Clinical Practice Guideline

Women's Reproductive Health and Rheumatic Diseases

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Abbreviations

ACE	Angiotensin-converting enzyme
ACR	American College of Rheumatology
APL	Anti-phospholipid antibodies
ARBs	Angiotensin receptor blockers
AS	Ankylosing spondylitis
axSpA	Axial spondyloarthritis
BHPR	British Health Professionals in Rheumatology
BMI	Body mass index
BSR	British Society for Rheumatology
csDMARD(s)	Conventional synthetic disease-modifying antirheumatic drug(s)
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
IBD	Inflammatory bowel disease
IL-17	Interleukin 17
IL-12/23	Interleukin 12/23
IUD(s)	Intrauterine device(s)
JAK	Janus kinase
LMW	Low molecular weight
MTX	Methotrexate
NIH	National Institutes of Health
NSAID(s)	Non-steroidal anti-inflammatory drug(s)
PDE4	Phosphodiesterase 4
PEG	Polyethylene glycol
PG	Polyglutamate
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
SpA	Spondyloarthritis
SSA	Anti-Sjögren's syndrome-related antigen A
SSB	Anti-Sjögren's syndrome-related antigen B
TNFi	Tumor necrosis factor inhibitor
US	United States

Introduction

Rheumatic diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), nonradiographic axial spondyloarthritis (axSpA), and systemic lupus erythematosus (SLE) are often diagnosed in women of childbearing age. Caring for these patients can be a challenge because one must not only deal with their rheumatic disease(s) and morbidities, but also with a possible pregnancy and potential fetal complications. Planning for a pregnancy and the high rate of unintended pregnancies also add challenges to the care of female patients of childbearing age. In 2001, close to 45% of pregnancies in the United States (US) were unplanned.[1] Rheumatologists must educate a woman not only about the treatment of her rheumatoid disease(s) and any other medical problems she may have but also about planning for a safe pregnancy with the best outcome for both, herself and her unborn child. This requires rheumatologists to work in close collaboration with other medical specialists as well as the patient's obstetrician/gynecologist, maternal fetal medicine specialist, or infertility or reproductive endocrinology specialist.[2, 3]

Family planning, including contraception, should be discussed at the patient's initial visit or very soon after. The importance of tight disease control prior to conception should be stressed. The patient must also be encouraged to avoid an unplanned pregnancy as this could increase the risk to her health and the health of her unborn child. She must also be informed that her rheumatic disease and any comorbidities such as but not limited to diabetes, metabolic syndrome, high blood pressure, obesity, and cardiovascular disease must be in the best control possible for at least 3 to 6 months before trying to conceive. The patient must also be educated about any medications that could be harmful to her unborn child.

To ensure that potentially harmful drugs are cleared from the patient's system prior to conception, drugs that decrease fertility or can cause congenital anomalies, fetal death, or spontaneous abortions should be discontinued as soon as the patient has an appropriate plan for contraception. Some women will require medication during pregnancy to control their rheumatic disease(s) and/or limit long-term disability. Medication choices should be discussed with the patient, her rheumatologist, and all her other providers to determine which one(s) is/are most appropriate for her (Table 1).

A survey of both rheumatic disease patients and their providers reported that only between 32% and 56% of providers discussed family planning with their female patients of childbearing age.[4] However, less than half indicated that they had consulted with the patient's primary care physician or gynecologist.[4] The majority of patients surveyed did not think that their family planning and/or pregnancy questions had been adequately answered by their rheumatologists; and even more concerning was the fact that only 40% of patients viewed the advice from multiple providers to be consistent with one another.[4]

In one study of women with SLE who were considered to be at risk for an unplanned pregnancy, 59% of patients reported that they had not had any discussions about birth control with their providers during the past year; 22% reported inconsistent use of contraception and 53% depended on barrier methods.[5]

In 2018, the American College of Rheumatology (ACR) published information about rheumatic/autoimmune diseases and pregnancy, which included the following recommendations:[6]

- Rheumatic/autoimmune diseases should be controlled for at least 3 to 6 months before trying to conceive.

- Patients can stay on their medications if they are safe for a fetus, but this should be a shared decision made by the patient, her rheumatologist and her obstetrician. No changes in medications used to treat rheumatic/autoimmune diseases should be made by any treating provider without the approval of the patient's rheumatologist.

Women with rheumatic disease and pulmonary hypertension have a significant risk for maternal morbidity and mortality (reported to be around 20% for women with pulmonary hypertension only) despite aggressive advanced care at tertiary institutions. The time considered to be of highest risk for both mother and baby is during labor and delivery, and in the postpartum period.[7] In the late first trimester and between weeks 20 to 24 the mother's pulmonary hypertension can also deteriorate and may become life threatening.[8] Depending on the severity of their lung disease some may be advised not to become pregnant.[3, 9] These women require careful counseling before they become pregnant. Reliable contraception with the lowest failure rate (see below) should be recommended.

With proper education and planning, most women with a rheumatic disease can have a safe and successful pregnancy.

Contraception

All women of childbearing age should be referred to their gynecologists or primary care providers for effective family planning (if they do not yet have a reliable plan with an obstetrician/gynecologist or primary care provider). It is important that the contraceptive plan is coordinated with the patient's rheumatologist, because not all contraceptive devices or medications are appropriate for women with rheumatic disease(s). Selection of the most effective and appropriate contraception should be a decision reached jointly by the patient and her provider(s). It is important to impress upon the patient that her rheumatic disease and any associated comorbidities must be well controlled for 3 to 6 months prior to conception.

Most of the information about contraception for patients with rheumatic diseases comes from studies of patients with SLE, RA, and inflammatory bowel disease (IBD). According to Mitchell et al.,[10] most forms of birth control are safe for women with most rheumatic diseases but not all.

