HHS Public Access

Author manuscript

Obstet Gynecol. Author manuscript; available in PMC 2022 March 17.

Published in final edited form as:

Obstet Gynecol. 2020 May ; 135(5): 1161–1176. doi:10.1097/AOG.0000000000003755.

Rheumatologic Medication Use During Pregnancy: A Review

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Abstract

Chronic rheumatic diseases often occur in women of reproductive age and the impact pregnancy has on rheumatic disease often varies depending on the condition. Medical management of rheumatic diseases during pregnancy may prevent joint or organ damage and minimize the adverse effects of the disease itself on pregnancy outcomes. Each patient requires individual assessment to control disease activity, while minimizing or avoiding medications with potential maternal or fetal toxicity. An open discussion with shared decision-making between patients, obstetricians, rheumatologists, and pharmacists is imperative to create an individualized treatment plan that meets patient's goals. This paper will review the current literature available for use of disease modifying anti-rheumatic drugs and biologics during pregnancy and lactation, providing healthcare professionals with the most up-to-date information available.

Precis:

Appropriate medical management of chronic rheumatic disease during pregnancy can prevent maternal end-organ damage and minimize the adverse effects of the disease on pregnancy outcomes.

Introduction

Chronic rheumatic diseases often occur in women of reproductive age. The impact pregnancy has on rheumatic disease varies by condition. [1] In rheumatoid arthritis, some women experience improvement in disease activity, some have increased disease activity, while others remain stable. [2,3] Patients with ankylosing spondylitis (AS) or systemic lupus erythematosus (SLE) commonly see no improvement or worsening of symptoms.[4]

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Without knowing how a woman's rheumatic disease will respond to her pregnancy, therapy options must be carefully considered. Treating rheumatic diseases during pregnancy may prevent joint or organ damage and minimize the adverse effects the disease itself can have on pregnancy outcomes. [5,6] However, it is important to control disease activity, while minimizing or avoiding medications with risk of maternal or fetal toxicity.

The limited number of drug safety studies and conflicting available information complicates treatment during pregnancy. In 2015 the US Food and Drug Administration updated the Pregnancy and Lactation Rule (PLLR), removing the pregnancy letter categories. The categories were intended to provide a summary of the amount and type of data available but often are inaccurately interpreted as relative levels of safety. Updates include the addition of three sub-sections titled a.) Pregnancy, b.) Lactation, and c.) Females and Males of Reproductive Potential. This information will provide more clinically relevant data to healthcare professionals to aid in better assessment of the benefits versus risks for medication use in patients of reproductive potential. This updated format is only required for prescription drugs and biologic products submitted after June 30, 2015. Products approved prior to this date are required to update the label when information becomes outdated. [1]

The European League Against Rheumatism (EULAR) task force defines overarching principles and considerations for use of antirheumatic drugs during pregnancy and lactation. [7] The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines also provide recommendations for selection of disease-modifying antirheumatic drug (DMARD) and biologic response modifier (biologics) during pregnancy. [8] The American College of Rheumatology (ACR) Reproductive Health in Rheumatic Diseases Guideline is anticipated for publication later in 2019. Since the publication of these earlier guidelines, there have been additional papers published that evaluate the safety of novel therapies in pregnancy.

A collaborative approach should be utilized when developing therapy plans for treatment of rheumatic disease in patients planning to become pregnant, are currently pregnant or lactating. Adequate patient and provider understanding of the risks and benefits for medication use during pregnancy are of utmost importance. Therefore, close communication and shared decision-making between patients, obstetricians, rheumatologists, and pharmacists is necessary to create individualized treatment plans that meet patient goals. This paper will review the current literature available for use of disease modifying anti-rheumatic drugs and biologics during pregnancy and lactation, providing healthcare professionals with the most up to date information available.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDS, which inhibit cyclooxygenase enzymes important for promoting inflammation, are used in a variety of rheumatologic conditions such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The FDA categorizes NSAIDs as category B agents in early pregnancy; however, conflicting data exists. NSAIDS may be used with caution after organogenesis but before the 3rd trimester. NSAID use should be avoided in 3rd trimester given the risks of premature closure of the ductus arteriosus. [9] The NSAID indomethacin was previously used for the treatment of preterm contractions. However, its use for this

purpose has dwindled over recent years due to risks of fetal oligohydramnios, renal failure, and premature closure of the ductus arteriosus. [10]

