SYSTEMIC LUPUS ERYTHEMATOSUS MANAGEMENT IN PREGNANCY

DR.P.AGHAJANZAH

NEPHROLOGYST

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-organ system disorder that predominantly affects reproductive aged women.

SLE pregnancies are associated with increased incidence of disease flares as well as adverse pregnancy outcomes

In this review, we will discuss SLE management during conception, through pregnancy and the post-partum period.

OVERVIEW OF SLE

SLE is a chronic disease characterized by ***autoreactive T and B cells*** leading to pathogenic autoantibodies and immune complex deposition resulting in tissue damage.

Diagnosing SLE can be challenging as the disease often develops slowly and evolves over time.

Diagnosis requires the ***presence*** of an ANA, and the presence of other autoantibodies and/or clinical manifestations.

Epidemiologic studies estimate the prevalence of SLE is between 45.2 and 102.9 per 100,000 with an incidence of 2.4–7.2 per 100,000/year.

The highest incidence of SLE is seen in women, peaking during their *reproductive years* with a female to male prevalence ratio of 7–9:1

The **X chromosome and sex hormones** may be responsible for the uptick in incidence among women as these have been associated with immune dysregulation.

REPRODUCTIVE POTENTIAL

Several factors impact the number of offspring in patients with SLE, including:

- active inflammatory disease,
- comorbidities (eg, renal insufficiency, lupus nephritis, and anti-phospholipid syndrome),
- exposure to gonadotoxic treatments,
- advanced maternal age,
- psychosocial aspects
- pregnancy loss

Lupus activity, even mild, can cause ***oophoritis*** and interrupt the hypothalamic pituitary ovarian axis.

Flares also have been associated ***with hyperprolactinemia***, affecting the ovulation process.

Patients may present with amenorrhea and menstrual irregularity.

Anti-Mullerian hormone (AMH) levels and antral follicular count (AFC) **are predictors** of ovarian reserve; a reduction in levels may indicate impaired fertility.

Cohort studies have found AMH and AFC levels in SLE patients were ***significantly lower*** compared to age-matched healthy controls even in those with normal menstruation.

- Cyclophosphamide *(CYC)* is an alkylating agent used in the treatment of severe manifestations of SLE (eg, class III/IV lupus nephritis, severe neurological inflammation, pulmonary alveolitis/hemorrhage).
- This medication can directly damage oocytes, however, gonadotropin-releasing hormone agonists can mitigate this toxicity.
- Women previously treated with CYC experienced greater rates of ***amenorrhea and early menopause***.
- Ovarian insufficiency is more likely with age (over 30) and cumulative doses greater than ***10 grams***.

DISEASE ACTIVITY DURING PREGNANCY

- Several studies have shown that active disease at the time of conception correlates with disease flares during pregnancy
- A study of 55 pregnancies in 39 women with SLE recorded clinical and laboratory data regularly six months prior to pregnancy through the first year post-partum. In this study, history of nephritis and high disease activity, as measured by the SLE Disease Activity Index (SLEDAI), predicted adverse maternal outcome during pregnancy.
- In another study of 155 patients with lupus who became pregnant, ***active lupus at the time of conception*** was associated with renal and hematologic flares.
- In this cohort, 6.1% of women with active disease during pregnancy died and 15.9% developed organ failure; in addition, hypocomplementemia and anti-dsDNA at the time of conception were also associated with disease flares.

- In the prospective study, Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISSE), fewer than 10% of 318 patients with mild –moderate disease during the first trimester of pregnancy had mild flares and only 3% had severe flares.
- Several studies have shown that *continuation of hydroxychloroquine during pregnancy reduces the risk of flare during pregnancy* and in the post-partum period.
- Moreover, in a study of 316 lupus pregnancies, hydroxychloroquine reduced the risk of preeclampsia

- Not only does disease activity in the six months preceding conception predict flare, but also the type of organ involvement in the pre-conception period predicts the type of disease flare during pregnancy.
- Tedeschi et al showed that the organ-system that was active in the six months prior to conception predicted the organ system involved in a pregnancy disease flare.
- Thus, women with ***hematologic manifestations prior to conception tended to have hematologic manifestations during pregnancy.***

