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Review

Targeted Treatment Strategies and Medication Management for Rheumatic Diseases During Pregnancy and Lactation: A Comprehensive Review

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Abstract

Pregnancy in women with immune-mediated rheumatic diseases poses significant challenges, including risks for both maternal and fetal adverse outcomes. This comprehensive review addresses the management of immune-mediated rheumatic diseases during pregnancy and lactation, focusing on medication strategies and treatment protocols to optimize pregnancy outcomes. The continuation or cessation of medications, including biologics and immunosuppressants, is a critical factor in managing disease activity while minimizing fetal risks. The review also explores the use of assisted reproductive technologies, fertility preservation methods for patients undergoing gonadotoxic treatments, and hormone replacement therapy. Additionally, the management of pregnancy in patients with conditions such as systemic lupus erythematosus, antiphospholipid syndrome, and Sjögren's syndrome is discussed. Key recommendations from the American College of Rheumatology 2020 guidelines are provided, outlining best practices for medication use during pre-conception, pregnancy, and postpartum care. The review underscores the importance of individualized treatment plans and interdisciplinary collaboration to ensure favorable outcomes for both mother and child.

Keywords: Immune-mediated rheumatic diseases, pregnancy, preconception counseling, medication safety, autoimmune disorders in pregnancy

INTRODUCTION

Pregnancy in women with immune-mediated rheumatic diseases (IRD) can lead to serious maternal or fetal adverse outcomes (1). The prognosis of the disease is influenced by multiple factors, including the diagnosis, extent of disease activity and damage, treatments, and the presence of anti-Ro/SSA, anti-La/SSB, and antiphospholipid (aPL) antibodies (1-4). Although pregnancy may not exacerbate all inflammatory rheumatic diseases, it can aggravate some. Pre-pregnancy counseling is necessary to assess and reduce the risks of adverse pregnancy outcomes for each patient. Some medications need to be adjusted before, during, and/or after pregnancy. Postpartum disease flare-ups should be closely monitored (1-4).

Fertility rates in individuals with IRD are significantly lower than in the general population, largely influenced by both the underlying disease and the medications administered (5,6). Cyclophosphamide (CYC), in particular, is a leading agent associated with gonadal failure (7). For some patients, pregnancy may be contraindicated either due to active disease or the use of teratogenic medications, while for others, severe organ dysfunction with elevated maternal mortality risks may preclude pregnancy. In such cases, it is crucial to counsel patients on appropriate contraception methods, strategies to preserve gonadal function, and the potential use of assisted reproductive technologies.

Patients with IRD should conceive during periods of disease remission to reduce the risk of disease flare-ups during pregnancy, but the exact duration of this remission period remains a topic of debate (8). For patients with well-controlled disease, no extra-articular symptoms, and no organ dysfunction, three months of disease remission with stable pregnancy-safe medications is sufficient. However, in conditions such as systemic lupus erythematosus (SLE), the risk of disease flare-ups during pregnancy increases in patients who have had

active disease within the 4-6 months prior to conception, those who have active disease at the time of conception, and those who discontinue hydroxychloroquine (even if the disease is in remission) (9). The European League Against Rheumatism (EULAR) recommends a 6-12 month period of disease remission before pregnancy, depending on various maternal factors such as the degree of organ damage, if present (10).

A systematic review combined with a meta-analysis has shown that the disease activity of rheumatoid arthritis (RA) improves by 60% during pregnancy but worsens again by 50% postpartum (11). Psoriatic arthritis (PsA) data during pregnancy are relatively limited. However, available studies indicate that approximately one-third of cases remain stable throughout pregnancy, one-third experience disease exacerbation, and another one-third show improvement (12). The data on SpA is equally controversial, with very variable courses of disease (ranging from stable to exacerbated) reported during pregnancy. A recent study reported that spondyloarthritis (SpA) appears to be linked with an elevated risk of pregnancy complications, including preterm birth, delivering small for gestational age infants, preeclampsia, and an increased likelihood of caesarean section (13). During pregnancy, disease flare-ups may occur in about a quarter of SLE patients (9,14). In patients with antiphospholipid syndrome (APLS), the risk of thrombosis increases 2 to 10 times during pregnancy and the postpartum period (4,15). Women with Sjögren's syndrome are at a higher risk of experiencing complications during pregnancy. Research indicates a significant incidence of adverse fetal outcomes in these patients, including an increased risk of miscarriage, preterm birth, and neonatal complications such as congenital heart block due to the presence of maternal autoantibodies (16). In systemic sclerosis, the disease generally remains stable in most pregnancies (17). Women with pulmonary hypertension should avoid pregnancy on account of the high maternal mortality risk. The adverse pregnancy outcomes in various types of IRD are given in **Table 1.**