The intrauterine device (IUD) is the most effective form of contraception. This includes ParaGard®, a copper-coated IUD, which should be replaced every 10 years and has a failure rate of <1%;[11] and the hormonal IUDs Skyla®,[12] Kyleena®,[13] and Mirena®[14] (all three IUDs contain levonorgestrel). Mirena and Kyleena must both be replaced every 5 years and have a failure rate of <1%. Another choice is a subdermal implant containing progestin only which also has a failure rate of <1%.[3] Patients with SLE who have stable or low disease activity and those positive for anti-phospholipid antibodies (APL) should only use the IUDs mentioned above, or progestin only pills, or subdermal implant. SLE patients with moderate or severe disease should only use IUD contraception.[3]

Other methods considered to be moderately effective include oral contraceptives, intramuscular injections of depot medroxyprogesterone acetate, and the transdermal patch. In one study published in 2001, adherence to the patch was reported to be better than to oral contraceptives.[15] However, both of these methods are considered to be only moderately effective with unintended pregnancy rates of 9% to 13%.[16] Barrier methods such as condoms, and diaphragms are considered to be the least effective method of contraception, with a failure rate between 12% to 18%.[17]

Oral contraceptives containing a combination of estrogen and progesterone can be used in most patients. Transdermal patches usually contain a combination of estrogen and progestin. For patients with SLE, these should not be used unless their disease is stable or inactive.[17] The SELENA study showed that oral contraceptives did not increase lupus flares; however, they should not be used in women with very active disease, hypercoagulability, elevated liver function tests, or migraines.[17]

Hormonal contraception containing estrogen may not be safe for all women with SLE (please refer to *United Rheumatology Clinical Practice Guideline—Systemic Lupus Erythematosus).* Estrogen should be avoided in women with active SLE or at high risk for blood clots (i.e. anti-phospholipid antibody syndrome [APS]).

Pregnancy in women with active SLE increases the risk of venous thrombosis, infection, preeclampsia, Cesarean section, probably lupus nephritis, and maternal death.[18] When a patient is treated with teratogenic medications, effective contraception is required before they start these medications. Teratogenic drugs include mycophenolate mofetil, methotrexate (MTX), leflunomide, cyclophosphamide,[19] and belimumab[20] as well as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins. These drugs should be stopped before conception.

No method is foolproof; therefore, patients must be counseled about the risks of unplanned pregnancies, as described above. In addition, the patient's comorbidities must be taken into consideration when deciding on an appropriate plan for contraception.

Emergency contraception should be discussed with women of child-bearing age. According to the ACR emergency contraception is safer than an unplanned pregnancy.[3] The ParaGard IUD is very effective as emergency contraception and can prevent pregnancy if placed within 5 days of unprotected sex.[11] Ella® (ulipristal acetate), given orally, is an emergency contraceptive pill that also works up to 5 days after unprotected sex but is less effective in women with a body mass index (BMI) over 30 kg/m^2.[21] Plan B OneStep® (levonorgestrel) is effective up to 3 days after unprotected sex, but less effective in women who weigh more than 165 lbs.[22]

Pregnancy and Lactation

A pregnancy is considered to be high risk, if the mother has any of the following medical problems:[23, 24]

- Preterm labor
- Preeclampsia
- Placental problems
- Twins or other multiples
- Diabetes
- Hypertension
- Renal disease
- Epilepsy
- Problems in a prior pregnancy, including but not limited to genetic abnormalities of the baby
- History of multiple miscarriages
- Fetal heart, lung, or kidney problems in a prior pregnancy

- Human immunodeficiency virus, hepatitis C, cytomegalovirus, chicken pox, rubella, toxoplasmosis, or syphilis
- Sickle cell anemia
- Positive APL test
- Asthma
- Autoimmune diseases such as SLE, RA, PsA, or AS
- Age of mother at delivery:
    - ≥35 years of age
    - Teenager
- Thyroid disease
- Obesity
- Zika infection
- Alcohol use
- Smoking
- Substance abuse

Pregnancy in women with rheumatic disease(s) is always considered to be high risk; however, additional clinical issues can further increase this risk. These include but are not limited to:

- Flare of known rheumatic disease
- History of prior blood clots
- In-vitro fertilization
- Presence of anti-Sjögren's syndrome-related antigen A (SSA) and/or antigen B (SSB) antibodies

It is critical that both the patient's rheumatic disease and comorbidities are under good control prior to conception. This may require the use of medications to control the mother's disease(s). The Food and Drug Administration (FDA) has not designated any medication used to manage patients with a rheumatic disease as safe for use in pregnancy. The provider and patient should carefully review the safety profile of the appropriate drugs and together determine which one is best for the patient.

Medications Used to Treat Rheumatic/Autoimmune Diseases and their Potential Effects on Pregnancy and Lactation

United Rheumatology strongly encourages providers to use only medications that are compatible with an entire pregnancy for all women of childbearing age. If women are in remission or have low disease activity for at least 3 to 6 months, then they can plan for a pregnancy at any time as long as they maintain low disease activity. If there is an unplanned pregnancy, then these mothers and fetuses are in a good position to have the best outcome possible, even for that pregnancy.

The new ACR Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases[3] strongly recommends that women with rheumatic diseases who are planning a pregnancy only take medications that are compatible with pregnancy. According to this Guideline, these women should be informed of the importance of being at remission or low disease activity before conceiving. This requires that, if a medication change is required, patients take it far enough in advance to allow for dose calibration and evaluation of both efficacy and tolerability, which requires several months. Once the patient is in either remission or low disease activity for 3 to 6 months, she can try to conceive.

The decision to use any drug during lactation should be a shared decision made by the patient and her provider(s) together, based on their current understanding of the drugs, including but not limited to the amount of the drug found in breast milk and its potential effects on a neonate. Information on the risk of any drug during lactation can be found at the National Institutes of Health (NIH) LactMed database.[25]

Table 1[2, 3, 26-30] summarizes key information about the medications used to treat rheumatic and autoimmune diseases.