PREGNANCY OUTCOMES

- Women with SLE have more adverse pregnancy outcomes than control women.
- In a study of the nationwide inpatient sample that included 4000 SLE pregnancies, *lupus pregnancies had longer hospital lengths of stay, increased hypertension, higher rates of intrauterine growth restriction (IUGR) and C-section rate.*
- In a subsequent study using the same database but expanded years, there was a *three-fold increased risk of risk of preeclampsia, a 20-fold increase in maternal death, and increased rate of infections of infections and thrombosis among SLE* patients.
- More recent data has shown improvement in maternal mortality and fetal death rates, although rates are still higher than in the control population

- The incidence of *cesarean section rates and pre-eclampsia continues to remain higher* in SLE pregnancies and have not significantly changed over time.
- In the aforementioned PROMISSE study, 19% of patients had *adverse pregnancy outcomes including*:
  - fetal loss after 12 weeks,
  - neonatal death,
  - preterm delivery
  - small for gestational aged infants.
- *Baseline predictors include*:
  - the presence of a lupus anticoagulant ,
  - antihypertensive use
  - thrombocytopenia,
  - maternal flares
  - , higher disease activity
  - lower increases in C3 later in pregnancy.
- The Medical Birth Registry of Norway reported outcomes of births in women with SLE and concluded active disease was associated with increased risk for preeclampsia and preterm births
- A study of maternal and fetal outcomes over 3 decades by the Mayo clinic found that patients with active lupus nephritis compared to those who had quiescent disease had higher incidence of maternal complications.
- Women with *active nephritis* were more likely to deliver preterm and to have fetal loss

PREECLAMPSIA VERSUS LUPUS FLARE

- One of the most challenging clinical conundrums is *differentiating SLE flare from pre-eclampsia*.
- This is particularly so because up to 20% of lupus pregnancies are complicated by pre-eclampsia.
- This differentiation is not merely academic as pre-eclampsia is treated with immediate delivery whereas lupus flare is managed with immunosuppression.
- While both conditions can present with hypertension and proteinuria, urinalysis in pre-eclampsia is *less likely to reveal an active sediment than in SLE flare.*
- Thrombocytopenia is common to both but elevations of liver function tests are more suggestive of pre-eclampsia.
- *In lupus flares, lower white blood cell counts, complement levels, and uric acid are seen than in pre-eclampsia*.

FETAL OUTCOMES
FETAL LOSS

- Previously, fetal loss in SLE pregnancies was as high as 43%. This rate declined to 17% in 2002.
- In a cross-sectional study of 356 SLE pregnancies, SLE pregnancies were more than twice as likely to end in fetal death than non-SLE pregnancies.
- Another study of 148 lupus pregnancies compared to 78,905 non-lupus pregnancies found the rate of stillbirth was higher with lupus and associated with severe maternal disease

- **Risk factors for pregnancy loss include:**
  - the presence of antiphospholipid antibodies (aPL),
  - lupus nephritis
  - increased lupus activity in the 6 months preceding or during pregnancy.

FETAL COMPLICATIONS

- One study from Taiwan of 2059 SLE offspring reported higher rates of intrauterine growth restriction, preterm birth and stillbirth.
- Similarly, an Italian group reported higher risk of preterm delivery and small for gestational aged infants in their SLE cohort.
- This group also found SLE pregnancies were more *likely to end in preterm delivery, particularly in patients with a history of lupus nephritis and hypertension.*
- *Intrauterine growth restriction was associated with hypertension, Raynaud's, and disease flares*.

NEONATAL LUPUS

- Approximately *one-third* of women with SLE will have anti-Ro/SSA and anti-La/SSB antibodies.
- In 10% of offspring of pregnant women with these antibodies, neonatal lupus can occur (NL). Neonatal lupus consists of *cutaneous or cardiac manifestations*. In cutaneous neonatal lupus, the infant has a photosensitive rash and can have elevated liver function tests.
- These findings disappear after six months of life. In 1–2% fetuses of mothers with anti-Ro and anti-La antibodies, congenital complete heart block (CCHB) can occur. This incidence increases to 17% if the mother has had a previous child with CCHB.
- Congenital complete heart block can lead to fetal death in 17.5% of affected fetuses most occurring before the 30th week of gestation.
- While no formal guidelines exist for monitoring for the development of heart block, professional societies recommend serial fetal echocardiography between 16 weeks and 26 weeks of gestation.
- Datasuggest *hydroxychloroquine* administration during pregnancy in anti-Ro and anti-La positive mothers can reduce the reoccurrence rate of CCHB.

