Pregnancy and Management in Women with Rheumatoid Arthritis, Systemic Lupus Erythematosus, and Obstetric Antiphospholipid Syndrome

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KEYWORDS

• Pregnancy • Rheumatoid arthritis • Systemic lupus erythematosus • Obstetric APS

KEY POINTS

- Women with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are at risk for disease activity during pregnancy and adverse pregnancy outcomes.
- Pregnancies in women with RA and SLE do best if disease is under good control on pregnancy-compatible medications at the time of conception.
- Women with obstetric antiphospholipid syndrome (APS) are at risk for adverse pregnancy outcomes and need to be anticoagulated during pregnancy.
- Many but not all antirheumatic drugs can be continued during pregnancy.

Rheumatic diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), frequently affect women during their reproductive years. Moreover, women with antiphospholipid syndrome (APS) can have distinct obstetric complications that warrant monitoring and treatment. In this article, the authors discuss the impact of pregnancy on RA and SLE and the risk of adverse pregnancy outcome in these conditions. The evaluation and management of women with obstetric APS also are reviewed. In addition, the safety during pregnancy and lactation of the most commonly used medications in treating RA and SLE are discussed.

RHEUMATOID ARTHRITIS AND PREGNANCY

RA is a chronic inflammatory disease that commonly affects women of childbearing age. For many years, the teaching was that RA would go into remission in the vast

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majority of patients and patients were taken off of their medications. More recently, data have shown that some patients with RA flare during pregnancy and good disease control is important prior to conception.

Fertility

Several studies have shown that women with RA have more difficulties conceiving, as indicated by a longer time to pregnancy (TTP), than those without RA.[1,2] Women with RA also have smaller-sized families than their peers.[3] Theories as to why there is increased infertility in these patients include physiologic changes and personal choices, due to either underlying disease or concerns regarding medications. There are unclear data regarding whether antimüllerian hormone (AMH), a marker of ovarian reserve, is abnormal in women with RA. Moreover, recent data suggest that levels of AMH in women with RA did not correlate with TTP or self-reported fertility.[4]

Pregnancy and Disease Flare

Slightly more than half of women with RA experience amelioration of disease during pregnancy. This improvement is associated with low disease activity at the time of conception and seronegativity (absence of a rheumatoid factor and/or anticitrullinated peptide antibodies). In one study, greater HLA disparity between mother and fetus was associated with successful pregnancy and induction of remission in patients with RA.[5] Additionally, some post-translational modifications like glycosylation and galactosylation on immunoglobulins have been shown to affect their immuno-effector functions, which have been associated with favorable pregnancy outcomes.[6]

Assessing RA disease activity during pregnancy can be challenging particularly because the physiologic changes of pregnancy can have an impact on markers of RA disease activity, such as the erythrocyte sedimentation rate. In addition, joint pain and fluid retention are common in pregnancy and can be difficult to distinguish from an RA flare. Furthermore, not all scales used to assess disease activity are accurate during pregnancy; however, a study showed that using the Disease Activity Score in 28 joints calculated with C-reactive protein without global health scoring was useful in ascertaining clinical remission during pregnancy.[7] This study also found that patients with low disease activity were more likely to remain stable or go into remission during pregnancy whereas patients with high disease activity prior to pregnancy did not remit until the second and third trimesters. Other studies have shown that women with seronegative disease (absence of rheumatoid factor and anticitrullinated peptide antibodies) were more likely to improve and sustain low disease activity during pregnancy.[8] In a study by van den Brandt and colleagues,[9] which included 75 pregnant patients with RA, it was found that most flares occurred within the first trimester and were associated with active disease prior to pregnancy along with discontinuation of therapies, such as tumor necrosis factor (TNF) inhibitors.

RA has been associated with adverse pregnancy outcomes, including intrauterine growth restriction (IUGR), premature rupture of membranes, and preterm delivery.[10] In a prospective study by de Man and colleagues,[11] which included patients from the Dutch health registry, higher RA disease activity as well as use of prednisone during pregnancy were associated with lower birth weights and increased cesarean sections. Thus, if possible, RA pregnancies should be planned for periods of low disease activity.