Some studies have found no increased risk of spontaneous abortions, preterm birth, congenital abnormalities, or infant survival with NSAID use; [11–13] others have suggested increased risk of spontaneous abortions and miscarriages. [11,14] In general, NSAIDs (Cox-1 and Cox-2 inhibitors) are not recommended for use in the third trimester of pregnancy due to a significant increase in the risk of premature closure of the ductus arteriosus, bleeding and oligohydramnios. [15,16]

Glucocorticoids

Steroids exert both anti-inflammatory and immunosuppressive effects through several mechanisms. They are frequently used for short duration, before long-term therapies can take effect in many rheumatologic conditions due to their rapid onset of action. [17]

Glucocorticoids may be used cautiously during pregnancy for flares, if clinically appropriate. [18] Prednisone, cortisone, and hydrocortisone have a rapid onset and minimal transplacental transfer. [19] Betamethasone and dexamethasone cross the placenta with similar maternal and fetal concentrations [20] and for this reason they are useful for conditions such as fetal heartblock. They also serve an important role in preterm labor for prevention of neonatal morbidity from conditions such as respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage.[21]

Initial studies demonstrated an increased incidence of oral clefts when used in the 1st trimester. [22,23] Conversely, some studies have found no increased risk of major anomalies, cleft lip/palate, congenital malformations or miscarriages.[23–25] Several studies have found an association between maternal glucocorticoid use and prematurity. [23,26,27] One study found an association between glucocorticoids and low birth weight, while others found no association. [23,26,27]

Disease-modifying Antirheumatic Drugs (DMARDs)

Apremilast—Apremilast is an oral phosphodiesterase-4 inhibitor approved for psoriatic arthritis. It is a pregnancy category C. [28] Secondary to the limited information available relating to apremilast use in pregnancy, this medication should only be continued if the benefit clearly outweighs the risk. Animal studies have demonstrated a dose-related increase in rates of abortion; however, the rate of placental transfer in humans is unknown. [28,29]

Azathioprine—Azathioprine, which inhibits purine synthesis important for white blood cell production, is used in a wide variety of rheumatologic conditions such as SLE and rheumatoid arthritis. [30] Azathioprine is considered pregnancy category D under the prior FDA classification scheme; however, recent studies have demonstrated it can be appropriately used during pregnancy when benefit outweighs possible risks.[31] Studies have found increased risk of prematurity and congenital abnormalities (including encephalocele, sternocleidomastoid anomalies, congenital cataracts, and atrial and ventricular septal defects) when used during pregnancy.[30,32] However, further studies have not replicated the congenital abnormality findings noted above. Recent studies have continued to note

increased rates of prematurity in addition to lower birth weight, [33,34] while others have found no adverse pregnancy risks. [35 36] In general, when azathioprine is needed to adequately control rheumatic disease and to prevent maternal end-organ damage, its use may be appropriate with careful discussion and shared decision-making.

Colchicine—Colchicine disrupts the polymerization of β-tubulin into microtubules, preventing the activation, degranulation, and migration of neutrophils to sites of inflammation.[37] It is utilized in crystal arthropathies, Behcet's disease and familial Mediterranean fever (FMF). Colchicine is a category C agent that crosses the placenta.[37,38] Its use is recommended only if potential benefit justifies the possible risk to the fetus.[37] Use during pregnancy is highly controversial due to initial high dose animal studies finding teratogenic effects, miscarriages and major congenital malformations. Despite a lack of available randomized controlled trials, there are several observational and retrospective studies in FMF patients that have found colchicine use during pregnancy to be beneficial in controlling disease without increasing the risk of miscarriages or malformation rates. [39–41] Higher rates of preterm delivery and lower median birthweight have been identified with colchicine use, however baseline rheumatic disease may have contributed to these adverse outcomes as well. [40,42]

