Rheumatoid Arthritis and Pregnancy: Managing Disease Activity and Fertility Concerns

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Abstract

Rheumatoid arthritis (RA) is a systemic autoimmune disease that more commonly affects women, including many women during the childbearing years. This can make management challenging for practitioners involved in the care of these patients. This review article will discuss the available data and expert recommendations pertaining to women with RA who are pregnant or planning pregnancy. Herein, we will consider pregnancy complications associated with RA, the benefits of maintaining low disease activity prior to conception and throughout pregnancy, flare management during pregnancy, ensuring pregnancy-compatible medications to treat RA, and the reduced rates of fertility in patients with RA. While research in this area has greatly expanded over the past decade, it continues to be an area where more research is needed to best support women with RA as they navigate pregnancy.

Keywords

- rheumatoid arthritis
- pregnancy
- infertility

Rheumatoid arthritis (RA) is a systemic autoimmune disease that is defined by its impact on the musculoskeletal system, where it causes inflammatory arthritis, joint pain, and often joint damage. RA can also affect other body systems, such as the lungs, heart, and eyes. As such, the systemic impact of RA, beyond just the joints, must be considered in the overall management of individuals with RA. Notably, RA affects women approximately three times more often than men, and disease onset for women commonly occurs during childbearing years.[1,2] In addition, many of the medications typically used to treat RA can have unwanted effects on pregnancy. Given this, pregnancy planning and perinatal care often must be considered in the disease management and treatment of women with RA. In this review, we will discuss disease considerations and disease management when planning pregnancy and throughout the peripartum period. We will also review what is known about the challenges of infertility or subfertility in women with RA.

Rheumatoid Arthritis Disease Overview

RA is the most common form of autoimmune arthritis, with an estimated prevalence of 0.5 to 1% in the general population.[1] While the pathogenesis of RA is incompletely understood, it has well-established genetic, clinical, and environmental risk factors, which come together in different patterns to trigger a wide spectrum of nonresolving immune dysregulation that can ultimately lead to the development of disease.[3] RA can also be characterized by disease-specific autoantibodies, including rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). These antibodies are used to distinguish "seropositive" and "seronegative" forms of RA, and there is ongoing debate regarding the direct impact of these antibodies in the pathogenesis of RA.[4]

As with many autoimmune diseases, RA impacts women more often than men.[1,2] There are also several risk factors for RA that have a sex-specific effect on women, including a lower risk of developing RA with oral contraceptive pill use and a higher risk of developing RA during the postpartum period following childbirth.[5–8] Overall, RA incidence is two to three times more common in women than in men, but it is notable that in individuals less than 40 years old, which includes premenopausal-aged women, the sex discrepancy is higher, with women being affected four to five times more often than men.

With this considerable prevalence of RA in premenopausal-aged women, pregnancy planning is a relatively common

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occurrence in the clinical management of RA, and this population requires unique considerations. Notably, RA pathogenesis involves a range of different immune cells, including T cells, B cells, neutrophils, and macrophages. Many of these cells are impacted by sex hormones and pregnancy (►**Fig. 1**). While it is not well established exactly how immune cell changes associated with pregnancy affect RA pathogenesis, it is likely that these changes play a central role in the pregnancy-associated disease activity changes which may lead to pregnancy complications that can be seen in women with RA and are discussed later.

Pregnancy Complications in Rheumatoid Arthritis

Women with RA have an increased risk for several pregnancy-related complications. As will be discussed in detail later, lower disease activity prior to conception and during pregnancy reduces these risks, but there is an overall estimated 1.5- to 2-fold increased risk of hypertensive complications in pregnancy, intrauterine fetal growth restriction leading to small-for-gestational-age (SGA) infants, preterm birth, and cesarean delivery, even after adjusting for parity, in women with RA.[9]

A study by Langen et al that examined 46 pregnancies in women with RA found that 28% were delivered prior to 37 weeks.[10] A separate study corroborated these findings, with an odds ratio of 1.48 for preterm birth in women with RA compared to women without RA.[11] This study additionally demonstrated significantly decreased placental weight in mothers with RA, on average 14 g lower, consistent with the occurrence of intrauterine growth restriction in this pregnancy population.[11]