PRE-PREGNANCY SCREENING AND CONTRACEPTION

- A planned pregnancy is important to allow time to optimize treatment and tighten disease control.
- End-organ damage may be a contraindication to pregnancy; examples include severe pulmonary hypertension, pulmonary fibrosis, cardiomyopathy, valvular dysfunction, severe renal insufficiency, or end stage renal disease, history of major strokes or catastrophic antiphospholipid syndrome.
- Patients with these conditions should avoid pregnancy. Additionally, pre-conceptual counseling will reduce risk of exposure to teratogenic medications, disease flares, and adverse pregnancy outcomes (APOs).
- An important part of pre-conception counseling is to ascertain the patient's pregnancy plans. One easy way to incorporate this into clinical practice is to ask "Would you like to become pregnant in the next year?." If the patient wants to avoid pregnancy, refer the patient for effective Contraception.

PRECONCEPTUAL RISK ASSESSMENT

- In patients desiring pregnancy, remission or low lupus disease activity state (LLDAS) is the goal before pregnancy is attempted.
- Active disease status will increase the risk of poor outcomes to mother and baby. Hence, to minimize risk for APOs, patients should be in LLDAS or remission for 6 months before trying to conceive on medications compatible with pregnancy.
- Those with moderate or severe disease activity should delay pregnancy until the disease is controlled on stable, pregnancy-compatible medications.

BIOMARKERS PREDICTIVE OF PREGNANCY OUTCOMES

- Women with SLE anticipating pregnancy should be tested for the presence of anti-Ro/SSA, anti-La/SSB and antiphospholipid antibodies (eg, anticardiolipin IgG and IgM, b2-glycoprotein-I IgG and IgM, and the lupus anticoagulant (LAC)); these antibodies portend serious complications during pregnancy.

- Moderate and high titers of antiphospholipid antibodies in combination with the LAC confers the highest risk for poor fetal and maternal outcomes.

PREGNANCY MONITORING

- Lupus pregnancies are high-risk pregnancies. A collaborative approach to monitoring the pregnant patient is essential; the team should comprise a rheumatologist, maternal fetal medicine specialist (also known as "high-risk OB"), and if applicable, a nephrologist and pediatric cardiologist.
- The patient should have regular assessments during pregnancy to identify potential complications and receive early intervention.
- Physiological pregnancy changes may resemble SLE disease activity, including arthralgias, fatigue, rashes, and swelling.
- Laboratory changes also occur during a healthy pregnancy.
- Distinguishing which changes are physiological versus pathological may be difficult, but understanding normal pregnancy physiology is essential.

- Pregnancy will cause significant anatomical and physiological transformations affecting every organ system.
- Plasma volume expands by 50% and is proportional to the baby's birthweight. With the expansion of volume cardiac output will increase by 40% during normal pregnancy Cardiac murmurs will be more evident and peripheral edema and pulmonary edema can occur.
- Renal changes also result from increased blood flow. A pregnant woman's glomerular filtration rate (GFR) is increased by 50–85%.
- This in turn increases the fractional excretion of protein and uric acid.

- Hemoglobin and platelet levels decrease in a normal pregnancy, while the erythrocyte sedimentation rate (ESR) increases.
- A study of more than 1000 healthy pregnant women found the ESR doubles in the second half of pregnancy from 18–48 mm/h to 30–70 mm/h; gestational age along with hemoglobin concentration will affect ESR levels.
- In contrast, C-reactive protein (CRP) levels do not rise during pregnancy; if elevated, this more likely indicates disease flare or infection.
- ***Hypercoagulability*** occurs in normal pregnancy; this is related to an increase of factor VIII, IX, X and fibrinogen; however, concentrations of anticoagulants, anti-thrombin and protein S are decreased contributing to thrombosis risk.
- This hypercoagulable state will persist from the first trimester to at least 6–12 weeks following parturition.

Additionally, complements will rise in a healthy pregnancy.

Elevated levels of C4, C3 and activation products C4d, C3a, and SC5b-9 are common in pregnancy; however, dysregulation of the complement system can cause preeclampsia and fetal loss.

Complement activation, likewise, is an important focus for lupus disease activity.

While levels may be low in some patients with active SLE, complements can be unreliable biomarker of disease activity.

FIRST TRIMESTER

- Common complaints in the first trimester of a normal pregnancy will include fatigue, weight gain, nausea, and urinary frequency.
- At each prenatal visit, the provider should complete a careful review of systems and physical exam with blood pressure monitoring for evidence of SLE disease activity.
- Laboratory assessments for medication toxicity and disease activity at least once a trimester should include:
  - a complete blood count with differential,
  - comprehensive metabolic panel,
  - C3, C4,
  - double-stranded DNA,
  - serum uric acid,
  - urinalysis with microscopy
  - a urine protein to creatinine ratio (UPCR).