Anti-Ro (SS-A) and Anti-La (SS-B) autoantibodies cross the placental barrier through active transplacental transfer at the 16th week of pregnancy and reach to a maximum titer at 18-24 weeks of pregnancy (18). The interaction of these antibodies' Fc region with neonatal Fc receptors on syncytiotrophoblast cells can lead to a number of adverse effects for the fetus and newborn (19). Cardiac manifestations associated with autoimmune conditions may include congenital heart block (CHB), endocardial fibroelastosis, and dilated cardiomyopathy, which are referred to as neonatal lupus syndrome (20). In mothers who had AVB in previous pregnancies, this risk of recurrent CHB rises to around 17%. During vulnerable cardiac development stages (usually between week 16 and 24 of gestation) this may not just lead to myocarditis, cardiomyopathy and irreversible fibrotic remodeling of the AV node but can also lead to cutaneous signs of disease, hepatic damage and pancytopenias in the neonate. Since maternal anti-SSA/Ro and anti-La (SS-B) antibodies are cleared from the infant's circulation, most of these symptoms resolve within the first 6-9 months of life (18-20).

Persistent positivity for aPL antibodies, such as B2-glycoprotein, anticardiolipin, and lupus anticoagulant, can lead to specific adverse pregnancy outcomes (21,22). These include one or more unexplained deaths of a morphologically normal fetus at or beyond 10 weeks of gestation, preterm birth before 34 weeks due to eclampsia, preeclampsia, or placental insufficiency, and three or more consecutive spontaneous pregnancy losses before 10 weeks of gestation, unexplained by chromosomal abnormalities, maternal anatomical or hormonal factors. Maternal thrombosis, which characterizes antiphospholipid syndrome, may also develop. Among these, lupus anticoagulant is the strongest antibody linked to adverse pregnancy outcomes. The concurrent presence of all three antibodies during pregnancy constitutes the highest risk (4,15,21,22).

The presence of organ dysfunction as a complication of inflammatory rheumatic diseases (IRD) significantly increases the likelihood of maternal and fetal morbidity and mortality, and therefore, it should be discussed during pregnancy planning. If a patient has active disease and organ dysfunction, conception should be postponed until disease remission and the improvement

Table 1. Adverse pregnancy outcomes in various types of IRD

Disease	Adverse Pregnancy Outcomes	Risk Factors
Rheumatoid Arthritis	Pregnancy-related hypertension, intrauterine growth restriction, preterm birth, small-for-gestational-age infants, low birth weight	Active disease during conception and pregnancy
Axial Spondyloarthritis	Increased risk of preterm birth, small-for-gestational-age infants, emergency or elective cesarean section	Active disease during conception and pregnancy
Systemic Lupus Erythematosus, Sjögren Syndrome , Antiphospholipid Syndrome	Pregnancy loss, pregnancy-related hypertension, intrauterine growth restriction, preterm birth, small-for-gestational-age infants, low birth weight, cesarean section, congenital heart block, neonatal lupus	Active disease, hypertension, lupus nephritis, antiphospholipid antibodies (triple positivity for anticardiolipin, B2-glycoprotein I, lupus anticoagulant), anti-SSA/Ro, anti-SSB/La antibodies
Scleroderma	Increased risk of preterm birth, intrauterine growth restriction	Presence of rapidly progressive diffuse disease

or normalization of organ function are achieved. For instance, the presence of active lupus nephritis at the time of conception is a strong indicator of adverse maternal and fetal outcomes (23). However, the risks associated with kidney disease are not exclusive to patients with rheumatic diseases. Prospective studies involving women with chronic kidney disease (CKD) from various etiologies have shown an increased risk of preeclampsia, preterm birth, small-for-gestational-age infants, and higher neonatal and perinatal risks (24). Additionally, women with advanced CKD (stages 4-5) prior to pregnancy are at risk of accelerated renal function decline, which may progress to end-stage renal disease and necessitate kidney replacement therapy during pregnancy or in the postpartum period (24,25).