SYSTEMIC LUPUS ERYTHEMATOSUS AND PREGNANCY

SLE is a multisystem disorder that occurs predominantly in reproductive-aged women. For many years, women with SLE were counseled to avoid pregnancy because of concerns regarding disease flare and adverse pregnancy outcome. More recently, data suggest that many women with women can have successful pregnancies if disease is under good control and planned.

Fertility

Women with SLE, like those with RA, have reduced family size.[12] Reduction in fertility is related to the use of cytotoxic medications, such as cyclophosphamide.[13] Disease itself, however, in the absence of such medications does not decrease fertility.[14] Data on AMH levels in SLE are conflicting, with some studies showing lower levels of AMH in SLE patients and other studies showing no difference once allowances were made for exposure to cytotoxic medications.[15,16] Secondary infertility, defined as spontaneous pregnancy loss, is increased in SLE patients but only in the setting of antiphospholipid antibodies (discussed later).

Pregnancy and Disease Flare

The advice, discussed previously, that women with SLE avoid pregnancy was based on concern for increase disease activity and adverse pregnancy outcome. Not all women with SLE, however, flare during pregnancy. Patients with a prior history of renal disease have a greater risk of disease flare during pregnancy. Primagravidas also have an increased risk of flare during pregnancy. Disease activity in the 6 months preceding pregnancy increases the risk of pregnancy-associated disease flare, with an estimated flare rate of 60% in women with active disease preconception. For this reason, SLE patients should be under good disease control with medications compatible with pregnancy for several months prior to conception. Disease manifestations during pregnancy are related to disease manifestations in the period of time preceding pregnancy.[17] For example, women who have skin manifestations in the prepregnancy period are more likely to have skin flares during pregnancy, whereas women with hematologic abnormalities prepregnancy are more likely to have hematologic abnormalities during a pregnancy flare.

Severe disease-related damage, such as significant renal insufficiency, pulmonary artery hypertension, and coronary artery disease, can cause severe maternal morbidity and, in some cases, mortality during pregnancy. Women with these conditions should be counseled about these risks prior to pursuing pregnancy.

Distinguishing lupus flare from preeclampsia can be challenging. Moreover, women with lupus have a higher incidence of preeclampsia than control populations. Active urine sediment, increasing double-stranded DNA titer, low complements, and leukopenia are suggestive of lupus flare whereas increasing liver-derived transaminases, uric acid levels, and proteinuria without an active sediment are more suggestive of preeclampsia. This distinction is important, however, because preeclampsia is an indication for emergent delivery, whereas SLE flare warrants aggressive immunosuppression.

SLE is associated with adverse pregnancy outcomes. A nationwide inpatient survey showed that women with SLE were more likely to have increased hypertension, IUGR, cesarean section rate, preeclampsia, and fetal death.[18] Although these data have improved somewhat over the past decade, the complication rate in SLE pregnancy still exceeds that in the general population.[19] The best prospective pregnancy study to date, the Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid

Syndrome and Systemic Lupus Erythematosus (PROMISSE) study, reported adverse pregnancy outcomes (fetal death, birth before 36 weeks' gestation, and small-for-gestational-age [SGA] infants) in 19% of women.[20] Primagravidas, lupus anticoagulant (LA), antihypertensive medication, and active disease all predict poor outcome. Overall, however, the complication rate was low and somewhat reflective of the low-disease-activity SLE patient population.

Patients with SLE should be on pregnancy-compatible medication to maintain low disease activity prior to pregnancy. Several studies have shown that hydroxychloroquine during pregnancy improves outcome.[21] Nonetheless, disappointingly, claims data suggest that only a small percentage of patients are adherent with their hydroxychloroquine during pregnancy.[22]

OBSTETRIC ANTIPHOSPHOLIPID SYNDROME

APS is a systemic autoimmune disorder associated with venous and arterial thrombosis and obstetric complications. It exists as primary APS, secondary or related to underlying autoimmune disease, or obstetric APS. This discussion focuses on obstetric APS. Clinically, obstetric APS is defined as pregnancy loss or delivery at less than 34 weeks of gestation because of preeclampsia or evidence of placental insufficiency, 1 or more unexplained fetal deaths at greater than 10 weeks' gestation, or 3 or greater unexplained spontaneous pregnancy losses before 10 weeks of gestation. Clinical manifestations must be associated with laboratory criteria, including the presence of persistent LA, anticardiolipin antibody (aCL), or anti–beta-2 glycoprotein I.[23] The LA and triple-positivity LA, aCL, and anti–beta-2 glycoprotein I are associated most commonly with adverse pregnancy outcome.[24,25] The significance of other antiphospholipid antibodies, such as antiphosphatidylserine /prothrombin antibodies, is unproved, although 1 study showed the presence of these antibodies in 86% of patients with APS.[26] In addition to fetal loss, women with obstetric APS have higher incidence of preeclampsia, eclampsia, and HELLP syndrome. Adverse fetal outcomes include prematurity and IUGR. Women who have a history of unexplained preeclampsia, premature infants, and recurrent pregnancy loss should be evaluated for antiphospholipid antibodies, including an LA, aCL and anti–beta-2 glycoprotein I.