All patients should be on ***hydroxychloroquine*** (HCQ) unless contraindicated***. Low dose aspirin*** (81mg/day) should be initiated early in pregnancy to reduce the risk for preeclampsia56

In patients with known obstetric antiphospholipid syndrome (OB-APS), prophylactic heparin or low dose molecular weight heparin in combination with low dose aspirin is indicated to prevent fetal loss and thromboses; anticoagulation should be continued 6 to 12 weeks post-partum.

Those patients with known thrombotic APS (T-APS) should receive therapeutic doses of heparin or low molecular weight heparin with low dose aspirin.

SECOND TRIMESTER

- Anti-Ro/SSA (in particular, anti-Ro 52 or 60 kDa) and/or anti-La/SSB antibodies may cross the placenta in the second trimester and cause neonatal cutaneous lupus or CCHB.

- fetal echocardiography by an experienced pediatric cardiologist or a maternal fetal medicine specialist starting at the 16th week of gestation to evaluate for cardiac conduction abnormalities as the vulnerable period is between 17 and 25 weeks gestation.
- First-, second-, and third-degree heart block may occur, but third-degree or CCHB is a permanent condition that carries significant morbidity and mortality; infants with CCHB often require permanent pacemakers.
- In mothers who have had a previous infant with CCHB or cutaneous neonatal lupus, consider monitoring with weekly fetal echocardiography. When a fetus presents with first or second-degree heart block, the ACR Reproductive Health Guidelines conditionally recommends that the anti-Ro/SSA and/or anti-La/SSB mother take oral ***dexamethasone*** 4 mg daily for several weeks.
- In contrast to CCHB, cutaneous neonatal lupus is typically transient; affected infants may present with a rash, abnormal liver enzymes or hematologic abnormalities.
- ***Hydroxychloroquine*** continued during pregnancy will reduce the risk of CCHB and NLE.

- Lupus flares may occur during pregnancy. For mild flares with arthralgias or myalgias, acetaminophen, topical pain creams and oral NSAIDs may be used, but at 20 weeks or later, nonsteroidal anti-inflammatory drugs (NSAIDS) shouldbe discouraged.
- In instances where NSAIDS cannot be used or if the flare is more severe, pregnancy compatible disease modifying anti-rheumatic medications *(DMARDS) should be added to hydroxychloroquine*.
- Keep prednisone at the lowest effective dose due to risk for mood changes, insomnia, infection, pregnancy-induced diabetes, macrosomia, adrenal insufficiency, and preterm delivery.

THIRD TRIMESTER

- Similar assessments should be conducted in the third trimester.
- Evaluate for pre-eclampsia or SLE flare regular or intrauterine growth restriction; Doppler sonography should continue at regular intervals.
- Mode and time of delivery will be determined by fetal and maternal conditions.
- Postpartum Mothers are at increased risk for thrombosis and disease flares during the postpartum period.
- Postpartum depression can be common and might be mistaken for ***neuropsychiatric lupus***.
- Many medications used for SLE disease during pregnancy can be continued ***during lactation***

CO-EXISTING ANTIPHOSPHOLIPID SYNDROME

- Antiphospholipid syndrome (APS) is characterized as recurrent venous or arterial thromboses and pregnancy morbidity in the setting of aPL. About 29–46% of patients with SLE have evidence of aPL, but only 5–8% develop thrombotic or pregnancy complications (eg, fetal loss, preeclampsia/eclampsia, small for gestational age).
- The revised classification criteria for APS defines vascular manifestations and obstetric complications; APS can occur by itself or in the setting of SLE. *Thrombotic APS (T-APS) is defined by: one or more episodes of arterial, venous, or small vessel thrombosis in any tissue or organ,*
- while ***obstetric APS is*** defined by:
  - 1. three or more consecutive spontaneous abortions before 10 weeks of gestation
  - 2. one or more premature births of a morphologically normal neonate before 34 weeks of gestation due to eclampsia or preeclampsia.
- The presence of aPL must occur on two or more occasions, separated by at least 12 weeks.