Other relative contraindications for pregnancies associated with IRD that necessitate multidisciplinary consultation and management include pulmonary hypertension unresponsive to treatment, severe interstitial lung disease, advanced heart failure, and a history of severe gestational hypertensive disorders. For these reasons, IRD patients require careful monitoring by a multidisciplinary team regarding contraception, pregnancy, and breastfeeding (including medications), assisted reproductive technologies (ART), fertility preservation, and hormone replacement therapy (HRT). To address this need, the American College of Rheumatology (ACR) published the latest guidelines in 2020 on the management of reproductive health in patients with rheumatic and musculoskeletal diseases (10). A summary of this guideline is provided below.

ACR 2020 RECOMMENDATIONS (10)

Contraception

For women with IRD (immune-mediated rheumatic diseases) should prioritize highly effective methods like IUDs or subdermal progestin implants. Emergency contraception, such as levonorgestrel, is recommended for all patients, including those with SLE or positive aPL antibodies, due to the lower risk compared to unplanned pregnancy (10).

For SLE patients with stable or low disease activity and negative aPL antibodies, IUDs and progestin implants are preferred, while estrogen-containing methods should be avoided due to thrombosis risk. In SLE patients with moderate or severe disease or nephritis, progestin-only or IUD contraceptives are advised, avoiding estrogen-containing methods.

Women with positive aPL antibodies should avoid combined estrogen-progestin contraceptives due to the increased thromboembolism risk, favoring IUDs or progestin-only options. Long-term use of depot medroxyprogesterone acetate (DMPA) is discouraged for women at risk of osteoporosis. For those on mycophenolate mofetil/mycophenolic acid (MMF), IUDs or combined contraceptive methods are recommended to counter the potential reduced efficacy of oral contraceptives (10).

Assisted Reproductive Technology (ART)

Assisted reproductive technology (ART) is strongly recommended for women with IRD who have stable or remission disease, are aPL antibody-negative, and are on pregnancy-compatible medications (10,26,27). However, for patients with moderate to severe disease activity, postponing ART is recommended due to the increased pregnancy risks associated with active IRD. A 6-month period of stable, inactive, or low-level disease is advised for pregnancy planning, though individual factors may vary.

In SLE patients, there is concern that ovarian stimulation might exacerbate active disease, but increasing prednisone during ART procedures is generally not recommended. Instead, treatment should be based on disease monitoring.

For subfertile patients with stable disease, asymptomatic aPL antibodies, obstetric APS, or treated thrombotic APS, ART with anticoagulation is conditionally recommended:

- For asymptomatic aPL antibody-positive patients, prophylactic anticoagulation with heparin or LMWH is recommended during ART.
- For women with obstetric APS, prophylactic anticoagulation is recommended, and for those with thrombotic APS, therapeutic anticoagulation is advised during ART.

Embryo and Oocyte Cryopreservation

For patients with stable conditions undergoing ovarian stimulation for oocyte or embryo cryopreservation, continuing necessary immunosuppressive or biological therapies is strongly recommended, except for CYC, which affects maturing follicles.

Fertility Preservation in Women with IRD Treated with CYC

In premenopausal women receiving monthly intravenous CYC, co-therapy with gonadotropin-releasing hormone agonists is conditionally recommended to prevent primary ovarian failure.

Fertility Preservation in Men with IRD Treated with CYC

Testosterone co-therapy is conditionally not recommended for men on CYC as it has been ineffective in preserving fertility during chemotherapy. Sperm cryopreservation before treatment is strongly recommended for men undergoing CYC therapy who wish to preserve fertility.