Hydroxychloroquine—Hydroxychloroquine's mechanism of action in rheumatologic conditions is not completely understood, though it is postulated to increase the pH in acidic vesicles, inhibiting receptor-mediated endocytosis resulting in decreased antigen presentation, toll receptor signaling and post-transcriptional modification of proteins. It is used in a number of rheumatologic conditions including SLE, rheumatoid arthritis and Sjogren's syndrome. [43] Under the prior FDA classification system, hydroxychloroquine was labeled a category C agent. [44] Placental transfer does occur but human pregnancies have resulted in healthy live births and no increased rates of birth defects have been documented. [43,45,46] One study found an association between lower birth weight, earlier gestational age, and higher preterm delivery with hydroxychloroquine exposure during pregnancy. However, confounding factors were present that may have impacted these results. [46] In fact, other studies have found that hydroxychloroquine use in pregnant patients with SLE was associated with lower disease activity, decreased risk of flare, and lower average doses of prednisone during pregnancy. [47] In general, it is recommended that patients with SLE continue hydroxychloroquine use during pregnancy. Hydroxychloroquine is also a reasonable medication to use for other rheumatologic conditions such as RA and Sjogren's syndrome during pregnancy as well, especially when active maternal disease could be harmful to the infant. [44]

Leflunomide—Leflunomide inhibits pyrimidine synthesis and is utilized in a number of rheumatologic conditions including rheumatoid arthritis, psoriatic arthritis, and vasculitis. [48] Leflunomide is classified as a category X drug and should be avoided in women who will be pursuing pregnancy in the near future. [48] Numerous human and animal studies have shown that leflunomide use during pregnancy causes significant minor and major abnormalities. [36,49,50] Due to leflunomide's long half-life and enterohepatic re-circulation, it can take up to 2 years to fully eliminate this medication from the body. If a woman is on therapy and

wants to conceive, a cholestyramine wash-out (8 grams three times per day for 11 days) is recommended. [48,51] Plasma levels should be <0.02 mg/L on two occasions at least 14 days apart. In addition, it is generally recommended to wait three menstrual cycles after elimination prior to attempting to conceive. [48,51]

Methotrexate—Methotrexate is used in a number of rheumatologic conditions including rheumatoid arthritis, psoriatic arthritis, SLE, a number of vasculitides and inflammatory myositis. It also exerts its rheumatologic effects through purine inhibition. [52] Methotrexate is contraindicated during pregnancy. [52,53] It is classified as a category X drug due to risk of spontaneous abortions and fetal abnormalities impacting the heart, central nervous system and skeletal deformities known as "aminopterin syndrome." [52,54,55] It should not be started in women of childbearing age until pregnancy is excluded, two different forms of contraception must be advised, and the patient is fully counseled on the risks to a potential pregnancy.[52] Since methotrexate accumulates in cells it is also recommended that methotrexate be stopped at least 3 months prior to attempting conception. [52] Folic acid supplementation should be continued after discontinuation of methotrexate, through preconception, and throughout the pregnancy. [56]

Initial teratogenic adverse effects were described primarily in individuals on methotrexate doses exceeding the standard weekly doses used in rheumatologic conditions (5 mg to 25 mg).[57] Small studies later failed to show these same typical abnormalities with methotrexate doses between 5mg-25 mg/wk. [56,58–60] However, case reports of low dose (≤7.5 mg/week) methotrexate embryopathy have been described, demonstrating that even low doses can confer risk. [59,61] There are reports of pregnant individuals receiving methotrexate without complications, but this should not lead to underestimating the risk of methotrexate during pregnancy. It could be used as a counseling point in individuals with unintentional pregnancies while receiving methotrexate. [62,63]