Conventional Synthetic Disease-modifying Antirheumatic Drug (csDMARDs)

According to ACR and the European League Against Rheumatism (EULAR), the csDMARD MTX (Rasuvo®, Otrexup®, Rheumatrex® or generic) should not be used during pregnancy or lactation and is contraindicated in the 3 to 6 months prior to conception. MTX has been associated with fetal death and serious congenital anomalies when used before and during pregnancy. In both men and women, MTX can also decrease fertility.[2, 3, 6, 30]

Leflunomide (Arava®) is also contraindicated in pregnancy and lactation as well as during the 3- to 6-month period prior to conception. This drug can remain in a patient's system for up to 2 years after it is discontinued. Before trying to conceive, women who have taken this drug within the past 2 years should be tested to determine if any of it is still detectable in their blood. Women who are currently taking leflunomide or have taken it in the past and test positive for it and want to become pregnant or find that they are unexpectantly pregnant must undergo a drug elimination procedure described in the FDA information for this drug.[2, 3, 29, 31]

Hydroxychloroquine (Plaquenil®) and sulfasalazine (Azulfidine®) are considered to be safe during pregnancy and lactation, according to the ACR and EULAR.[2, 3, 6]

Steroids

If absolutely needed, nonfluorinated glucocorticoids (such as prednisone, methylprednisolone, or prednisolone) may be used at the lowest possible dose throughout pregnancy (a dose equivalent to ≤10 mg of prednisone a day). These medications are inactivated by enzymes in the placenta and do not enter the fetal circulation.[32] They should be used at the lowest possible dose and for the shortest time possible. If higher doses of nonfluorinated glucocorticoids are needed for a long time during pregnancy, the provider should consider changing to a pregnancy compatible immunosuppressive drug instead of a glucocorticoid.

Low-dose nonfluorinated glucocorticoids (doses equivalent to <20 mg of prednisone daily) can be continued during breast feeding, but if the mother requires a higher dose, ACR suggests discarding breast milk up to 4 hours after the last dose of the glucocorticoid.[3]

Fluorinated glucocorticoids (such as dexamethasone and betamethasone) are known to cross the placenta and should be used with extreme caution. ACR recommends against routine use of stress-dose glucocorticoids at the time of vaginal delivery but this could be considered if the patient is to have a cesarean section.[2, 3, 6]

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs), which includes aspirin, are commonly used to treat pain, fever and inflammation, and are the initial drug choice for management of axial SpA and PsA. Patients may also take over-the-counter NSAIDs without a prescription while pregnant.

The use of NSAIDs can be associated with infertility and miscarriage in early pregnancy. Infertility may be related to unruptured follicle syndrome, which often resolves once NSAIDs are discontinued.[33, 34]

In 2003, Li et al.[27] published a report on the effects of NSAIDs on pregnancy. The authors reported that, if NSAIDs were used early in pregnancy (especially near the time of conception) or for more than 1 week, the risk of miscarriage increased. The risk for miscarriage was reported to be 10% for any NSAID use; 35% for use near conception, and 52% for more than 1 week of use. In a more recent 2018 study,[35] the researchers confirmed that women who had used NSAIDs near conception had an increased risk for miscarriage when compared to those who had not used NSAIDs. The association of NSAID use and miscarriage was stronger for women who had a low BMI or with increasing exposure to NSAIDs during pregnancy. None of the women in this study were reported to have inflammatory arthritis or an autoimmune disease. Nakhai-Pour et al.[36] reported on the results of a nested case-controlled study from Canada, which found that women who used non-aspirin NSAIDs in early pregnancy had a 2.4-fold increase of miscarriage when compared to women who did not use NSAIDs. The increased rate of miscarriage in women who have used NSAIDs in the first trimester may be related to problems with implantation related to these drugs.

In 2020, the FDA published a Drug Safety Communication regarding the use of NSAIDs (prescription or over-the-counter) in pregnancy past the 19th week of gestation.[37] The use of these drugs has been associated with oligohydramnios. The decrease in amniotic fluid is the result of decreased production of fetal urine that makes up most of the amniotic fluid. Oligohydramnios can compromise the development

of the fetal lungs, GI tract and muscles. The only exception is the use of low-dose aspirin (81 mg daily) for a pregnancy-related condition and only on the recommendation of a healthcare provider.

In the third trimester, NSAID use has been known to cause premature closure of the fetal ductus arteriosus.[3, 28, 33] Østensen et al.[33] suggest that NSAIDs be stopped at week 32 to protect the fetus from this potential serious complication.

There can be circumstances when the patient's healthcare provider decides that the use of NSAIDs is absolutely necessary. NSAIDs should only be given for the shortest duration and the lowest dose possible. The provider in consultation with the patient's obstetrician should use ultrasound to monitor the patient's amniotic fluid level if treatment with NSAIDs is for more than 2 days.

If NSAIDs are taken by a woman during pregnancy, they should be one of the nonselective cyclooxygenase2 inhibitors.[7] These include:

- Aspirin
- Fenoprophen
- Naproxen
- Ibuprofen
- Flurbiprofen
- Piroxicam
- Indomethacin
- Ketoprofen
- Sulindac
- Diclofenac
- Ketorolac
- Tolmetin
- Nabumetone
- Mefenamic acid
- Meloxicam
- Etodolac
- Oxaprozin

Based on this information, United Rheumatology does not recommend the use of any NSAIDs during any part of a pregnancy.

Tumor Necrosis Factor Inhibitor (TNFi) Drugs

The only TNFi drug which is considered to be **safe for an entire pregnancy is certolizumab pegol** (Cimzia).[3] Placental transfer of this drug was studied prospectively in the CRIB study that followed 16 women during their pregnancies. Eleven patients had RA, one PsA, one SpA/AS, and three Crohn's disease.[26] Study participants were treated with either certolizumab pegol 200 mg every 2 weeks or 400 mg every 4 weeks, as determined by their providers. Two neonates were not included in the final analysis, because they did not meet study protocol requirements. The drug was not detectable in 13 neonates at birth; one had minimally detectable levels of the drug (.09% of the level detected in the mother). All the mothers had the expected blood levels of certolizumab pegol at delivery. In three infants, a very low level of certolizumab could be detected in cord blood. The drug was not detectable in the any of the newborns at 4 and 8 weeks after birth. The investigators concluded that there was no or minimal transfer of certolizumab pegol to the fetus via the placental circulation, because certolizumab, unlike other TNFi drugs, does not contain a fragment crystallizable (Fc) segment that interacts with the fragment crystallizable receptor (FcRn) in the placenta. In certolizumab pegol, the Fc segment is replaced by a polyethylene glycol (PEG) segment, which prevents the transport across the placenta and into the fetal circulation as is seen with other TNFi drugs. The authors concluded that certolizumab pegol can be safely used in all three trimesters of pregnancy, if needed to control the mother's rheumatic disease.