In addition, a U.S. study by Aljary et al that included more than 6,000 RA pregnancies found an increased odds of 1.7-fold for preeclampsia risk in women with RA.[12] Similarly, a systematic review of eight studies and more than 10 million pregnancies found that women with RA were more likely to develop preeclampsia again with an odds ratio of 1.7.[13] Another study by Secher et al found that the odds of preeclampsia was 1.3-fold higher in women with RA, and although not significantly increased overall in this study, preeclampsia was significantly higher in RA women taking combination immunosuppressive therapy before and during pregnancy, which the authors suggested could be a potential surrogate for higher RA disease activity.[14] Due to the association of RA with preeclampsia risk, some experts suggest the consideration of low-dose aspirin for pregnant patients with RA to reduce this risk.

In addition to adverse outcomes related to pregnancy and delivery, women with RA also have higher rates of postpartum depression.[15,16] In a large population-based study including postpartum women from Danish, Finnish, and Swedish birth registries, women with RA who had no prior history of psychiatric disorders were more likely to have postpartum depression (hazard ratio [HR]: 1.65, 95% confidence interval [CI]: 1.09–2.48) and other postpartum psychiatric disorders (HR: 1.59, 95% CI: 1.13–2/24) compared to women without RA.[15]

Due to these increased risks for adverse pregnancy outcomes, rheumatologists often recommend that RA patients follow up with maternal–fetal medicine specialists for at least one visit during their prenatal care. Additionally, pregnant women with RA have an increased risk for thrombosis, with venous thromboembolism occurring up to two to four times more frequently than in healthy pregnant women, and this, along with screening for postpartum depression, should also be considered in the routine peripartum management of women with RA.[9]

Fetal Outcomes in Rheumatoid Arthritis

In addition to the maternal complications of pregnancy discussed earlier, there is also an increased risk of adverse fetal outcomes among pregnant women with RA. As

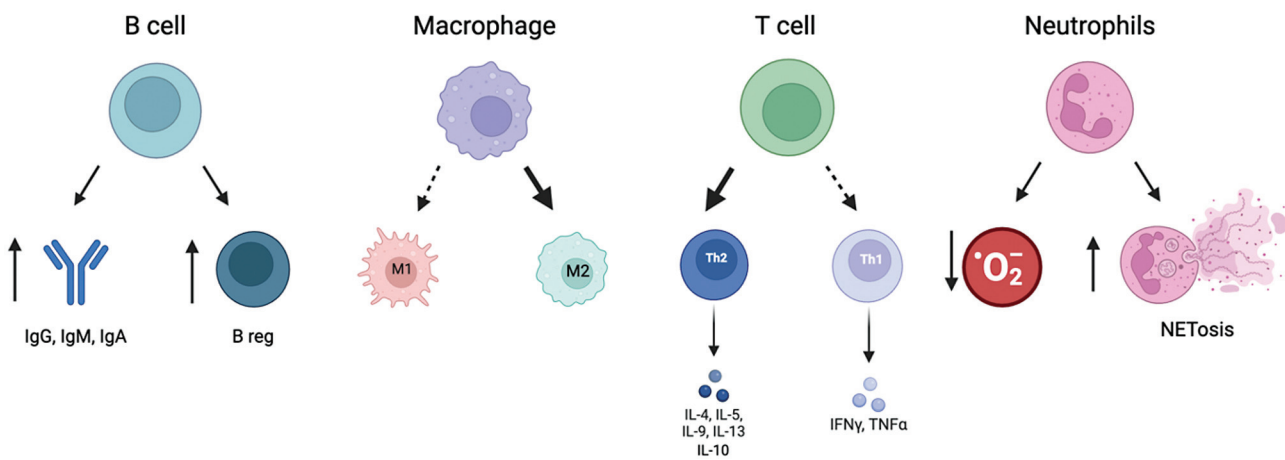

Fig. 1 Impact of pregnancy on immune cells. The figure depicts the cellular effects of pregnancy that may impact rheumatoid arthritis (RA) disease activity. Many of these changes, such as increased B regulatory cells and a shift from M1-like to M2-like macrophages, could contribute to improved RA disease activity in pregnancy. However, changes such as increased antibody production or increased neutrophil extracellular traps (NETosis) could contribute to the worsening of RA disease activity in pregnancy. Thickened arrow = increased production; dashed arrow = diverted away from.

