*‡</td>
<td>3*‡</td>
<td>3*‡</td>
<td>3*‡</td>
<td>3*‡</td>
<td>3*‡</td>
<td>4*‡</td>
</tr>
<tr>
<td>Severe thrombocytopenia</td>
<td>3*‡</td>
<td>2*†</td>
<td>2*†</td>
<td>2*§</td>
<td>3*§</td>
<td>2*§</td>
<td>2*§</td>
<td>2*§</td>
<td>2*§</td>
<td>2*§</td>
<td>2* §</td>
</tr>
<tr>
<td>Immuno-suppressive therapy</td>
<td>2*</td>
<td>1*</td>
<td>2*</td>
<td>2*</td>
<td>2*</td>
<td>2*</td>
<td>2*</td>
<td>2*</td>
<td>2*</td>
<td>2*</td>
<td>2*</td>
</tr>
<tr>
<td>None of the above</td>
<td>1*</td>
<td>1*</td>
<td>2*</td>
<td>2*</td>
<td>2*</td>
<td>2*</td>
<td>2*</td>
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</table>


**CHC**, combined hormonal contraceptive (including pill, patch, and ring); **Cu-IUD**, copper-containing IUD; **DMPA**, depot medroxyprogesterone acetate; **LNG-IUD**, levonorgestrel-releasing IUD; **POP**, progestin-only pill; **SLE**, systemic lupus erythematosus; **VTE**, venous thromboembolism.

**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.

*Clarification: Persons with SLE are at increased risk for ischemic heart disease, stroke, and VTE. Categories assigned to such conditions in U.S. 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.

†Evidence: Antiphospholipid antibodies are associated with a higher risk for both arterial and venous thrombosis.

‡Comment: Severe thrombocytopenia increases the risk for bleeding. The category should be assessed according to the severity of 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.

§Comment: Severe thrombocytopenia increases the risk for bleeding. POCs might be useful in treating menorrhagia in women with severe thrombocytopenia. However, given the increased or erratic bleeding that might be seen on initiation of DMPA and its irreversibility for 11–13 weeks after administration, initiation of this method in women with severe thrombocytopenia should be done with caution.
References


79. U.S. Food and Drug Administration. FDA recommends avoiding use of NSAIDs in pregnancy at 20 weeks or later because they can result in low amniotic fluid. 2020 Accessed May 19, 2021; Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-avoiding-use-nsaids-pregnancy-20-weeks-or-later-because-they-can-result-low-amniotic


All authors and committee members have filed a disclosure of interests delineating personal, professional, business, or other relevant financial or nonfinancial interests in relation to this publication. Any substantial conflicts of interest have been addressed through a process approved by the Society for Maternal-Fetal Medicine (SMFM) Board of Directors. SMFM has neither solicited nor accepted any commercial involvement in the specific content development of this publication.

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All questions or comments regarding the document should be referred to the SMFM Publications Committee at pubs@smfm.org.

Reprints will not be available.
Clinical question

**What adverse obstetric outcomes are associated with SLE during pregnancy?**

Recommendation statement

**We recommend low dose aspirin beginning at 12 weeks of gestation until delivery in patients with SLE to decrease the occurrence of preeclampsia.**

**GRADE**

**1B**-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.

Other organization recommendations

**ACOG CO 743**- Non-systematic review. Low-dose aspirin (81 mg/day) prophylaxis is recommended in women at high risk of preeclampsia and should be initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks) and continued daily until delivery. Low-dose aspirin prophylaxis should be considered for women with more than one of several moderate risk factors for preeclampsia.

**USPSTF 2014**- Systematic review. The USPSTF recommends the use of low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia. (B recommendation)

<table>
<thead>
<tr>
<th>Category A Evidence:</th>
<th>Category B Evidence:</th>
<th>Category C Evidence:</th>
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<tr>
<td>n/a</td>
<td>n/a</td>
<td>Moroni 2003- Literature review/editorial. The fetal risk, although progressively reduced during the last 40 years, continues to be higher [in patients with lupus nephritis] than</td>
</tr>
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</table>
in pregnancies of healthy women particularly in patients with antiphospholipid antibodies.