Clowse et al.[38] also reported that women who wanted to breastfeed their newborns could safely use certolizumab pegol to control their rheumatic disease. This was again attributed to the replacement of

the Fc region found in other TNFi drugs with a PEG segment, which does not allow certolizumab to be transported into breast milk.

A larger, both, prospective and retrospective study of the effect of certolizumab pegol on maternal and fetal outcomes was published in 2018.[39] This study demonstrated that women who took certolizumab pegol throughout their entire pregnancy did not have a greater incidence of congenital anomalies or fetal deaths than the population in general. When analyzing breast milk—little or none of the certolizumab pegol present in the mother's blood was transferred into breast milk.

The British Society for Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR) published a joint guideline for the use of drugs in pregnancy and breastfeeding,[40] which states that **if certolizumab pegol** is transported across the placenta, it is in much smaller amounts than other TNFi drug. The society states that certolizumab pegol is the **only TNFi that should be used in all three trimesters of pregnancy and during lactation**.

The 2020 ACR guideline[3] *conditionally* recommends that **infliximab (Remicade®), etanercept (Enbrel®), golimumab (Simponi®, Simponi® Aria), or adalimumab (Humira®)** can be used during pregnancy. However, etanercept, golimumab, and adalimumab should be stopped in the third trimester, if the patient is well controlled. This recommendation is based on the finding that these drugs cross placenta and can be found in the newborn's blood for some time after birth. According to the ACR; infliximab, etanercept, adalimumab, golimumab, and rituximab can all be used during lactation[3].

EULAR,[2] states that **infliximab** can be safely used up to week 20 and, thereafter only if there is no other safer drug to treat the patient for the remainder of her the pregnancy. In addition, the EULAR states that this drug is safe during lactation.[2] The BSR/BHPR Guideline on Prescribing Drugs in Pregnancy and Breastfeeding[40] recommends stopping infliximab at 16 to 26 weeks, because it has been shown to cross the placenta and can be detected in both cord blood and the newborn's blood at birth. The FDA prescribing information for infliximab[41] indicates that this drug should only be used in pregnancy if "clearly needed." According to the prescribing information, infants exposed to infliximab may have an increased risk for post-natal infection, because the drug is detectable in their blood. Therefore, these infants should not receive live virus vaccinations for at least 6 months after birth. The ACR also indicates that infliximab should be discontinued in the third trimester.[3]

Etanercept can be used up to gestational week 30 to 32, according to the EULAR,[2] and for the entire pregnancy, if absolutely indicated. The EULAR Guideline also suggests that **etanercept** can be used during lactation.

EULAR[2] recommends against the use of **golimumab** during pregnancy because there is inadequate evidence to support its safety. However, golimumab can be use during lactation.[2, 3]

Adalimumab can be used up to week 20 and, if necessary, it may be used for the entire pregnancy, according to EULAR.[2] Adalimumab can also be used during lactation.[2, 3]

The 2020 guidelines from ACR[3] recommend that etanercept, golimumab and adalimumab be discontinued in the third trimester.

T Cell Costimulatory Inhibitor

Abatacept (Orencia®) is a T cell costimulatory inhibitor. EULAR[2] reports that there is limited information regarding abatacept in pregnancy and recommends that it be replaced with a safer drug before and during pregnancy, unless there is no other safer medication that can control the mother's rheumatic disease. Women should wait at least 14 weeks after the last dose of abatacept before trying to conceive. In addition, abatacept should be avoided during lactation.[2] According to the LactMed database,[25] if this drug is essential for the control of the mother's disease, it can be used while nursing, unless the mother and her provider(s) prefer a different medication. At this time, there are no studies that address the safety of abatacept in a nursing mother.[42]

Janus Kinase (JAK) Inhibitor

Tofacitinib (Xeljanz®) is a JAK inhibitor for which there is insufficient data to determine the potential risk of adverse fetal outcomes. Both, the EULAR[2] and ACR[3] recommend that this drug be avoided during pregnancy. There are also no data on tofacitinib in human milk. According to both, the Xeljanz prescribing information[43] and EULAR,[2] nursing while taking tofacitinib is not recommended.

Baricitinib (Olumiant®) is another a JAK inhibitor for which there is insufficient information to determine its safety for use during pregnancy or lactation.[44]

Upadacitinib (Rinvoq®) is a newer JAK inhibitor that has been approved for use in patients with RA. There is very little information about the use of this drug during pregnancy and lactation. According to the Rinvoq prescribing information,[45] there is a suspicion that it may be harmful to a developing fetus. The prescribing information suggests that women of childbearing age who are taking this drug use effective contraception for 4 weeks after the last dose. The information regarding the safety of upadacitinib during lactation is scarce, but it is suspected that it may be found in breast milk, and women are advised not to use this drug during lactation.

Interleukin 17 (IL-17) Antagonists

Secukinumab (Cosentyx®) is an IL-17 antagonist. According to the FDA[46] and the ACR,[3] there is inadequate information regarding the use of this drug during pregnancy; therefore, it should only be used if the benefits outweigh the risks. This should be a shared decision made by the patient and her provider. This drug should be used in nursing mothers with caution.[46] It is recommended that this drug be discontinued when pregnancy is confirmed.[3]

Ixekizumab (Taltz®) is also an IL-17 antagonist. According to the FDA,[47] insufficient data are available about the use of this drug during pregnancy to determine its potential risks. This drug may cross the placenta. It is not known whether ixekizumab is excreted in human milk be used with caution in lactating women.[47]

Interleukin 12/23 (IL-12/23) Antagonist

Ustekinumab (Stelara®) is an IL-12/23 antagonist. According to the FDA,[48] insufficient information is available about the use of ustekinumab in pregnancy to comment on its safety. For the same reason,

EULAR also cautions using of this drug during pregnancy.[7] This drug should be discontinued as soon as the mother knows that she is pregnant and should not be used in pregnancy[3]. There is no data showing whether this drug is found in human milk. However, the FDA[48] states that ustekinumab is probably found in human milk because of its large molecular structure but that there are no data regarding the safety of this drug during lactation. The EULAR[2] also discourages use of ustekinumab during lactation but indicates that the drug can be used if there is no alternative for the mother. The ACR[3] gives this drug a *conditional* recommendation for use during lactation.