mentioned earlier, women with RA have higher rates of preterm birth and SGA infants. Postnatally, babies born preterm, or SGA, have been found to have higher rates of cardiovascular disease and cardiometabolic disorders in childhood and adulthood.[17]

Another important consideration for fetal outcomes in mothers with RA is whether the mother has anti-SSA/SSB positivity. Approximately 5% of patients with RA have anti-SSA and/or SSB positivity.[18] The presence of these antibodies in the mother, notably at high levels, places the fetus at risk for the development of neonatal lupus syndrome including fetal heart block due to the transfer of antibodies across the placenta.[19] The overall rate of neonatal lupus syndrome with fetal heart block in anti-SSA-positive women is low (1–4% of seropositive mothers),[19] but if the fetus develops complete congenital heart block due to these antibodies, there is a high rate of perinatal mortality as well as short- and long-term morbidity for the baby.[9] As such, the presence of these antibodies in a pregnant woman does change the current recommendations for fetal monitoring during pregnancy as well as the recommendation for ECG in the baby postpartum.

The Impact of Disease Activity on RA Pregnancy Outcomes

Rheumatologists must weigh a number of clinical factors when deciding which treatment options would be most appropriate for an individual patient with RA. These can include the level of disease activity, disease severity, and comorbidities. When a woman with RA is considering pregnancy, these same factors must still be considered, but through a different lens that considers a goal to minimize adverse pregnancy outcomes for both the patient and the developing fetus. As discussed earlier, women with RA have higher rates of adverse pregnancy outcomes, including preterm birth, SGA infants, and preeclampsia,[10,11,14,20] but proactive disease management when planning pregnancy can reduce the chances of these unwanted outcomes.

An important consideration for women with RA who are planning pregnancy, and one that has been gaining wider recognition over the past several years, is the impact of disease activity on pregnancy outcomes.[21] There are a number of studies on RA pregnancy that examine the impact of disease activity, either at conception or during pregnancy, on obstetric outcomes and support a strong relationship between low RA disease activity and better pregnancy outcomes. In one prospective study of 440 pregnant women with RA from the United States and Canada, Bharti et al found that higher RA disease activity in early pregnancy was independently associated with preterm birth and SGA infants.[22] This study used only patient-reported measures of disease activity, including health assessment questionnaire (HAQ), patient global score, and pain score, rather than joint examination-based disease activity measures. However, in another prospective study by Harris et al, both patient-reported and physician assessment of higher disease activity correlated with a risk of preterm birth.[23] In this study, for each one-unit increase in HAQ, the rate of preterm birth was increased sixfold and gestational age at delivery was shortened by 1.5 weeks. Higher physician global assessment in pregnancy also correlated with caesarian section delivery and SGA infants.

Furthermore, Gerardi et al retrospectively collected disease activity from 73 pregnant RA patients, and found that active disease in the first trimester, measured by elevated CRP or DAS28-CRP, was again significantly associated with the risk of preterm delivery.[24] The study also found that having an RA flare *during* pregnancy was associated with higher rates of preterm birth. Similarly, in one of the largest studies to evaluate pregnancy outcomes and disease activity in RA patients, Hellgren et al collected data from 1,739 RA pregnancies and 17,390 control pregnancies using a prospective registry of Swedish and Danish women.[25] Multivariable analyses demonstrated that elevated DAS28-CRP (modified for pregnancy) during pregnancy was significantly associated with an increased risk of preterm birth (OR: 1.92, 95% CI: 1.56–2.35) and SGA (OR: 1.93, 95% CI: 1.45–2.57). Similarly, HAQ $\geq$1 increased the odds of SGA threefold. Interestingly, while the use of oral corticosteroids during pregnancy was associated with preterm birth in this study, this relationship was not significant when accounting for RA disease activity: a finding that highlights the importance of considering RA disease activity when interpreting the impact of RA treatments on pregnancy outcomes. For example, it could be that studies reporting an increase in preterm birth associated with corticosteroid use in women with RA[26,27] may confound the results by actually identifying the effects of RA disease activity. Similar considerations should also be made for biologic disease-modifying antirheumatic drugs (DMARDs) given that RA flares in pregnant women have been found to occur most often in women who discontinued biologic DMARDs at the time of conception.[24]