Hormone Replacement Therapy (HRT)

- For women with SLE who are aPL-negative and have

severe vasomotor symptoms, HRT is conditionally recommended if there are no contraindications.
•In asymptomatic women with aPL, HRT is conditionally not recommended.
•HRT is strongly discouraged for women with obstetric and/or thrombotic APS.
•In APS patients on anticoagulation or those previously aPL-positive but now negative, HRT is conditionally not recommended. However, for women with a history of aPL positivity but no clinical APS history, HRT may be conditionally considered. If the goal of ovarian stimulation is to induce oocyte development for oocyte or embryo cryopreservation, it is strongly recommended to continue necessary immunosuppressive and/or biological therapies in patients with stable conditions, with the exception of CYC, which directly affects maturing follicles.

Pre-Pregnancy Counseling and Medication Adjustments

Women with IRD who are planning a pregnancy should receive counseling on how to improve maternal and fetal outcomes, as supported by numerous studies. These women should be followed closely by specialists in obstetrics-gynecology, maternal-fetal medicine, and neonatology as needed.

For women on medications incompatible with pregnancy, transitioning to pregnancy-safe drugs is recommended, allowing enough time to evaluate the effectiveness and tolerability of the new medication. Pregnant women with active IRD requiring treatment should use pregnancy-compatible steroid-sparing agents, as both active disease and prolonged high-dose glucocorticoids pose risks to the mother and fetus.

For women with SLE or related conditions (e.g., Sjögren's syndrome, systemic sclerosis, rheumatoid arthritis), testing for anti-Ro/SSA and anti-La/SSB antibodies before pregnancy or early in pregnancy is recommended. Repeating these tests during pregnancy is not advised due to the stability of antibody titers.

Patients with Scleroderma Renal Crisis (SRC)

In cases of active SRC during pregnancy, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are strongly recommended, as the risk of untreated SRC outweighs the risks associated with these medications during pregnancy (28,29).

Patients with SLE

Women with SLE planning to become pregnant, or who are already pregnant, should be tested for lupus anticoagulant (LA), anticardiolipin (aCL), and anti-B2 glycoprotein I antibodies before or early in pregnancy, without repeating the tests during pregnancy. Hydroxychloroquine (HCQ) should be taken during pregnancy by all women with SLE, if possible (30). If already on HCQ, continuation is strongly recommended, and if not, starting HCQ is conditionally advised, barring contraindications. Additionally, starting low-dose aspirin (81 or 100 mg daily) from the first trimester is conditionally recommended (10). As active disease impacts maternal and pregnancy outcomes, monitoring SLE disease activity every three months through clinical history, physical exams, and lab tests is strongly recommended for good practice.

Patients with Positive Antiphospholipid Antibodies (aPL)

For pregnant women who are aPL antibodies-positive but do not meet the criteria for obstetric or thrombotic APS, prophylactic aspirin (81 or 100 mg per day) is recommended during pregnancy to prevent preeclampsia (10). For patients with obstetric APS, a combination of low-dose aspirin and prophylactic-dose heparin (typically low molecular weight heparin, LMWH) is strongly recommended. Additionally, for women with obstetric APS, prophylactic anticoagulation for 6-12 weeks postpartum is also advised. For pregnant women with thrombotic APS, treatment with low-dose aspirin and therapeutic-dose heparin (usually LMWH) during pregnancy and the postpartum period is strongly recommended (10,31). However, for aPL-positive patients who do not meet the criteria for obstetric APS, combining prophylactic-dose heparin with low-dose aspirin is not recommended. In cases of pregnancy loss despite standard treatment with low-dose aspirin and prophylactic heparin or LMWH, the use of intravenous immunoglobulin (IVIG) or increased doses of LMWH is conditionally not recommended due to lack of significant benefit. The addition of prednisone to prophylactic-dose heparin or LMWH and low-dose aspirin is strongly not recommended, as no controlled studies demonstrate its benefit. For patients with primary APS, adding HCQ to prophylactic-dose heparin or LMWH and low-dose aspirin is conditionally recommended. In pregnant women who are aPL-positive but do not meet APS criteria and have no other medical indication (e.g., SLE), prophylactic HCQ is conditionally not recommended (10).