Phosphodiesterase 4 (PDE4) Inhibitor

Apremilast (Otezla®) is a PDE4 antagonist. There is insufficient information about the use of this drug in pregnant women or the risks to the fetus.[49] The FDA[49] suggests that this drug be used in pregnant or lactating women only if there is no other alternative. The ACR[3] gives no opinion on the use of apremilast in pregnancy or lactation due to lack of data.

CD-20 Directed Cytolytic Antibody

Rituximab (Rituxan®) is a CD-20 directed cytolytic antibody that can be used for the treatment of RA if there has been an inadequate response to **one or more** TNFi drug(s) **in patients who are not of childbearing age**. According to the Rituxan prescribing information,[50] infants exposed to it *in utero* can develop B-cell lymphocytopenia that can last up to 6 months. The ACR Guideline[3] states that rituximab can be used in pregnancy, only "if severe life- or organ-threatening maternal disease so warrants" (Page 18).

In patients treated with rituximab for non-Hodgkin's lymphoma, the drug could be detected in the serum for up to 6 months after treatment was stopped; therefore, the Rituxan prescribing information[50] recommends that women who may become pregnant should use effective contraception for 12 months after rituximab has been discontinued. According to EULAR,[2] rituximab should be avoided during lactation, because there is insufficient information to determine if it is safe.

Immunosuppressive Agents

Mycophenolate Mofetil (CellCept®) is a immunosuppressive agent used to treat patients with SLE and to prevent organ rejection in those who have received allogenic kidney, liver, or heart transplant.[51] It is teratogenic and associated with an **increased risk of first-trimester miscarriage and congenital malformations** (Table 1). **It should not be used while trying to conceive or during pregnancy**. This drug should not be used while breastfeeding.[2, 3] Patients who are of childbearing age and taking this drug should have effective contraception either and IUD or 2 other forms of contraception[3]. This drug should be stopped at least 6 weeks prior to conception and not used in pregnancy or lactation.

Tacrolimus (Prograf®) is also used for the treatment of patients with SLE and the prevention of organ rejection in patients who have had solid organ transplants.[52] It is considered to be fairly safe in pregnancy, according to Healthy Outcomes in Pregnancy with SLE Through Education of Providers (HOP-STEP),[53] a website directed by researchers at the Duke University School of Medicine. However, the ACR[3] cautions that, when tacrolimus is used, the mother's blood pressure should be carefully monitored. The LactMed database[25] indicates that tacrolimus is safe for breastfeeding mothers.

Azathioprine (Imuran®) is an anti-inflammatory immunosuppressive agent often applied to prevent the rejection of kidney transplants. In the past, it was used as a treatment for patients with RA, although it has not been studied in combination with DMARDs.[54] Azathioprine is also used for the management of patients with SLE; it can be taken before and during pregnancy and lactation.[3, 55]

Alkylating Cytotoxic Agent

Cyclophosphamide (Cytoxan®) is a cytotoxic drug used to treat some patients with SLE.[19] It has been reported to decrease fertility in both, men and women and can result in sterility. Cyclophosphamide is considered harmful to a developing fetus and **should not be used during pregnancy or for 3 to 6 months prior to conception**. Patients taking cyclophosphamide have an increased susceptibility to infection, because this drug can decrease immune responses. According to the LactMed database,[25] EULAR,[2] and the ACR,[3] cyclophosphamide is excreted into human milk in significant amounts, and its toxic metabolites are found in human milk. This drug should **not be used during lactation**.[3] Some infants breastfed by women taking cyclophosphamide have reportedly been diagnosed with neutropenia, anemia, thrombocytopenia, and diarrhea at birth. A mother taking this drug who wants to breastfeed her newborn should discuss the pros and cons with her provider and decide whether to stop cyclophosphamide or not to breastfeed.

Other Medications Commonly Used in Patients with Rheumatoid/Autoimmune Diseases

ACE Inhibitors and ARBs

ACE inhibitors and ARBs are not safe for use in the second and third trimesters of pregnancy, because they are associated with an increased risk of fetal renal disease and oligohydramnios; these drugs also increase the risk of newborns being small for gestational age or having skeletal or facial deformities. These drugs should only be used in pregnant women, if the mother has a life-threatening disease such as a renal crisis.[3]

There is little information about ACE inhibitors and ARBs in breastfeeding women (Table 1). According to information reported on the LactMed database,[25] most of these drugs are safe to use by breastfeeding mothers, but providers should refer to the Database for more specific information about individual drugs.

Belimumab (Benlysta®)

Belimumab is a targeted monoclonal antibody inhibiting B-lymphocyte stimulation that is used to treat patients with SLE who have tested positive for autoantibodies and receive standard therapy. Currently, **it is not recommended for use in patients with severe lupus nephritis or active central nervous system disease**. Both, the ACR and EULAR recommend **stopping belimumab during at conception and during pregnancy**.[2, 3]

Belimumab should be used during pregnancy only if there is no other safer drug available, and the patient and her provider decide that the benefit to the mother "justifies the risk to the fetus."[20] Women of childbearing age should use effective contraception while treated with belimumab, and continue contraception for at least 4 months following the last treatment.

There is insufficient information about the excretion of belimumab into human milk or whether it is absorbed by the infant after ingestion. The patient and her provider should decide whether the mother should stop this drug and breastfeed her infant or whether she should continue the drug and not breastfeed.[20]

Statins

Available data are insufficient to determine whether statins are safe to use during pregnancy. Currently, these drugs are considered potentially teratogenic and should not be used during pregnancy. Additional studies are needed before this question can be answered conclusively.[56, 57]

There are limited data for most statins during pregnancy and lactation. Providers should investigate each specific drug in the LactMed database[25] for more complete information. In some cases, it is recommended that a different drug be used during nursing to control cholesterol levels.