Given the strength of the relationship between RA disease activity and adverse pregnancy outcomes, the 2020 American College of Rheumatology (ACR) Reproductive Health Guidelines suggest that women with RA try to conceive during periods of low disease activity to lower the risks of adverse pregnancy outcomes.[28] These guidelines recommend the use of pregnancy-compatible nonbiologic or biologic DMARDs as necessary to achieve quiescence prior to and during pregnancy. Although the exact biologic mechanism by which increases in RA disease activity could contribute to poor pregnancy outcomes is not entirely clear, several adverse pregnancy outcomes are rooted in systemic inflammation, such as preeclampsia or vascular insufficiency due to endothelial abnormality, and may therefore be driven by the systemic inflammation associated with active RA.

Disease Monitoring during Pregnancy

Routine monitoring of RA in a pregnant patient can be complicated, making clinical evaluation of the disease difficult to accurately measure in a reproducible fashion. Commonly experienced symptoms in a routine pregnancy can include decreased mobility, edema, and joint pain, which can obscure or mimic true disease activity. When this was

examined by de Man et al, it was shown that healthy pregnant women without autoimmune disease answered "with some difficulty" or "with much difficulty" to several questions assessing functioning during pregnancy, demonstrating the relative unreliability of these types of questions in measuring disease activity for patients with RA during pregnancy.[29] These types of questions are included in the HAQ that assesses the degree of daily functioning limitations from RA. For example, some of these questions on the HAQ include "bending down to pick up clothing from the floor" or "getting in and out of a car," which would be expected to become increasingly difficult over the course of pregnancy even in individuals without RA.

In addition to physical manifestations of pregnancy that can confuse the clinical picture, there are also changes in laboratory values that can confound the clinical assessment. A study completed to assess the utility of scoring metrics for rheumatologic disease in pregnant RA patients demonstrated a statistically significant increase in ESR between the first and third trimesters as well as during pregnancy and the postpartum period.[29] CRP levels were also found to be slightly elevated during pregnancy; however, they did not continue to increase as pregnancy progressed.[29] Although edema and joint pain do frequently occur in pregnant patients, there was no evidence of an increased swollen joint count in healthy pregnant patients assessed during this study. In the same study, the disease activity scale of 28 joints (DAS28), which is commonly used to assess RA disease activity, was influenced by pregnancy. However, this study found that a modified DAS28-CRP, which did not include the global health assessment, had the best performance in pregnant RA patients.

A more recent study by Raine et al used musculoskeletal ultrasound to assess RA disease activity in pregnant and nonpregnant women with RA.[30] They also found that a modified DAS28-CRP, which included only three instead of the usual four variables, performed well in pregnant RA patients. In this study, they found significant correlations between the modified DAS28-CRP and power Doppler scores of joint inflammation throughout pregnancy and in the postpartum period, confirming that this assessment tool is both sensitive and specific for active RA during pregnancy.

Flare Management during Pregnancy

It was previously believed that a vast majority of patients with RA would go into disease remission during pregnancy. Due to this expectation, many patients had their RA therapy dramatically modified or even stopped during pregnancy, which resulted in poor disease management and more flares during pregnancy. With newer and more rigorous studies that include objective measures of RA disease activity, it is now demonstrated that approximately half of women with RA experience disease remission or low disease activity during their pregnancy.[31,32] This leaves a modest proportion of women who will experience disease flare or moderate-to-severe disease activity during pregnancy.[9,33]

There has been evidence to suggest that good RA disease control prior to conception reduces the chances of having an RA flare during pregnancy. de Man et al found that women with low disease activity during the first trimester remained with low disease activity throughout pregnancy.[32] One study by van den Brandt et al found that RA flares during the course of pregnancy were preceded by higher markers of disease activity and elevated CRP in early pregnancy. Not surprisingly, discontinuation of disease-modifying agents such as tumor necrosis alpha inhibitors (TNFis) in early pregnancy also predicted higher disease activity later in the course of pregnancy.[34]