Management

Women with obstetric APS required anticoagulation.[27] Although unfractionated heparin can be used, low-molecular-weight heparin (LMWH) is preferred because steady-state levels are easier to maintain. In women with only obstetric manifestations, prophylactic-dose LMWH can be used whereas those women with thrombotic manifestations as well need therapeutic anticoagulation during pregnancy. Warfarin is contraindicated during pregnancy. There are insufficient data to conclude the efficacy of the direct oral anticoagulants during pregnancy in APS or the safety of these medications during pregnancy. In addition to LMWH, patients should be treated with a baby aspirin.[28]

MANAGEMENT OF RHEUMATOID ARTHRITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS DURING PREGNANCY

The key component of management of RA and SLE during pregnancy is having patients under good control on medications compatible with pregnancy (**Table 1**) prior to conception. Importantly, patients ideally should be managed by a team of

Table 1
Medication compatibility with pregnancy and lactation

Pregnancy Risk	Pregnancy	Lactation
Compatible	Monitor mother for hypertension	Compatible
Hydroxychloroquine		Compatible
Sulfasalazine		Compatible
Azathioprine		Compatible
Cyclosporine		Compatible
Tacrolimus		Compatible
Low-dose aspirin		
Some risk	Stop by 30 weeks—risk of patent ductus arteriosus	Preference for short-acting >20 mg/d discard breastmilk for 40 following dose
NSAIDs	Keep dose as low as possible	
Glucocorticoids	Discontinue third trimester[a]	
TNF-α blockers	Discontinue at conception	Compatible
Rituximab	Discontinue at conception	Compatible
Belimumab	Discontinue at conception	Compatible
Abatacept	Discontinue at conception	Compatible
Tocilizumab		Compatible
		Compatible
Avoid during pregnancy	Stop 1–3 mo before conception	Incompatible
Methotrexate	Levels should be undetectable	Incompatible
Thalidomide		Incompatible
Leflunomide		Incompatible
Mycophenolate mofetil		Incompatible
Cyclophosphamide		
Insufficient data		Avoid during lactation—small molecules readily pass into breast milk
Tofacitinib		
Baricitinib		

[a] Certolizumab may be continued throughout pregnancy. Other TNF-α blockers can possibly continue through pregnancy if disease activity is high.

providers, including those familiar with rheumatic diseases and skilled in maternal fetal medicine.

MEDICATIONS DURING PREGNANCY AND LACTATION

Data on medication safety during pregnancy and lactation often are limited. For many years, providers relied on the US Food and Drug Administration (FDA) use in pregnancy ratings A, B, C, D and X. These ratings were inappropriately interpreted as a grading system, when in actuality they reflected the amount of available data regarding a specific drug's safety during pregnancy. In order to mitigate these shortcomings, the FDA instituted the Pregnancy and Lactation Labeling rule in 2015 an attempt to provide clinicians with comprehensive and up-to-date information regarding medication safety during pregnancy and lactation in order to inform decision making.[29] Nonetheless, the information provided within the new system leaves much of the interpretation of the data up to the individual clinician. Fortunately, over the past few years, several professional organizations, including the British Society for Rheumatology, the European League Against Rheumatism, and more recently the American College of Rheumatology, have published guidelines regarding use of medications during pregnancy and lactation.[30–32]

Medications that are Compatible during Pregnancy and Lactation

Hydroxychloroquine is the mainstay of therapy for women with SLE and connective tissue disease (diseases that have features of rheumatic disorders but who cannot be definitively categorized). This medication has no teratogenic risk when taken during pregnancy. Moreover, ample evidence suggested continuation of hydroxychloroquine during pregnancy improves outcome. In a retrospective study of 257 pregnancies from the Johns Hopkins Lupus Cohort, discontinuation of hydroxychloroquine was associated with increased risk of lupus flare.[21] This medication is compatible with breastfeeding.[33]