Pregnancy Registries

There are pregnancy registries to gather information on maternal-fetal outcomes in patients taking Enbrel, Xeljanz, Orencia, Cimzia, and Benlysta. Information on how to provide information to the registries is listed in the prescribing information for each drug. Providers are encouraged to register their patients. The telephone number for each registry may be obtained from the prescribing information at the URLs provided in the reference list.

United Rheumatology strongly encourages rheumatologists to work collaboratively with obstetricians and/or maternal fetal specialists and primary care providers when treating women of childbearing age who are pregnant or wish to become pregnant. United Rheumatology also encourages rheumatologists to discuss family planning with their patients including using the safest drug possible for those with RA, PsA or AS. It is best if they are started on certolizumab pegol early on in their treatment because this is the safest available drug for conception and pregnancy if the patient adequately responds to it.

Additional Information Regarding Pregnancy and Rheumatic Diseases

Pregnancy and RA

In 2011, a Danish retrospective study of pregnancy in women with and without RA concluded that women with RA had a slight decrease in fertility compared to those without RA, with time to conception slightly longer for women with RA than for those without it.[58]

A retrospective study of pregnancy outcomes in women with and without RA between 1987 and 2001 was published in 2006.[59] The results indicated that pregnant women with RA were at increased risk for primary Cesarean section, premature delivery, and babies small for gestational age when compared to women without RA. In addition, babies born to mothers with RA were likely to be hospitalized longer after birth than babies born to mothers without RA.

It also has been reported that between 25% and 50% of patients with RA may experience a spontaneous decrease in disease activity during pregnancy.[60] After delivery, as many as 40% of patients with RA have

postpartum flares, which can be very severe. Therefore, the need for RA medication during pregnancy may actually decrease in some women, but this is often followed by a need for increased medication in the postpartum period.[2, 60]

Pregnancy and PsA

In 2017, Polachek et al.[61] published a retrospective report on patients with PsA who were pregnant between 1990 and 2015. The study group included 29 women with PsA who had 42 pregnancies during the study period. Forty of the pregnancies resulted in a live birth. Disease activity in 58.5% of the pregnancies either improved or was stable at low disease activity. In the postpartum period, 52.5% either improved or had stable low disease activity, 40% had worsening or stable high disease activity.

Berman et al.[62] published a retrospective review of disease activity of 25 pregnant women with PsA. The 25 women had 35 pregnancies with 33 live births during the study period. Only the 33 live births were included in the results. Twenty-one of these patients had been treated with biologics—infliximab, adalimumab, etanercept, golimumab, and ustekinumab—before conception. Fifteen of the 21 women in this group stopped biologics close to conception or in the first trimester of pregnancy. Five of the 15 had mild to severe disease prior to conception. Over the course of the pregnancy and the first year postpartum, 14 of these 15 women developed mild to severe disease, whereas in the six women who had stayed on biologics (TNFi or ustekinumab) throughout the course of their pregnancy, disease activity was unchanged. The authors reported that maintaining patients on biologics while pregnant decreased the incidence of pregnancy and postpartum flares. In women who had never been treated with biologics before or during pregnancy or in the year following delivery, disease activity tended to improve during pregnancy but worsen in the postpartum period.

No fetal anomalies were reported in this study.[62] Infliximab, adalimumab, and ustekinumab are IgG1 monoclonal antibodies that are actively transported across the placenta. High levels of these drugs can be found in newborns exposed to them in the late second and third trimester. Etanercept, a fusion protein, has been found to cross the placenta at a much lower rate than the IgG1 monoclonal antibody drugs.[63] Women with psoriasis were reported to have a higher rate of spontaneous abortions than women without psoriasis. They were also reported to have an increased risk of the following:[64, 65]

- High blood pressure
- Preeclampsia
- Premature rupture of membranes
- Gestational diabetes
- Elective and emergency Caesarean section
- Neonatal macrosomia
- Low birthweight
- Babies large for gestational age

There is very limited literature regarding pregnancy outcomes of women with PsA. There is more information about pregnancy outcomes in women with RA, SLE, and IBD (Crohn's disease and ulcerative colitis). Many of the available results are based on small studies and, generally, the changes during pregnancy reported tend to be inconsistent.

Pregnancy and AS or Nonradiographic axSpA

Data about AS or nonradiographic axSpA during pregnancy is also limited, but most women are likely to carry their babies to term, especially if the disease was controlled before and during pregnancy.[66] If the disease is not well controlled, the symptoms may become worse during pregnancy. It is not always possible to discontinue all medications that are taken to control AS or nonradiographic axSpA. At times, it may be necessary for the patient to continue some medication for symptom control. The choice of which medications to use should be made after a discussion between the patient and her providers. Everyone treating the patient (rheumatologist, primary care provider, and obstetrician/gynecologist, etched) must be kept informed of any changes in medications; however, no medication used to treat AS or nonradiographic axSpA should be stopped or changed without the agreement of the patient's rheumatologist.

There are no reports of any improvement in disease activity during pregnancy in women with AS or nonradiographic axSpA. In fact, pregnant patients with AS or nonradiographic axSpA may experience increased pain and morning stiffness in the second trimester. They also may have a higher risk for gestational diabetes, preeclampsia, infection, preterm rupture of membranes, babies small for gestational age, and preterm delivery than women without this disorder. Active disease at any time during pregnancy is associated with an increased risk of preterm delivery.[67]

The incidence of a postpartum flare is very high (up to 87%) in women with AS or nonradiographic axSpA.[68, 69]

Pregnancy and SLE

Please refer to the United Rheumatology Clinical Practice Guideline—Systemic Lupus Erythematosus