Anti-Ro/SSA and/or Anti-La/SSB Antibodies During Pregnancy

For pregnant women who are positive for anti-Ro/SSA and/or anti-La/SSB antibodies but have no history of a baby with CHB or neonatal lupus erythematosus (NLE), serial fetal echocardiography starting between 16 and 18 weeks is recommended, with less frequent intervals (though the specific interval is not determined) (10). For women with a previous baby with CHB or other forms of NLE, weekly fetal echocardiography from 16-18 weeks until 26 weeks is conditionally recommended. HCQ is conditionally recommended for all pregnant women who are positive for anti-Ro/SSA and/or anti-La/SSB antibodies. For those with first or second-

degree fetal heart block detected on echocardiography, treatment with oral dexamethasone (4 mg per day) is recommended. However, if CHB (without other heart inflammation) is present, the use of dexamethasone is conditionally not recommended.

MEDICATION USE

Before conception, CYC and thalidomide are not recommended for men. CYC can impair spermatogenesis or be mutagenic, and should be discontinued at least three months before conception (10,32). Thalidomide, a potent teratogen detectable in seminal fluid, should be discontinued at least one month prior to conception. For men with IRD planning fatherhood, the continuation of hydroxychloroquine (HCQ), azathioprine, 6-mercaptopurine, colchicine, and tumor necrosis factor inhibitors is strongly recommended. Continuation of methotrexate (MTX), mycophenolate mofetil (MMF), leflunomide, sulfasalazine, calcineurin inhibitors, and NSAIDs is conditionally recommended, despite MTX labels suggesting discontinuation due to lack of evidence of mutagenesis or teratogenicity. Sulfasalazine may affect sperm quality, but is not linked to teratogenicity, so its continuation is conditionally recommended. If conception is delayed, semen analysis is advised. Limited evidence supports the conditional continuation of anakinra and rituximab (Table 2).

It is recommended to discuss medication use with patients before conception, especially for those starting treatments that affect gonadal function, such as CYC. Teratogenic drugs like MTX, MMF, CYC, and thalidomide should be discontinued at least three months before conception. For women on leflunomide, a cholestyramine washout is recommended before conception or upon pregnancy confirmation if serum metabolites are present. If serum metabolites are undetectable, the risk of pregnancy loss or birth defects does not increase. For life-threatening conditions in the second or third trimester, CYC may be conditionally recommended (10).

After stopping teratogenic drugs, a period of observation is advised to ensure disease stability after transitioning to pregnancy-compatible medications or going drug-free. If a woman is accidentally exposed to teratogenic drugs, referral to a maternal-fetal medicine specialist or genetic counselor is strongly recommended (10) (Table 3).

Medications such as HCQ, azathioprine/6-mercaptopurine, colchicine, and sulfasalazine are safe during pregnancy and should be continued. Calcineurin inhibitors (tacrolimus and cyclosporine) and NSAIDs are conditionally recommended for pregnancy use, but NSAID discontinuation before conception is advised if fertility issues arise, as NSAID-induced unruptured follicle syndrome may cause subfertility. NSAIDs should be avoided in the third trimester to prevent premature closure of the ductus arteriosus, and non-selective NSAIDs are preferred over COX-2 inhibitors in early pregnancy (10,33).

Low-dose glucocorticoid therapy (≤10 mg prednisone per day) is recommended during pregnancy if clinically necessary. If a higher dose is required, adding a steroid-sparing agent is advised to keep glucocorticoid doses below 20 mg per day. Stress-dose glucocorticoids are not routinely recommended for vaginal deliveries, but they may be conditionally recommended for cesarean deliveries.

Tumor Necrosis Factor Inhibitors (TNFi) During Pregnancy

The continuation of tumor necrosis factor inhibitor (TNFi) therapy with infliximab, etanercept, adalimumab, or golimumab before and during pregnancy is conditionally recommended (10). Certolizumab, which lacks an Fc chain and has minimal placental transfer, is strongly recommended to continue before and during pregnancy.