- to prevent pregnancy loss for healthy, non-SLE patients with ***aPL*** but no prior history of thrombosis or pregnancy complications; however, aspirin 81–100 mg daily is conditionally recommended by the ACR Reproductive Health guidelines.
- We recommend, low dose aspirin with prophylactic doses of heparin (usually low molecular weight heparin) in women with obstetric ***APS***. Continue anticoagulation for 6–12 weeks postpartum, as this is a vulnerable period for clotting.
- Pregnant women ***with T-APS*** should be prescribed aspirin and therapeutic dose heparin throughout pregnancy and postpartum.
- HCQ may help reduce the risk for thrombosis and APS-related poor outcomes. There is not enough evidence to show that prednisone, intravenous immunoglobulin, or higher doses of heparin will help APSrelated outcomes

MEDICATIONS

Hydroxychloroquine is considered compatible with pregnancy.

Reassuringly, studies of neonates exposed to hydroxychloroquine in utero have not shown retinal toxicity or prolongation of neonatal QTc intervals.

Several studies have demonstrated that continuation of hydroxychloroquine during pregnancy decreases disease flares and reduces the risk of pre-eclampsia. this, we emphasize to our patients the importance of staying on hydroxychloroquine during pregnancy. This medication is also compatible with breastfeeding.

Non-steroidal anti-inflammatory medications ***(NSAIDs)*** help control arthralgias and arthritis in SLE patients.

The Food and Drug Administration (FDA) recently issued a warning that NSAIDS as a class may cause "rare but serious kidney problems in an unborn baby" that can lead to oligohydramnios and death around 20 weeks or later.

After 30 weeks of gestation, NSAIDs can cause premature closure of the ductus arteriosus.

We recommend that patients stop NSAIDs after week 20 of gestation. The exception to these recommendations is *low dose aspirin that can be continued for the duration of the pregnancy. NSAIDs are compatible with breastfeeding*.

Early data suggested that ***glucocorticoids*** increased the risk for cleft palate formation.

Nonetheless, glucocorticoids can contribute to gestational hypertension and diabetes, preterm premature rupture of the membranes and small for gestational age infants.

Current recommendations advise keeping prednisone dose as low as possible during pregnancy. Similarly, in women on *>20mg/d* of prednisone, ACR guidelines suggest discarding breast milk for four hours following dosing.

Sulfasalazine is sometimes used to control arthritis in SLE patients. Data gleaned from the inflammatory bowel disease literature supports its use during pregnancy. There has been a case of diarrhea in a nursing child whose mother was taking sulfasalazine, so lactating women should consider discontinuing this medication if their infant develops diarrhea.

- Patients with significant organ involvement may require ongoing immunosuppression during pregnancy. Leflunomide, methotrexate and cyclophosphamide are either suspected or confirmed teratogenic medications and should be discontinued prior to conception. ***Leflunomide*** has a long half-life; women should undergo a drug elimination procedure with cholestyramine prior to conception; metabolite blood levels <0.03 μg/mL has been regarded as safe for pregnancy.
- ***Methotrexate*** should be stopped one to three months prior to anticipated conception and ***cyclophosphamide*** treatment should be discontinued three months prior to conception.

- Mycophenolate mofetil/mycophenolic acid, are now the most commonly prescribed medication for lupus nephritis, is teratogenic and increases the risk for pregnancy loss in the first trimester.
- A review of cumulative mycophenolate data in pregnancy showed the frequency of malformations is 22% and for spontaneous abortions to be 45%; inhibition of purine synthesis by mycophenolic acid is believed to be the cause of genotoxicity
- Mycophenolate should be stopped six weeks respectively prior to conception.

- Fortunately, azathioprine, cyclosporine and tacrolimus are compatible with pregnancy and can be substituted for the aforementioned potential teratogens.44,55
- The biologics *rituximab, belimumab, and abatacept do not significantly cross the placenta until the 15th week of gestation;* these medications can be continued through conception.
- In patients who are dependent on these biologics for disease control, discussing the potential risks of and benefits of these medications and through shared decision-making one can ***consider continuing these medications*** during pregnancy.
- The Federal Drug Administration (FDA) recently *approved voclosporin for the treatment of SLE nephritis*; current recommendations are to avoid this medication in pregnant and lactating women.

TREATMENT APPROACH

- All women with SLE who are pregnant should continue hydroxychloroquine. Given the risk of pre-eclampsia, we recommend adding low dose aspirin at the end of the first trimester.
- Transition women who need ongoing immunosuppression for disease control to an immunosuppressive agent compatible with pregnancy (eg, *tacrolimus, azathioprine or cyclosporine*) and observe for four to six months to make certain that disease is stable prior to conception.
- For non-renal flares during pregnancy, treat with the *lowest possible dose of prednisone*. For renal flares, we recommend *combination therapy of azathioprine with tacrolimus*.