Chakravarty 2006- Retrospective cohort study of 4.04 million deliveries in the US, 3,264 in women with SLE. Women with SLE...had significantly increased rates of hypertensive disorders compared with the general obstetric population (23.2% vs 7.8%)

<table>
<thead>
<tr>
<th>Clinical question</th>
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<tbody>
<tr>
<td><strong>What is the approach to medical management of SLE in pregnancy?</strong></td>
<td></td>
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<table>
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<tr>
<th>Recommendation statement</th>
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<tbody>
<tr>
<td><strong>We recommend that all patients with SLE, other than those with very quiescent disease, either continue or initiate HCQ in pregnancy</strong></td>
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<tr>
<th>GRADE</th>
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<tr>
<td><strong>1B</strong>- 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.</td>
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<tr>
<th>Other organization recommendations</th>
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<tr>
<td><strong>ACR 2020</strong>- We recommend that all women with SLE take hydroxychloroquine (HCQ) during pregnancy if possible. If a patient is already taking HCQ, we strongly recommend continuing it during pregnancy (Strong recommendation); if she is not taking HCQ, we conditionally recommend starting it if there is no contraindication (Conditional recommendation).</td>
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</table>
We suggest that for patients with quiescent disease, shared decision making is used to decide whether to initiate HCQ during pregnancy.

**GRADE**

2B - 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.

**Other organization recommendations**

**ACR 2020** - We recommend that all women with SLE take hydroxychloroquine (HCQ) during pregnancy if possible. If a patient is already taking HCQ, we strongly recommend continuing it during pregnancy (Strong recommendation); if she is not taking HCQ, we conditionally recommend starting it if there is no contraindication (Conditional recommendation).

We recommend that prolonged use of NSAIDs (>48 hours) should be avoided during pregnancy.

**GRADE**

1A - 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.
Other organization recommendations

**ACR 2020** - Avoid NSAIDs in third trimester (Strong recommendation)

**FDA NSAID 2020** - FDA recommends avoiding use of NSAIDs in pregnancy at 20 weeks or later because they can result in low amniotic fluid

**Maternal Critical Care 2013** - Can cause closure of fetal ductus.

<table>
<thead>
<tr>
<th>Category A Evidence:</th>
<th>Category B Evidence:</th>
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**Recommendation statement**

*We recommend that Cox-2 inhibitors and full dose aspirin should be avoided during pregnancy.*

**GRADE**

1B - 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.

Other organization recommendations

**ACR 2020** - Use nonselective rather than COX-2–specific NSAIDs (Conditional recommendation)

<table>
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</table>

**Recommendation statement**

*We recommend discontinuing methotrexate and mycophenolate mofetil/mycophenolic acid at least three months prior to attempting pregnancy.*

**GRADE**

1A - 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.
**Clinical question**

**What is the approach to medical management of SLE in pregnancy?** *Biologic Agents*

**Recommendation statement**

*We suggest against initiating newer biologic medications with pregnancy unless alternatives with better safety profiles are ineffective.*

**GRADE**

2C- 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.

**Other organization recommendations**

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</table>

### Rovin 2012 - Randomized, double-blind, placebo controlled phase III trial of rituximab in 144 patients with lupus nephritis treated concomitantly with mycophenolate mofetil and corticosteroids. Rituximab therapy led to more responders and greater reductions in anti-dsDNA and C3/C4 levels, but it did not improve clinical outcomes after 1 year of treatment.

### Diav Citrin 2014 - Prospective, comparative, observational study of 83 pregnancies exposed to anti-TNF-alpha in first trimester compared with 86 disease-matched and 341 non-teratogenic-exposed pregnancies. The rate of major congenital anomalies did not significantly differ between the three groups [3/65 (4.6%) (anti-TNF-alpha), 5/79 (6.3%) (DM), 8/336 (2.4%) (NTE)]. There were no cases of VATER/VACTERL association.
| Chakravarty 2011 | Retrospective analysis of 231 pregnancies associated with maternal rituximab exposure in rituximab global drug safety database. Most cases were confounded by concomitant use of potentially teratogenic medications and severe underlying disease. Of 153 pregnancies with known outcomes, 90 resulted in live births. 22 infants were born prematurely; with one neonatal death at 6 weeks. 11 neonates had hematologic abnormalities. 4 neonatal infections were reported. |
| Allen 2021 | Literature review. The monoclonal antibody belimumab inhibits BLyS and was the first new FDA approval for SLE in >50 years. In two Phase III trials, belimumab reduced the numbers of plasma and B cells while significantly reducing SLE disease activity and severe flare risk. Belimumab is indicated for adults and children with active, autoantibody positive SLE receiving standard treatment. In a promising Phase III clinical trial, 43.0% of lupus nephritis patients receiving belimumab plus standard therapy met primary endpoints versus 32.3% of lupus nephritis patients given placebo. |