Table 2. Medication safety during pregnancy and lactation in IRD patients

Medication	Safety Category	Recommendation
Hydroxychloroquine (HCQ)	Safe	Strongly recommended throughout pregnancy
Azathioprine/6-Mercaptopurine	Safe	Strongly recommended throughout pregnancy
Colchicine	Safe	Strongly recommended throughout pregnancy
Sulfasalazine	Safe	Strongly recommended throughout pregnancy
Tumor Necrosis Factor Inhibitors (Infliximab, Adalimumab, Etanercept)	Safe	Conditionally recommended before and during pregnancy; discontinue in 3rd trimester if disease is well-controlled
Certolizumab	Safe	Strongly recommended throughout pregnancy due to minimal placental transfer
Calcineurin Inhibitors (Tacrolimus, Cyclosporine)	Safe	Conditionally recommended during pregnancy
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	Conditional	Discontinue before conception if subfertility; not recommended in 3rd trimester due to risk of ductus arteriosus closure
Methotrexate (MTX)	Unsafe	Strongly recommended to discontinue 3 months before conception
Mycophenolate Mofetil (MMF)	Unsafe	Strongly recommended to discontinue 3 months before conception
Cyclophosphamide (CYC)	Unsafe	Strongly recommended to discontinue 3 months before conception; can be used in life-threatening conditions during 2nd/3rd trimester
Thalidomide	Unsafe	Strongly recommended to discontinue 1 month before conception

Table 3. Preconceptional counseling for IRD patients

Counseling Aspect	Recommendation
Medication Review	Evaluate current medications and discontinue teratogenic drugs (e.g., MTX, MMF, CYC, Thalidomide) at least 3 months before conception.
Disease Activity	Ensure disease is in remission for at least 6-12 months before attempting pregnancy.
Fertility Preservation	Discuss fertility preservation options for patients undergoing gonadotoxic therapies (e.g., CYC).
Contraception	Recommend effective contraceptive methods (e.g., IUDs, progestin implants) for women who are not planning pregnancy.
Assisted Reproductive Technologies (ART)	For women with stable IRD and on pregnancy-compatible medications, ART is an option. Delay ART in cases of moderate to severe disease activity.
Hydroxychloroquine (HCQ)	Strongly recommended for women with SLE or related conditions to maintain disease control during pregnancy.
Risk of Flares	Counsel on the increased risk of disease flare-ups postpartum and ensure a management plan is in place.
Thromboembolism Risk	For women with positive aPL antibodies or APS, consider prophylactic anticoagulation therapy during pregnancy.
Monitoring	Recommend regular monitoring of disease activity and organ function throughout pregnancy.
Genetic Counseling	For women at risk of congenital heart block or neonatal lupus (anti-Ro/SSA, anti-La/SSB positive), consider genetic counseling and serial fetal echocardiography.

The placental transfer and fetal exposure of most biological therapies depend on the stage of pregnancy. Most IRD biological therapies, containing an Fc IgG1 structure, do not significantly pass into fetal circulation until the second trimester. In the third trimester, TNF inhibitors with the IgG1 Fc structure (infliximab, etanercept, adalimumab, and golimumab) show significant placental transfer, leading to substantial drug levels in the newborn. Although limited evidence indicates no adverse effects from these TNF inhibitors, particularly during the first trimester, the 'Voting Panel' concluded that if the disease is well-controlled, TNF inhibitors can be discontinued in the third trimester. However, if the disease remains active, TNF inhibitors may be continued through delivery, though newborns will likely have significant serum drug levels for some time after birth.

Other Biologics

There is limited data on the compatibility of non-TNF biologics with pregnancy. Since most of these agents likely do not cross the placenta until the second trimester, the panel conditionally recommends that IgG-based non-TNF biologics can be considered compatible during the periconception period but should be discontinued as soon as pregnancy is confirmed (with the first positive pregnancy test). For women attempting to conceive, the continuation of therapies such as anakinra, belimumab, abatacept, tocilizumab, secukinumab, and ustekinumab is conditionally recommended (34). However, these therapies should be discontinued once pregnancy is confirmed. If disease control cannot be maintained with medications compatible with pregnancy, it is important for the physician and patient to discuss the risks of uncontrolled disease during pregnancy compared to the potential risks posed by continuing these medications.

Rituximab

For women trying to conceive, the continuation of rituximab is conditionally recommended, especially in cases where there is life- or organ-threatening disease activity, and it may also be continued during pregnancy. However, the use of this medication during the second half of pregnancy increases the risk of the neonate being born with reduced B cell levels at birth (34).