Appropriate disease control during pregnancy and effective management of flares, if they occur, is paramount in the management of RA pregnancies. When flares do occur during pregnancy, there are safe options for management, including the following. Frequently, low doses of steroids are used for rapid symptom relief and control of disease activity. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also sometimes used during pregnancy, but have potential risks as discussed later. For patients with severe and refractory disease before or during pregnancy, there should be consideration for continuation or new initiation of pregnancy-compatible DMARDs, TNFis, or rituximab.[35,36]

RA Medication Use in Pregnancy

Since RA pregnancy outcomes improve with better RA disease control, knowledge of RA medication safety is paramount for rheumatologists who care for these patients. Older cohort studies reported on the use of only a limited number of medications during RA pregnancy and perhaps not surprisingly, there was a high rate of medication discontinuation in the first trimester.[37,38] However, there is now guidance available for the use of both nonbiologic and biologic DMARDs during pregnancy with the 2020 ACR Reproductive Health Guidelines.[28] There are a number of helpful resources detailing the risks of antirheumatic drugs in pregnancy,[39–44] and we will summarize important pregnancy considerations for medications commonly used in patients with RA later and in ►**Fig. 2**.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs or cyclooxygenase inhibitors, such as ibuprofen, should likely be avoided for individuals planning pregnancy and during pregnancy. One study suggested an increased time to conception for RA patients using NSAIDs.[45] It is suspected that inhibition of cyclooxygenase may interfere with ovulatory processes and therefore may contribute to an inability to conceive.[46] Some studies have associated ibuprofen use with early pregnancy loss, although this has not been clearly replicated.[47] In addition, second-trimester and third-trimester exposure has been linked to an increased risk of oligohydramnios and premature closure of the ductus arteriosus, respectively.[48–50] With that, in 2020, the U.S. Food and Drug Administration (FDA) issued a warning that expectant mothers should avoid using NSAIDs after 20 weeks of gestation (i.e., the second half of pregnancy).