Clinical question

**How should pregnant patients with SLE and specific complications be managed during pregnancy? Antiphospholipid Syndrome**
## Recommendation statement

We suggest treatment with a combination of prophylactic unfractionated or low molecular weight heparin and low dose aspirin for patients without a prior thrombotic who meet obstetric criteria for APS.

### GRADE

2B-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.

### Other organization recommendations

**ACOG PB 132** - Non-systematic review guideline. In women with APS and a history of stillbirth or recurrent fetal loss but no prior thrombotic history, prophylactic doses of heparin and low-dose aspirin during pregnancy and 6 weeks of postpartum should be considered (Level B). For women with APS who have not had a thrombotic event, expert consensus suggests that clinical surveillance or prophylactic heparin use antepartum in addition to 6 weeks of postpartum anticoagulation may be warranted (Level C).

**ACCP 2012** - Systematic review guideline. For women who fulfill the laboratory criteria for antiphospholipid antibody (APLA) syndrome and meet the clinical APLA criteria based on a history of three or more pregnancy losses, we recommend antepartum administration of prophylactic or intermediate-dose unfractionated heparin or prophylactic low-molecular-weight heparin combined with low-dose aspirin (75-100 mg/d) over no treatment (Grade 1B).

<table>
<thead>
<tr>
<th>Category A Evidence:</th>
<th>Category B Evidence:</th>
<th>Category C Evidence:</th>
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## Recommendation statement

We recommend therapeutic unfractionated or low molecular weight heparin in combination with low dose aspirin for patients with a history of thrombosis and aPL antibodies.

### GRADE

1B- 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.
### Other organization recommendations

**ACOG PB 132** - For women with APS who have had a thrombotic event, most experts recommend prophylactic anticoagulation with heparin throughout pregnancy and 6 weeks postpartum (Level C).

<table>
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<tr>
<th>Category A Evidence</th>
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</table>

### Clinical question

**How should pregnant patients with SLE and specific complications be managed during pregnancy? Antiphospholipid antibodies without APS**

**Recommendation statement**

We suggest treatment with low dose aspirin alone in patients with SLE and antiphospholipid antibodies without clinical events meeting criteria for APS.

**GRADE**

2C - 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.

### Amengual 2015

- Systemic review. 5 studies involving 154 pregnancies. Three studies were meta-analyzed. The risk ratio and 95% confidence interval (CI) of live birth rates, preterm birth, low birth weight and overall pregnancy complications in treated and untreated pregnancies were 1.14 (0.187.31); 1.71 (0.32–8.98); 0.98 (0.07–13.54) and 2.15 (0.63–7.33), respectively. Results from the meta-analysis revealed that prophylactic treatment with aspirin is not superior to placebo to prevent pregnancy complications in asymptomatic aPL carriers.

### Lockshin 2012

- Retrospective analysis of 144 pregnant patients between 2003 and 2011. Thirty-nine percent of the patients with LAC had adverse pregnancy outcome, compared to 3% of those who did not have LAC (P < 0.0001). LAC is the primary predictor of adverse pregnancy outcome after 12 weeks’ gestation in aPL-associated pregnancies.

### Yelnik 2016

- Prospective observational study of pregnancy outcomes between 2003 and 2015 in 44 women with aPL and/or systemic lupus erythematosus (SLE). Thirteen patients had APOs, which occurred in 80% of cases during the second trimester of pregnancy.
LAC was present in 69% of patients with APOs compared with 27% of patients without APOs (p=0.01). No association was found between anticardiolipin antibodies (aCL) or anti-β2 glycoprotein I antibodies (aβ2GPI) IgG or IgM positivity and APOs. The findings from the study, confirm that LAC, but not aCL and aβ2GPI, is predictive or poor pregnancy outcomes after 12 weeks of pregnancy.