Small Molecule Agents

As there is no current evidence regarding the use or safety of newer small-molecule agents such as tofacitinib, baricitinib, and apremilast during pregnancy, the 'Voting Panel' chose not to make specific recommendations about these drugs. However, it is likely that small molecules can cross the placenta.

Targeted Treatment Strategy for IRD During Pregnancy (10)

SLE or other autoimmune diseases:

- •Baseline treatment: Low-dose aspirin, hydroxychloroquine, vitamin D ± low-dose glucocorticoids.
- •Modifications for moderate disease flare-ups: Azathioprine ± cyclosporine, ± tacrolimus, ± moderate-dose glucocorticoids.
- •Modifications for severe disease flare-ups: High-dose glucocorticoids, ± cyclophosphamide, ± plasmapheresis, ± IVIG.

RA or other inflammatory arthritis:

- •Baseline treatment: Hydroxychloroquine, ± sulfasalazine, ± TNF inhibitor, vitamin D.
- •Modifications for moderate disease flare-ups: Low-dose glucocorticoids, ± other biologic DMARDs.
- •Modifications for severe disease flare-ups: High-dose glucocorticoids, ± cyclosporine, ± tacrolimus.

APS:

- •Baseline treatment: Low-dose aspirin, LMWH, vitamin D.
- •Recurrent obstetric APS: Hydroxychloroquine.
- •Recurrent thrombosis or catastrophic APS: Rituximab, ± IVIG, ± plasmapheresis (Note: Recommendations from a 2019 review, differing from ACR-2020 guidelines).

Medication Use Recommendations for Men with IRD Planning to Have Children

•Strongly recommended to continue: Azathioprine/6-mercaptopurine, colchicine, hydroxychloroquine, all TNF inhibitors.
•Conditionally recommended to continue: Anakinra, COX-2 inhibitors, cyclosporine, leflunomide, methotrexate, mycophenolate mofetil, mycophenolic acid, NSAIDs, rituximab, sulfasalazine (if conception does not occur, perform semen analysis), tacrolimus.
•Strongly not recommended to continue: Cyclophosphamide (should be discontinued 12 weeks before conception).
•Conditionally not recommended to continue: Thalidomide (should be discontinued 4 weeks before conception).
•No recommendation due to limited data: Abatacept, apremilast, baricitinib, belimumab, secukinumab, tocilizumab, tofacitinib, ustekinumab.

Maternal Medication Use Overview of medication use before and during pregnancy and lactation

•If planning pregnancy: Discuss medication use, including CYC (best clinical practice: BCP).
•If pregnant and exposed to teratogenic drugs: Immediately discontinue drugs and seek counseling (BCP).
•If experiencing difficulty conceiving, discontinue NSAIDs (conditional recommendation). Avoid NSAIDs in the third trimester (strong recommendation).
•Prefer NSAIDs over COX-2 inhibitors (conditional recommendation).
•Discontinue MTX, MMF, thalidomide, and CYC before conception (strong recommendation).
•Use CYC only in the second and third trimesters in life-threatening diseases (conditional).
•Discontinue leflunomide 24 months before conception or check serum metabolite levels and treat with cholestyramine washout (strong recommendation).
•Continue HCQ, sulfasalazine, AZA, colchicine (strong recommendation). Continue cyclosporine and tacrolimus (conditional). Continue certolizumab (strong recommendation).
•Continue infliximab, etanercept, adalimumab, golimumab (conditional recommendation).
•Discontinue rituximab, belimumab, anakinra, abatacept, tocilizumab, secukinumab, ustekinumab when pregnancy is confirmed (conditional recommendation).
•Use rituximab during pregnancy in cases of organ or life-threatening disease (conditional recommendation).
•No recommendations for tofacitinib, baricitinib, apremilast due to lack of data. Continue regular low-dose prednisone (conditional recommendation).
•Reduce high-dose prednisone by adding pregnancy-compatible medications if necessary (strong recommendation).
•Stress-dose steroids at delivery: not recommended for vaginal delivery, conditionally recommended for cesarean (conditional).
•Encourage breastfeeding and maintain disease control with compatible medications if possible (BCP).