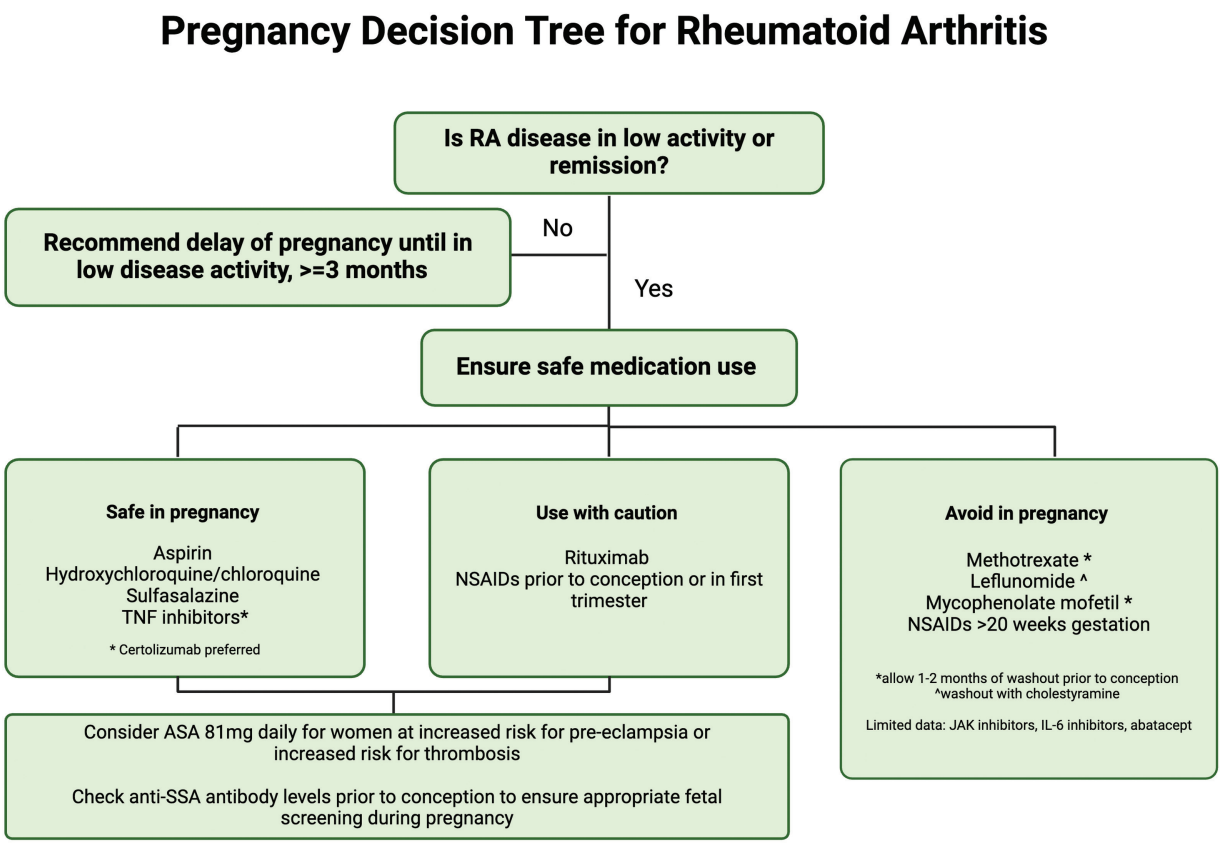

Fig. 2 Pregnancy decision tree for medication management in rheumatoid arthritis patients.

Corticosteroids

Use of nonfluorinated corticosteroids, such as prednisone and prednisolone, at lower doses (<10 mg/day), is generally considered safe in pregnancy. Ninety percent of these drugs are metabolized by the enzyme placental dehydrogenase, resulting in a small exposure for the fetus.[51] Use of steroids, particularly in higher doses (>20 mg/day) in pregnancy, may increase the risk of congenital malformation (e.g., cleft lip/palate), hypertensive disorders during pregnancy, or premature rupture of membranes.[52]

Hydroxychloroquine and Chloroquine

Hydroxychloroquine and chloroquine are generally considered safe in pregnancy, and perhaps even beneficial for some pregnancies in women with autoimmune disease. For example, hydroxychloroquine reduced the risk of recurrent congenital heart block in women who had a previous child with congenital heart block[53]; it reduced the risk of preeclampsia in women with autoimmune disease[54]; and in systemic lupus erythematosus (SLE), where higher disease activity in pregnancy is also associated with adverse pregnancy outcomes, the withdrawal of hydroxychloroquine at conception was linked to subsequent higher SLE disease activity.[55]

In 2021, a large database study suggested a possible association between hydroxychloroquine use and the risk of congenital malformation at a dose of ≥400 mg/day.[56] The study found the risk of malformation to be 54.8 per 1,000 children with first-trimester exposure versus 35.3 per 1,000 children with unexposed pregnancies (RR: 0.95, 95% CI: 0.60–1.50). Notably, no specific pattern of abnormalities was noted, and the study lacked the ability to detect other possible contributing factors. These results have led to a change in some summary statements about hydroxychloroquine use in pregnancy. However, when considering the full scope of data available regarding hydroxychloroquine use in pregnancy, including several recent studies in SLE and RA that found no adverse pregnancy effect,[54,57–61] the 2020 ACR Reproductive Health Guidelines[28] and comments from experts in reproductive health care in rheumatology[62] conclude that hydroxychloroquine is compatible with pregnancy, particularly at the doses typically used in pregnant rheumatology patients, which are not recommended to exceed 400 mg/day.

Sulfasalazine

Recommendations from both rheumatology and gastroenterology guidelines indicate that sulfasalazine can be safely used in pregnancy.[28,63,64] While cases of neural tube defects, macroglossia, and cleft lip/palate have been reported in pregnant women taking sulfasalazine,[39] these findings have not been replicated in larger studies, and the use of sulfasalazine continues to be considered compatible with pregnancy. Gastroenterology guidelines do suggest supplementation with folic acid during pregnancy (2–5 mg/day) as this pathway may be altered by the use of the drug.

Methotrexate

Methotrexate is a folic acid inhibitor and abortifacient which is contraindicated in pregnancy and has been associated with

pregnancy loss and/or fetal malformation.[65,66] European Alliance of Associations for Rheumatology (EULAR) and ACR guidelines recommend avoiding methotrexate during pregnancy and 1 to 3 months preceding conception.[28,64] One large retrospective Italian study reported that methotrexate use at any time prior to conception had a higher risk of subsequent fetal loss; however, the study did not control for disease activity and the patients with methotrexate exposure prior to pregnancy took higher doses of prednisone than the matched RA controls[67] perhaps indicating more active disease.