How should patients with SLE and specific complications be managed during pregnancy? anti-SSA antibodies

Recommendation statement

We recommend that steroids should not be used routinely for treatment of fetal heart block due to SSA/SSB antibodies, given the known risks for both the pregnant patient and fetus.

GRADE

1C- Benefits appear 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.

Other organization recommendations

Category A Evidence: 

**Ciardulli 2018**- Systematic review. 5 studies of fetuses with second-degree immune-mediated congenital atrioventricular block diagnosed on prenatal ultrasound and treated with fluorinated steroids compared

Category B Evidence: 

**Friedman 2008**- Prospective, multicenter, observational study of 95 pregnant women with anti-SSA/Ro antibodies (98 pregnancies). Fetal echocardiograms were performed weekly from 16 to 26 weeks’ gestation and
with those not treated. The progression rate to congenital atrioventricular block at birth in fetuses treated with steroids was 52% (95% confidence interval 23–79) and in fetuses not receiving steroid therapy 73% (95% confidence interval 39–94). The overall rate of regression to either first-degree, intermittent first-/second degree or sinus rhythm in fetuses treated with steroids was 25% (95% confidence interval 12–41) compared with 23% (95% confidence interval 8–44) in those not treated. Stable (constant) second-degree congenital atrioventricular block at birth was present in 11% (95% confidence interval 2–27) of cases in the treated group and in none of the newborns in the untreated group, whereas complete regression to sinus rhythm occurred in 21% (95% confidence interval 6–42) of fetuses receiving steroids vs. 9% (95% confidence interval 0–41) of those untreated.

Friedman 2009- Prospective, multicenter, observational study of 40 pregnant women with anti-SSA/Ro antibodies and a CHB-fetus. 30 mothers elected to take dexamethasone (DEX); 10 did not. ix deaths occurred in the DEX group. There was no reversal of 3rd degree block, with therapy or spontaneously. In fetuses treated with DEX, 1/6 with 2nd degree progressed to 3rd degree and three remained in 2nd degree (postnatally-- one paced, two progressed to 3rd); two reverted to normal sinus rhythm (NSR) (postnatally-- one progressed to 2nd). DEX reversed both fetuses with 1st degree to NSR by seven days with no regression upon discontinuation. Absent DEX, the one 1st degree detected at 38 wks had NSR at birth (overall stability or improvement 4/8 DEX vs. 1/1 non-DEX). Median gestational birth age was 37 weeks vs. 38 weeks, DEX vs. non-DEX, p=0.019.
Prematurity and small for gestational age were restricted to the DEX group. Pacemaker use and growth parameters at birth and one year were similar between groups.

**Eliasson 2011** - Retrospective, multinational study of 175 fetuses diagnosed with second- or third-degree atioventricular block between 2000-2007. In 80% of 162 pregnancies with documented antibody status, atrioventricular block was associated with maternal anti-Ro/SSA antibodies. Sixty-seven cases (38%) were treated with fluorinated corticosteroids for a median of 10 weeks (1–21 weeks). Ninety-one percent were alive at birth, and survival in the neonatal period was 93%, similar in steroid-treated and untreated fetuses, regardless of degree of block and/or presence of anti-Ro/SSA.

**Izmirly 2016** - Retrospective study of fetuses expose to anti-SSA/Ro presenting with isolated advanced heart block in utero who either received fluorinated steroids within 1 week of detection (N=71) or no treatment (N=85). fluorinated steroids did not significantly prevent development of disease beyond the AV node (adjusted HR=0.90; 95% CI 0.43 to 1.85; p=0.77), reduce mortality (HR=1.63; 95% CI 0.43 to 6.14; p=0.47) or forestall/ prevent pacemaker implantation (HR=0.87; 95% CI 0.57 to 1.33; p=0.53).

| Recommendation statement |
|---------------------------|--|---|
|                           |   |   |
We recommend that serial fetal echocardiogram for assessment of PR interval not be routinely performed in patients with anti-SSA and anti-SSB antibodies.