Medications Compatible with Breastfeeding

•Strong recommendation: HCQ, infliximab, etanercept, adalimumab, golimumab, certolizumab, rituximab.
•Conditional recommendation: NSAIDs, sulfasalazine, colchicine, AZA, cyclosporine, tacrolimus, anakinra, belimumab, abatacept, tocilizumab, secukinumab, ustekinumab.
•Strong recommendation: Prednisone or non-fluorinated steroid equivalent <20 mg daily. For daily doses ≥20 mg, discard breast milk collected within 4 hours of taking the medication.
•Strongly not recommended: Leflunomide, MMF, CYC, thalidomide.
•Conditionally not recommended: MTX.

Recommended TNF Inhibitor Discontinuation Timing During Pregnancy

•Infliximab: 16-20 weeks.
•Etanercept: 24-32 weeks.
•Adalimumab: 20-24 weeks.
•Certolizumab: Safe throughout pregnancy.
•Golimumab: Limited information; likely safe in the first trimester.

Limitations of the Review

The review relies heavily on existing literature, which may be subject to publication bias or varying quality of evidence. Data on some rheumatic diseases during pregnancy and lactation, such as PsA and SpA, is limited, reducing the ability to generalize findings across all types of inflammatory rheumatic diseases. Some recommendations for medication management during pregnancy are based on limited evidence or expert opinion, especially regarding newer biologics and small-molecule agents. The review did not include direct patient data or clinical trials, making it more reliant on theoretical conclusions and previous studies.There may be regional differences in the availability of medications and clinical guidelines that were not fully addressed in the review.

Strengths of the Review

The review provides a comprehensive overview of medication safety and treatment strategies during pregnancy and lactation for women with inflammatory rheumatic diseases, summarizing key guidelines and recommendations. It covers a wide range of immune-mediated rheumatic conditions, including SLE, rheumatoid arthritis, antiphospholipid syndrome, and Sjögren's syndrome. The inclusion of detailed

recommendations from the American College of Rheumatology (ACR) 2020 guidelines provides a valuable resource for clinicians in managing pregnant and lactating patients with rheumatic diseases. The review emphasizes the importance of individualized treatment plans and interdisciplinary collaboration to optimize outcomes for both mother and child. It highlights both the need for pre-conception counseling and the management of disease flares during pregnancy, providing practical insights into clinical care.

CONCLUSION

This comprehensive review underscores the complexity of managing inflammatory rheumatic diseases during pregnancy and lactation, emphasizing the need for individualized treatment strategies. Key takeaways include the critical importance of pre-conception counseling and the management of disease activity to optimize both maternal and fetal outcomes. Women with well-controlled disease prior to conception generally experience better pregnancy outcomes, while active disease increases the risk of complications such as preterm birth, intrauterine growth restriction, and maternal mortality.

The safety of medications during pregnancy and lactation is a focal point, with clear guidelines favoring certain immunosuppressants, biologics, and anti-inflammatory agents over others. Drugs such as hydroxychloroquine, azathioprine, and certolizumab are recommended during pregnancy due to their favorable safety profiles, while medications like methotrexate and mycophenolate mofetil should be discontinued well before conception due to their teratogenic risks.

The review also highlights the importance of interdisciplinary collaboration, involving rheumatologists, obstetricians, and maternal-fetal medicine specialists, to ensure that both disease control and pregnancy management are aligned. Continuous monitoring during pregnancy and postpartum, coupled with personalized medication adjustments, is essential to mitigate the risks of disease flare-ups and adverse pregnancy outcomes.

DECLARATIONS

Ethics: In this review, the authors declare that there are no ethical concerns or conflicts of interest. All authors have contributed to the review in accordance with ethical standards, and no part of the study has involved any activities that could raise ethical issues. Additionally, the authors confirm that there are no financial or personal relationships that could be perceived as a conflict of interest in the preparation or publication of this review. All decisions and interpretations have been made independently, with no influence from any external funding sources, institutions, or commercial entities.

AI: This review used the language revision and structural improvement processes provided by the latest Chat GPT-4.0; however, all final decisions have been made by the authors.

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