Leflunomide

It is recommended to avoid leflunomide, a pyrimidine synthesis inhibitor, during pregnancy. Studies have not shown consistent teratogenicity in humans with a washout of the drug prior to or after conception.[64,68,69] The drug can harbor within the body for as long as 2 years after ingestion. For a woman desiring pregnancy with prior leflunomide use, cholestyramine washout should be completed which entails administration of 8 g of cholestyramine three times daily for a duration of 11 days, although the duration may be modified at the discretion of the clinician based on clinical or lab assessment. Low serum drug levels should also be confirmed prior to conception.

Azathioprine

Azathioprine (AZA) and 6-mercaptopurine (6-MP) have been used extensively for inflammatory bowel disease (IBD) management in pregnant patients. Although this medication is not considered the first line in the management of RA, it is sometimes used in patients with prior intolerances to other medications or contraindications due to organ dysfunction. In patients with IBD, there is no association with the risk of congenital malformations or adverse pregnancy outcomes. In one Danish registry, it was found that women who were exposed to AZA and 6-MP had an association with a higher risk of preterm birth and congenital abnormalities. However, in multivariable analysis, the association was found to more likely be due to the disease process and not the drug.[70] While uncommon, the FDA has recently added a new warning to AZA and 6-MP for the potential risk of intrahepatic cholestasis of pregnancy.

Tumor Necrosis Alpha Inhibitors

In prior studies, TNFis have been detected in fetal cord blood samples and therefore the question has been raised concerning fetal exposure.[71] Yet, TNFis have not been associated with fetal loss or congenital abnormalities.[28,39,64] Certolizumab, a PEGylated TNFi, notably lacks an antibody Fc portion, which is necessary to cross the placenta and enter fetal circulation in significant amounts. Other TNFis that do contain an Fc portion and are not PEGylated more avidly cross the placenta as the pregnancy progresses, especially during the third trimester. Some guidelines suggest considering discontinuation of TNFis, other than certolizumab, in the late second or third trimester to avoid significant fetal exposure and potential fetal immunosuppression. However, this risk must be considered in the context of the importance of RA disease control during pregnancy, as discussed earlier.[28,43] When using TNFi in pregnant patients, a detailed discussion on risks and benefits and shared decision-making can aid in disease management during pregnancy.

Rituximab

Rituximab is a monoclonal antibody that targets CD20 located on some B cells. Recommendations for the use of rituximab in pregnancy have evolved over recent years. Previous guidelines suggested stopping the drug up to 1 year prior to conception. However, the 2020 ACR Reproductive Health Guidelines state that a woman of reproductive potential can continue rituximab until conception, and during pregnancy for life-threatening disease.[28] Since rituximab is a monoclonal antibody, the passage across the placenta elevates in the third trimester increasing fetal exposure. No clear pattern of teratogenicity has been reported with the use of rituximab during pregnancy, but care must be taken after delivery to avoid live vaccines for the infant for 6 months postpartum.[72] Again, shared decision-making between patient and provider should be employed when considering the use of rituximab during pregnancy.

Reduced Rates of Fertility in Patients with RA

Another important aspect to consider in pregnancy planning for women with RA is the increased rates of infertility or subfertility in this population. More than half of women with RA report having fewer children than they had originally planned.[73]

While infertility can be defined by an inability to conceive naturally, subfertility is a reduced level of fertility, but still with the potential to conceive naturally. Subfertility is often defined by a prolonged time to conception, usually more than 12 months of attempting to conceive without success. In the Pregnancy in RA Patients (PARA) study, which is an observational nationwide study in the Netherlands, 42% of women with RA report that their time to pregnancy was more than 12 months.[45] Several factors associated with this longer duration of conception were specifically related to RA, including RA disease activity, preconception NSAID use, and a dose-dependent relationship with prednisone use. Regarding disease activity, 67% of women with high disease activity (DAS28-CRP > 5.1) and 43% of women with moderate disease activity (DAS28-CRP: 3.1–5.1) reported time to pregnancy >12 months.[45] These findings further support the importance of planning pregnancy when RA disease activity is low or in remission.