Patients with SLE and hypertension may be treated with ACE inhibitors such as but not limited to lisinopril (Zestril® and Prinivil®), benazepril (Lotensin®), captopril (Capoten®), enalapril (Vasotec®)/enalaprilat injection, fosinopril (Monopril®), moexipril (Univasc®), perindopril (Aceon®), quinapril (Accupril®), ramipril (Altace), and trandolapril (Mavik®). Angiotensin-converting enzyme inhibitors should be stopped in pregnant patients as soon as possible because, in the second and third trimester, they can be associated with decreased fetal renal function causing oligohydramnios that can result in pulmonary hypoplasia and skeletal deformities. These drugs are also associated with hypoplasia of the skull, anuria, hypotension, renal failure, and death in the neonatal period.[70-79] In addition, ARBs such as Entresto® (a combination of sacubitril and valsartan) should be stopped as soon as possible in pregnant patients, because they can produce the same problems as those reported for ACE inhibitors.[80, 81, 42-49]

It is particularly important to plan ahead when a woman has lupus nephritis. She may be taking mycophenolate mofetil, which must be stopped at least 3 months prior to conception; the patient should be switched to azathioprine (Imuran®) and/or tacrolimus (Prograf®),[52, 54] both of which are considered safe during pregnancy by both, EULAR and ACR.[2, 3] This 3-months can be used to assess whether the new regimen is adequately controlling the patient's lupus and/or lupus nephritis before conception. Women taking hydroxychloroquine can continue with this drug, if needed. This drug may also reduce some pregnancy complications.[3, 82] The 2020 ACR Guideline[3] recommends hydroxychloroquine as the drug of choice for pregnant women with SLE. This drug can be used throughout pregnancy.

Lupus nephritis is more likely to flare in pregnancy; therefore, women should be seen every 6 weeks. Patients with anti-Ro and/or anti-La antibodies will require fetal cardiac ultrasounds beginning in week 16 of gestation. Hydroxychloroquine may reduce the risk of congenital heart block.[83] Women testing positive for APL (with the lupus anticoagulant being the most important one) and no previous pregnancy or past successful pregnancies should take aspirin and hydroxychloroquine. If there is a history of one or more first-trimester losses or even one late loss, prophylactic low molecular weight (LMW) heparin twice daily and low-dose aspirin are recommended. In women with a history of thrombosis, therapeutic LMW heparin may also be used. LMW heparin must be transitioned to unfractionated heparin prior to delivery.

For additional information regarding lupus and pregnancy, please refer to HOP-STEP, a website to improve pregnancy planning and management for patients and rheumatologists.[53]

Table 1. Drugs commonly used in the management of rheumatic/autoimmune diseases—key information

Medication	Type of Medication	Commonly Used in these Rheumatic/ Autoimmune diseases	Effects on Fertility	Passes Through the Placenta	Teratogenic	Adverse Effects on Fetus	Long-term Effects in Children	Safe for use In Pregnancy	Lactation
MTX[84] (Rasuvo®, Otrexup®, Rheumatrex®, or generic)	csDMARD	RA PsA SLE	• Impaired fertility • Menstrual dysfunction	+ (MTX and PG)	+	• Cytopenia • Fetal death • Congenital anomalies	–	No	No
Leflunomide[31] (Arava®)	csDMARD	RA PsA SLE	Unknown	Unknown	Inconclusive data	Unknown	Unknown	No • If the patient has taken this drug within the previous 2 years and has an unintended pregnancy, blood levels should be assessed and if above 0 points should have a cholestyramine washout (see text)	No
Sulfasalazine[85] (Azulfidine®)	csDMARD	RA PsA	In men • Oligospermia • Decreased sperm motility • Abnormal sperm	+	–	• Reports of aplastic anemia at >2g maternal dose	Unknown	Yes	Yes
Hydroxychloroquine[86] (Plaquenil®)	csDMARD	RA PsA SLE	Unknown	+	Unknown	Unknown	Unknown	Yes	Yes

Medication	Type of Medication	Commonly Used in these Rheumatic/ Autoimmune diseases	Effects on Fertility	Passes Through the Placenta	Teratogenic	Adverse Effects on Fetus	Long-term Effects in Children	Safe for use In Pregnancy	Lactation
Rituximab[50] (Rituxan®)	CD-20 directed cytolytic antibody	RA	Unknown	Unknown	Unknown	• Can cause B-cell lymphocytopenia in infants exposed in utero lasting approximately 6 months	Unknown	No	Yes
Etanercept[87] (Enbrel®)	TNFi	RA PsA SpA/AS	Unknown	+	Not reported	Unknown	Not reported	• Up to Weeks 30 to 32, if needed	Yes
Infliximab[88] (Remicade®)	TNFi	RA PsA SpA/AS	Unknown	+	Not reported	Unknown	Not reported	• Up to Weeks 16 to 26, if no other safer drug can be used	Yes
Certolizumab[89] (Cimzia®)	TNFi	RA PsA SpA/AS	None to date	Minimal to none	Unknown	Unknown	Unknown	Yes	Yes
Adalimumab[90] (Humira®)	TNFi	RA PsA SpA/AS	Unknown	Unknown	Unknown	Unknown	Unknown	• Up to Week 20, if absolutely necessary	Yes
Golimumab[91] (Simponi®, Simponi Aria®)	TNFi	RA PsA SpA/AS	Unknown	+	Unknown	Unknown	Unknown	No	Yes
Tofacitinib[43] (Xeljanz®)	JAK inhibitor	RA PsA	Unknown	Unknown	Unknown	Unknown	Unknown	No	No
Baricitinib[44] (Olumiant®)	JAK inhibitor	RA	Unknown	Unknown	Unknown	Unknown	Unknown	• Insufficient information	• Advise not to use during lactation

Upadacitinib[45] (Rinvoq®)	JAK inhibitor	RA	Unknown	Unknown	Possibly	Possibly	Possibly	• No • Patients should be advised to use adequate contraception when taking this drug	• Advise not to use during lactation