- Many medications used for lupus management are compatible with lactation.
- Hydroxychloroquine, NSAIDs, sulfasalazine, and the immunosuppressive agents cyclosporine, azathioprine and tacrolimus are all compatible with breastfeeding.
- Biologics such as rituximab, and belimumab and likely abatacept are also compatible with lactation as these medications are all large molecules and do not readily get transferred into breast milk.
- Current recommendations are to avoid ***methotrexate*** in lactating women although there is growing evidence that little of this medication gets secreted in breast milk.
- Mycophenolate mofetil, cyclophosphamide and leflunomide should not be taken by lactating women

CONCLUSION

- Systemic lupus erythematosus is a disease of reproductive aged women. Whereas formerly, providers counseled SLE patients to avoid pregnancy, improved disease management and a better understanding of medication safety render pregnancy a possibility for most SLE patients. Careful pregnancy planning for when disease is under good control with pregnancy compatible medications is crucial. Assembling a team that includes a maternal fetal medicine provider or obstetrician who is familiar with caring for SLE patients is likewise important.

- All patients with SLE should remain on hydroxychloroquine during pregnancy unless contraindicated.
- We encourage patients at high risk for developing preeclampsia (older or younger age, primigravida, patients with hypertension, prior renal disease, presence of antiphospholipid antibodies) to initiate aspirin therapy (81mg/day) during the first trimester.
- Sulfasalazine, and the ***immunosuppressive agents*** cyclosporine, azathioprine, and tacrolimus are compatible with pregnancy. Rituximab, belimumab and other ***biologic agents*** can continue through conception. Glucocorticoids can help manage flares but providers should use the lowest dose possible for disease control.
- All of the aforementioned medications are compatible with breast- feeding. Cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, and voclosporin should be stopped prior to pregnancy and avoided in lactating women.
- Women with *anti-Ro and anti-La antibodies* will need fetal screening for the development of congenital complete heart block. Successful pregnancies in patients with SLE are possible with close monitoring and a collaborative framework.

Factors helpful in distinguishing preeclampsia from an SLE flare

SLE flare	Preeclampsia
Low complement level	Normal complement level
Increased double-stranded DNA	Unchanged double-stranded DNA
Leukopenia	Leukocytosis
Cellular casts/hematuria	Acellular urine
Low uric acid level	High uric acid
Thrombocytopenia	Thrombocytopenia
	Abnormal liver function tests
	Schistocytes

Frontline Medical News

eTABLE. Risks and Side Effects of Medications for Cutaneous Lupus Erythematosus in Pregnancy

Therapy	MOA	FDA pregnancy category	Teratogenic effects	Additional recommendations
Systemic steroids	Systemic immunosuppression	B	Cleft lip/palate	Stress dose at delivery
Sulfasalazine	Systemic immunosuppression	B	No major known or documented effects	Can affect sperm
Hydroxychloroquine	Increases lysosomal pH, decreases antigen presentation	C	No major known or documented effects	Standard retinopathy screening
Dapsone	Folic acid inhibitor	C	No major known or documented effects	Daily folic acid supplementation
Rituximab	CD20 monoclonal antibody	C	Hematologic abnormalities, infection	Avoid in third trimester because of B-cell depletion
IVIG	Systemic immunosuppression	C	No major known or documented effects	
Cyclosporine	Cytokine production inhibitor	C	Low birth weight and premature delivery	
Mycophenolate mofetil	IMPDH inhibitor	D	Skeletal deformities	Discontinue 6 week prior to attempting to conceive
Azathioprine	Purine synthesis inhibitor	D	Congenital abnormalities, fetal cytopenia, prematurity, and low birth weight	Limit dose to 2 mg/kg/d
Oral retinoids	Vitamin A derivative	X	Craniofacial, cardiovascular, and CNS abnormalities	Avoid in pregnancy
Thalidomide	Immune modulator	X	Limb deformities	Avoid in pregnancy
Methotrexate	Folic acid antagonist	X	Aminopterin syndrome	Can affect sperm; men should discontinue 3 mo prior to conceiving

Abbreviations: CNS, central nervous system; FDA, US Food and Drug Administration; IMPDH, inosine-5′-monophosphate dehydrogenase; IVIG, intravenous immunoglobulin; MOA, mechanism of action.

THANKS FOR YOUR ATTENTION