The exact etiology of increased subfertility rates in women with RA remains unclear, but it is likely multifactorial. For example, some women with RA may delay pregnancy due to disease activity or teratogenic medication use. There can be psychosocial stressors that contribute to subfertility in RA as well, such as concerns about disease flaring during or after pregnancy, concerns about functional limitations in caring for a child, and/or stress about the heritability of RA to their offspring.[74] RA can also have a negative impact on sexual

activity for some women,[75] with limitations that could be due to pain, vaginal dryness, fatigue, depression, or other factors. The higher rate of subfertility in women with high disease activity also raises the question of whether disease-associated immune dysregulation or more generalized systemic inflammation could have a direct effect on subfertility. One study found higher rates of ACPA positivity in women with subfertility, but this was not an independent risk factor for subfertility after accounting for other variables.[45] More studies are needed to better understand the contribution of RA-specific immune dysregulation on conception.

Given these challenges to conceive, women with RA may choose to pursue assisted reproductive technologies (ART), such as ovarian stimulation, in vitro fertilization, or embryo transfer. ART is generally considered safe for women with RA. Notably, the 2020 ACR Reproductive Health Guidelines strongly recommend moving forward with ART if needed in women with uncomplicated autoimmune disease who are in low disease activity or remission and do not have antiphospholipid antibodies.[76] Conversely, it is recommended that ART be deferred in women with moderate-to-high disease activity. It is also notable that women with RA may have lower rates of success with ART. Nørgård et al found that embryo transfer in women with RA was less likely to result in live birth compared to women without RA (OR: 0.78, 95% CI: 0.65–0.92).[77] While more research is needed in this area, it remains an important option for some patients with RA experiencing fertility challenges.

Knowledge Gaps and Research Needs

Pregnancy planning and management is a vital component of comprehensive rheumatologic care for many patients with RA. As highlighted in this review, various aspects require further research to ensure optimal care of young women with RA. We believe the following areas are knowledge gaps of particular importance that need to be addressed in research studies going forward.

1. *Safety of biologic medications in RA*: There are limitations to the types of studies that can be done to evaluate the safety profile of biological medications during pregnancy in RA; yet, additional data that can support the timing and types of biologics that can be used safely in pregnancy could greatly inform and improve the clinical management for these patients.
2. *Changes in RA-associated immune dysregulation during pregnancy*: There are a range of immune changes that occur in normal pregnancy, and there is a range of immune dysregulation characteristic of RA. Yet, little is known about how RA-specific immune dysfunction changes during pregnancy in women with RA or whether these baseline immune deficits contribute to some of the adverse pregnancy outcomes that occur more often in women with RA. Importantly, such understanding could lead to personalized approaches to pregnancy management in women with RA.
3. *Better biomarkers to predict adverse pregnancy outcomes*: Despite the increased rates of adverse pregnancy outcomes in RA, there is a lack of biomarkers that can reliably predict these outcomes. Such biomarkers could dramatically change clinical approaches to monitoring and medical management.
4. *Education of providers and patients*: Patient counseling by rheumatologists is a key component of optimal pregnancy planning that can improve adverse pregnancy outcomes for patients with RA. However, not all rheumatologists are sure of current practice guidelines or comfortable with these types of discussions. Large-scale as well as local efforts to improve the education of providers and patients could have positive impacts on the management of RA patients throughout pregnancy and the postpartum period.

Conclusions/Summary

RA presents unique challenges for women of childbearing potential, particularly regarding pregnancy planning and perinatal care. The systemic nature of RA, combined with the potential impact of various medications on pregnancy, necessitates careful and individualized management strategies. Women with RA often face subfertility, and for these patients ART may be appropriate if desired by the patient. It is important to adjust medications appropriately and maintain low disease activity before and during pregnancy, to minimize adverse pregnancy outcomes, which can be increased in women with RA. Collaboration between rheumatologists and obstetric providers can optimize care and improve both maternal and fetal outcomes. Moving forward, continued research is essential to better understand the mechanisms by which RA and its treatments impact pregnancy and to develop more refined guidelines and therapeutic approaches for managing this complex interplay.

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Conflict of Interest
The authors have no relevant disclosures or conflict of interest.

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