Medication	Type of Medication	Commonly Used in these Rheumatic/ Autoimmune diseases	Effects on Fertility	Passes Through the Placenta	Teratogenic	Adverse Effects on Fetus	Long-term Effects in Children	Safe for use In Pregnancy	Lactation
Abatacept[42] (Orencia®)	T cell costimulation inhibitor	RA PsA	Unknown	Unknown	Unknown	Unknown	Unknown	No	• No, limited information • Use, if no other choice
Nonselective NSAIDs Aspirin Ibuprofen Indomethacin Diclofenac Etodolac Fenoprophen Flurbiprofen Ketoprofen Ketorolac Nabumetone Naprocin Piroxicam Sulindac Tolmetin	NSAIDs	RA PsA	• Cases of unruptured follicle syndrome which usually reverses when drug is discontinued	+	–	• Decreased renal blood flow and late narrowing of the ductus arteriosus in 3rd trimester • Increased incidence of miscarriage	Unknown	• Only use in 1st and 2nd trimesters • DO NOT USE in 3rd trimester, if possible • Associated with premature closure of the ductus arteriosus (see text for more information)	Yes
Prednisone[92] (nonfluorinated glucocorticoid)	Glucocorticoid	RA PsA	Unknown	Limited	• Increase in oral clefts	• Rare cataracts • Adrenal insufficiency • Infection	Unknown	• Use nonfluorinated glucocorticoids at lowest dose possible at <20 mg per day	Yes

Dexamethasone[93] (fluorinated glucocorticoid)	Glucocorticoid	RA PsA	Unknown	+	Unknown	• Neuro developmental abnormalities	Unknown	• Prefer nonfluorinated glucocorticoids at lowest dose possible • Limited use for 1st or 2nd degree fetal heart block in women with antiRo/SSA and/or anti-La/SSB antibodies*	

Medication	Type of Medication	Commonly Used in these Rheumatic/ Autoimmune diseases	Effects on Fertility	Passes Through the Placenta	Teratogenic	Adverse Effects on Fetus	Long-term Effects in Children	Safe for use In Pregnancy	Lactation
Ustekinumab[48] (Stelara®)	IL-12/23 antagonist	PsA	Unknown	+	Unknown	Unknown	Unknown	• Only use if no other drug is safe for the mother	• Only use if there is no safer alternative for the mother
Ixekizumab[47] (Taltz®)	IL-17 antagonist	PsA	Unknown	Unknown	Unknown	Unknown	Unknown	See text	See text
Secukinumab[46] (Cosentyx®)	IL-17 antagonist	PsA SpA/AS	Unknown	Unknown	Unknown	Unknown	Unknown	See text	See text
Apremilast[49] (Otezla®)	PDE4 inhibitor	PsA	Unknown	Unknown	Unknown	Unknown	Unknown	See text	See text

Lisinopril[70] (Zestril®, Prinivil®) Benazepril[71] Lotensin®) Captopril[72] (Capoten®) Enalapril[73] (Vasotec®) Fosinopril[74] (Monopril®) Moexipril[75] (Univasc®) Perindopril[76] (Aceon®) Quinapril[77] (Accupril®) Ramipril[78] (Altace) Trandolapril[79] Mavik®) Entresto®[80] (combination of sacubitril and valsartan)	ACE inhibitors	SLE	Unknown	+	• Can cause fetal injury and death • If used in 2nd and 3rd trimesters, can decrease fetal renal function causing oligohydramnios that may result in fetal lung dysplasia and skeletal deformities • Hypoplasia of the skull • Anuria • Hypotension • Renal failure			• Do not use in 2nd or 3rd trimesters	• Discuss with provider

Medication	Type of Medication	Commonly Used in these Rheumatic/ Autoimmune diseases	Effects on Fertility	Passes Through the Placenta	Teratogenic	Adverse Effects on Fetus	Long-term Effects in Children	Safe for use In Pregnancy	Lactation

Azilsartan[94] (Edarbi®) Candesartan[95] (Atacand®) Eprosartan[96] (Teveten®) Irbesartan[97] (Avapro®) Losartan[98] (Cozaar®) Olmesartan[99] (Benicar®) Telmisartan[100] (Micardis®) Valsartan[101] (Diovan®)	ARBs	SLE	Unknown	Unknown	• If used in 2nd and 3rd trimester, can cause fetal and neonatal injury, including hypotension skull hypoplasia, anuria reversible or irreversible renal failure and death • Oligohydramnios can also occur resulting in limb contractures, facial deformities, and hypo-plastic lungs • Premature birth • Small for gestational age • Patent ductus arteriosus			• Do not use in 2nd or 3rd trimester	• Discuss with provider
	Statins	SLE	Unknown	Unknown	+			No	See text
Mycophenolate mofetil[51] (CellCept®)	Immuno-suppressive agent	SLE			• Increased risk of 1st trimester loss • Associated with congenital malformations, including external ear, cleft lip, cleft palate, anomalies of distal limbs, heart, esophagus, and kidney			No	No
Medication	**Type of Medication**	**Commonly Used in these Rheumatic/ Autoimmune diseases**	**Effects on Fertility**	**Passes Through the Placenta**	**Teratogenic**	**Adverse Effects on Fetus**	**Long-term Effects in Children**	**Safe for use In Pregnancy**	**Lactation**

Cyclophosphamide[19] (Cytoxan®)	Alkylating drug	SLE	+		• Malformations of palate, limbs, and eyes	• Miscarriage • Premature labor • Fetus small for dates • Leukopenia • Anemia • Bone marrow hypoplasia		No	No
Azathioprine[54] (Imuran®)	Purine metabolite	SLE		+		Unknown		Yes	Yes
Tacrolimus[52] (Prograf®)	Macrolide immune suppressant	SLE	Unknown	+	Unknown	• Neonatal hyperkalemia • Renal dysfunction		• Yes, but monitor mother's blood pressure	Yes
Belimumab[20] (Benlysta®)	Targeted monoclonal antibody	SLE	Unknown	+	Unknown	Unknown		No Should be discontinued at conception and during pregnancy	• Limited information • Discuss with provider

+, yes, or positive; −, no or negative

*Anti-Ro/SSA and anti-La/SSB antibodies are usually found in patients with SLE and primary Sjogren's syndrome; at lower levels, they are also present in patients with RA, systemic sclerosis, and polymyositis.

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; AS, ankylosing spondylitis; csDMARD, conventional disease-modifying antirheumatic drug; JAK, Janus kinase; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PG, polyglutamate; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; SSA, anti-Sjögren's syndrome-related antigen A; SSB, anti-Sjögren's syndrome-related antigen B; RA, rheumatic arthritis; TNFi, tumor necrosing factor inhibitor

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