**GRADE**

**1B**- 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.

**Other organization recommendations**

**ACR 2020**- In pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies but no history of an infant with CHB or NLE, we conditionally recommend serial fetal echocardiography (less frequent than weekly; interval not determined) starting between 16 and 18 weeks and continuing through week 26. For women with a prior infant with CHB or other NLE we conditionally recommend fetal echocardiography weekly, starting at week 16–18 and continuing through week 26. Recommendations regarding monitoring for and treatment of CHB in women with anti-Ro/SSA and/or anti-La/SSB are all conditional. Given the rarity of CHB, large case series are not available; most studies are retrospective and not randomized. An argument against screening includes the risk of identification and treatment of artifacts that do not impact offspring health, thus exposing both fetus and mother to long-term side effects of dexamethasone; this risk must be balanced against the potentially devastating impact of CHB. All discussions should acknowledge the limited data and consider the patient’s values and preferences.

**AIUM 2019**- Fetal echocardiography is indicated if there is autoimmune disease with anti-Sjogren syndrome–related antigen A antibodies and with a prior affected fetus. Fetal echocardiography may be considered if there is autoimmune disease with Sjogren syndrome–related antigen A positivity and without a prior affected fetus.

**EULAR 2016**- Fetal echocardiography is recommended in cases of suspected fetal dysrhythmia or myocarditis, especially in patients with positive anti-Ro/SSA and/or anti-La/SSB antibodies. The substatement on fetal echo in women with SLE/APS and positive anti-Ro/La is rated with LoE=2 (ie, sufficient evidence for the association between anti-Ro/La and congenital heart block) but GoR=C due to lack of strong evidence for the clinical implications of this association, namely for the efficacy of interventions.

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**Clinical question**

*What is the appropriate obstetric management for pregnant patients with SLE? Prepregnancy counseling*
Recommendation statement

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- Benefits appear 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.

Other organization recommendations

n/a

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<tr>
<td>n/a</td>
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<td>Ruffatti 2009- Retrospective study of 97 pregnancies occurring in 79 primary APS patients. 12 pregnancies were lost (12.3%).</td>
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Recommendation statement

We recommend that pregnancy should be generally discouraged in patients with severe maternal or fetal risk, including patients with active nephritis; severe pulmonary, cardiac, renal, or neurologic disease; recent stroke; or pulmonary hypertension.

GRADE

1C- Benefits appear 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.

Other organization recommendations

n/a

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<td>Yasmeen 2001- Retrospective study of 555 pregnant women with SLE compared with 600,000 pregnant women without SLE between 1993-1994. Adverse pregnancy</td>
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outcomes, including hypertensive complications, renal disease, preterm delivery, non-elective Cesarean section, postpartum hemorrhage and delivery-related deep vein thrombosis all occurred more frequently in the SLE group as compared to controls (p < 0.001). Neonatal and fetal outcomes were significantly worse in the SLE group, as documented by a higher prevalence of fetal growth restriction and neonatal death, as well as longer hospital stays (p < 0.0001).

Clinical question

**What is the appropriate obstetric management for pregnant patients with SLE?** *Pregnancy Management*

Recommendation statement

We recommend antenatal testing and serial growth scans in pregnant patients with SLE due to the increased risk of FGR and stillbirth.

**GRADE**

1B- 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.

Other organization recommendations

**ACOG CO 828**– For individuals with uncomplicated systemic lupus erythematosus (eg, stable or low-activity disease and no internal organ dysfunction), weekly antenatal fetal surveillance may be considered by 32 0/7 weeks of gestation. For pregnant patients with complicated systemic lupus erythematosus (eg, active lupus nephritis, recent lupus flare, antiphospholipid antibodies with previous fetal loss, anti-Ro/SSA or anti-La/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 specialists and may be considered upon diagnosis or at a gestational age when delivery would be considered because of abnormal test results.

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**Clinical question**

**What is the appropriate obstetric management for pregnant patients with SLE? Contraception**

**Recommendation statement**

*We recommend adherence to the Centers for Disease Control and Prevention (CDC) medical eligibility criteria for contraceptive use in patients with SLE.*

**GRADE**

1B- 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.

**Other organization recommendations**

**CDC 2016** SLE is associated with increased risk for adverse health events as a result of pregnancy [specific recommendations for contraceptive use included in Table 7 in text].

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