Sulfasalazine is used to manage joint inflammation in persons with RA and, less commonly, SLE. A large meta-analysis did not show any increase in fetal anomalies after in utero exposure.[34] Although there has been 1 report of a breastfeeding infant who had bloody diarrhea after his mother was given sulfasalazine, this medication is considered compatible with lactation.[35]

The immunosuppressive agents azathioprine, cyclosporine, and more recently tacrolimus are used as immunosuppressive agents in women with SLE, in particular for induction and maintenance therapy for lupus renal disease. There is ample literature from the transplant population that these medications do not increase the risk for congenital anomalies.[11,12,36–40] These medications are compatible with pregnancy and with nursing.[32]

Aspirin does not appear to be teratogenic in humans. One large study of 5128 pregnancies in which there was in utero aspirin exposure did not show increased congenital anomalies.[41] Moreover, this medication has been part of the regimen for the management of obstetric APS.[42] Moreover, data suggest that baby aspirin may decrease the risk of preeclampsia.[43] The American College of Obstetricians and Gynecologists recommends the use of this medication in persons with disorders, such as SLE and APS, because these patients may have an increased risk for preeclampsia. Aspirin is compatible with breastfeeding.

Medications with Some Risk for use during Pregnancy and Lactation

Glucocorticoids frequently are used to manage disease flares in a variety of rheumatic diseases. The nonfluorinated medications used most commonly to manage rheumatic diseases are prednisone and prednisolone. These medications do not readily cross the placenta.[44] Although 1 meta-analysis suggested that glucocorticoids increased the risk of cleft palate formation 2-fold after in utero exposure,[45] a large Danish cohort study that examined 51,973 first-trimester glucocorticoid exposure failed to show any increase risk of cleft lip and/or palate formation.[46] Although there does not appear to be an increased risk of congenital anomaly in infants exposed to this medication in utero, these medications increase the risk of preeclampsia, preterm premature rupture of the membranes, gestational diabetes, hypertension, and SGA infants. Prednisone and prednisolone are compatible with breastfeeding; however, it is recommended in women who are using doses of greater than 20 mg a day discard breast milk for the first 4 hours after dosing.[30]

Non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX-2) inhibitors are used to manage pain and inflammation in individuals with RA and SLE. Although NSAIDs do not increase the risk of congenital anomalies,[47] 1 meta-analysis found the risk of ductal closure to be 15-fold higher in women exposed to indomethacin during the third trimester of pregnancy.[48] There are conflicting data on whether nonsteroidal use during the first trimester increases the risk for spontaneous miscarriage. One large case-control study suggested that there was an

increased odds ratio for miscarriage in pregnancies exposed to NSAIDs[49]; however, another study of more than 65,000 pregnancies did not show any increased risk for spontaneous abortion after NSAID exposure.[50] Data suggest that NSAIDs are compatible with nursing, although there is a slight preference for ibuprofen given its short half-life. There are insufficient data to evaluate pregnancy safety of COX-2 inhibitors.

Although initially there were concerns that the TNF-α blockers may contribute to the vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities (VACTERL) syndrome, subsequent data have not supported this finding.[51,52] There is ample evidence that TNF-α blockers not only are compatible with pregnancy but also are important for good disease control of inflammatory arthritis that contributes to improved pregnancy outcome. There are no clear-cut recommendations for when TNF-α blockers should be discontinued, but several professional organizations recommend discontinuing these medications during the third trimester.[30–32] This recommendation is based on reducing the risk of immunosuppression of neonates.[53] In patients with active disease, however, continuing these drugs through delivery can be considered. Certolizumab is a TNF-α blocker that is pegylated and does not cross the placenta in any significant amount.[54] This medication may be continued throughout pregnancy. The TNF-α blockers all are large molecules and little drug gets transferred into breast milk. Lactating women can take these medications.

The biologics, such as rituximab, belimumab, tocilizumab, and abatacept, do not effectively transfer to the placenta until 12 weeks to 15 weeks of gestation. Although data are limited, studies in which belimumab and rituximab were continued through early pregnancy did not show any significant safety signals.[55,56] Current recommendations by several professional organizations are that these medications can be included until conception.

MEDICATIONS THAT ARE CONTRAINDICATED IN PREGNANCY

The medications leflunomide, methotrexate, mycophenolate mofetil, and cyclophosphamide are contraindicated during pregnancy. Leflunomide is an antimetabolite that inhibits dihydroorotate dehydrogenase. Its major metabolite, teriflunomide, is detectable in the serum for up to 2 years. This drug is major teratogen in animals and for this reason is contraindicated during pregnancy.[57] Human data are more reassuring because there has no pattern of congenital anomalies reported after preconception and early pregnancy exposure to leflunomide[58]; nonetheless, this medication should be discontinued prior to conception and blood levels should be undetectable. The latter can be achieved by cholestyramine washout or by discontinuing the medication for 2 years prior to conception. Methotrexate is both teratogenic and abortogenic and women should discontinue this medication 1 months to 3 months prior to conception.[59,60] Mycophenolate mofetil causes a higher than expected rate of congenital anomalies and should be discontinued 6 weeks prior to conception.[61] Likewise, cyclophosphamide is teratogenic and should be avoided during pregnancy.[62] Cyclophosphamide, however, has been used in the late pregnancy for cancers and lupus nephritis with no minimal risk to the fetus.[63,64] None of these medications is compatible with lactation.

Insufficient Data

Although 1 small case series did not suggest there were safety concerns after in utero exposure to tofacitinib,[65] there are insufficient data to conclude safety of

the small molecules tofacitinib and baricitinib during pregnancy. These molecules are small and readily pass into breast milk and, therefore, should be avoided in lactating women.

SUMMARY

RA, SLE, and APS are associated with risk of disease activity during pregnancy and pregnancy complications. Many but not all RA patients go into remission during pregnancy. Active disease prior to conception and discontinuation of medications, in particular TNF-α blockers, portend greater disease activity during pregnancy. RA pregnancies in which disease is poorly controlled have higher risks of adverse pregnancy outcome, including preeclampsia, prematurity, and SGA infants. SLE patients who have a prior history of lupus nephritis are particularly vulnerable to increased disease activity during pregnancy. This, is turn, is associated with adverse pregnancy outcome, including preterm premature rupture of the membranes, SGA infants, and preeclampsia. Patients with SLE should be maintained on their hydroxychloroquine during pregnancy, and conception should be deferred until disease is under good control with pregnancy-compatible medication for several months. Comanagement with a maternal fetal specialist is crucial. Obstetric APS carries risks of adverse pregnancy outcome. Anticoagulation with fractionated or unfractionated heparin along with baby aspirin mitigates this risk. Although not all medications can be used during pregnancy, many medications used to treat RA and SLE can be continued. Hydroxychloroquine, sulfasalazine, and the immunosuppressive agents azathioprine, cyclosporine, and tacrolimus can be continued throughout pregnancy and during lactation. NSAIDs can be used but must be stopped by the third trimester due to the risk of patent ductus arteriosus. Glucocorticoids can be used but do carry risks of comorbidity. The TNF-α blockers can be continued to the third trimester of pregnancy and on a case-by-case basis consideration can be given to consider continuing them through delivery. Biologics, such as rituximab, belimumab, abatacept, and tocilizumab, may be continued through conception. Leflunomide, methotrexate, thalidomide, mycophenolate mofetil, and cyclophosphamide are contraindicated during pregnancy. There are insufficient data to conclude the safety of the small molecules during pregnancy and lactation; therefore, they should be discontinued prior to conception. With good disease control and a team approach with both a rheumatology provider and, if possible, a maternal-fetal-medicine provider, many RA, SLE, and APS patients can anticipate a good pregnancy outcome.

CLINICS CARE POINTS

- Women with RA and SLE should have their disease under good control on pregnancy-compatible medications and observed for several months prior to attempting conception.
- Methotrexate, thalidomide, leflunomide, mycophenolate mofetil, and cyclophosphamide are teratogenic, and these medications should be avoided in pregnant and lactating women.
- Women with SLE should be encouraged to take hydroxychloroquine during pregnancy because this medication improves outcomes for mother and fetus.
- Women with APS (obstetric and clotting manifestations) should be anticoagulated during pregnancy.

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