Mycophenolate—Mycophenolate inhibits nucleotide synthesis and is used in a number of rheumatologic conditions including SLE, systemic sclerosis, inflammatory myopathies and vasculitis. [64] It is a category D agent under the prior FDA classification system and should be stopped prior to pregnancy. [64] Placental transfer appears to occur but it has not been well characterized. [64] Due to its adverse effects there is a risk evaluation and mitigation strategies (REMS) program to ensure appropriate use of the medication. This requires females of reproductive potential to be counseled regarding pregnancy prevention (two forms of birth control starting 4 weeks prior to initiating therapy), a negative pregnancy test one week prior to beginning therapy, and effective contraception continuing for at least six weeks after stopping mycophenolate. [64]

Use of mycophenolate during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations.[64–66] The incidence of anomalies and the miscarriage rate reported in the National Transplantation Pregnancy Registry (NTPR) is 23% and 49%, respectively. [67] The congenital malformations identified have a consistent pattern with microtia atresia, cleft lip and palate, microphthalmia, and coloboma. Less commonly documented malformations include defects

of the heart, distal limbs, esophagus, vertebrae, kidney, central nervous system, and diaphragm. [64,68–71]

Sulfasalazine—The exact mechanism of action of sulfasalazine in rheumatologic patients is still not completely known but is likely related to anti-inflammatory or immunomodulatory properties. [72] It is utilized in a number of conditions including rheumatoid and psoriatic arthritis. It is a category B agent under the former FDA classification system. Transplacental transfer occurs, with equal maternal and cord blood levels reported. [73] Despite this transfer, large studies have found no increased risks in congenital abnormalities, stillbirth, spontaneous abortion, preterm delivery, or low birth weight. [26,74–76]

Conversely, there have been a few single case studies of abnormalities including cleft palate, macroglossia, congenital deafness, transient neutropenia, hemolytic anemia and neural tube defects.[72,74–76] None of these adverse outcomes have been confirmed in large patient population studies; therefore, sulfasalazine is felt to be generally safe to continue during pregnancy if indicated in the appropriate setting to control disease. However, patients should supplement with additional folate, 2 mg daily, prior to and throughout pregnancy as sulfasalazine is a folate antagonist.[72,77]

Biologic Medications

Abatacept—Abatacept is a selective T-cell costimulation modulator indicated for rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic arthritis. Abatacept is considered pregnancy category C. [78] It is known that abatacept crosses the placenta but use in animal studies has not shown an increased risk of fetal harm. Alterations in immune function, however, have occurred at elevated doses. [2] A case series of 152 patients showed an increased rate of miscarriage and congenital malformation when used with methotrexate.[7] Due to limited available data in humans, the recommendation is to stop abatacept 10 weeks prior to a planned pregnancy or at a minimum during the first trimester. [78,79]

Anti-B-Cell Agents—Belimumab blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B-cells. It is indicated for the treatment of active systemic lupus erythematosus. Belimumab is pregnancy category C and is a monoclonal antibody with known placental transfer during the third trimester. [80] Animal studies have not shown embryo-toxicity or fetal malformations with exposure nine-times the highest expected dose in humans.[80] However, a case series of 153 patients demonstrated a high rate of miscarriage and congenital malformations, though this did not control for confounders.[7] Due to the risks of poorly controlled SLE on the mother and fetus, risks versus benefits must be considered prior to discontinuing therapy. [7,80,81]

Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes, mediating B-cell lysis. In rheumatology, this agent is approved for treatment of rheumatoid arthritis and vasculitis. Rituximab is considered pregnancy category C.[82] Human data has identified an increased rate of miscarriage and congenital and fetal hematologic abnormalities. The fetal harm risks associated with this

medication have led to the recommendation to discontinue 12 months prior to conceiving.[2,79,82]

Interleukin-1 Inhibitors—Anakinra blocks the activity of IL-1 alpha and beta by competitively inhibiting IL-1 binding to the IL-1 type 1 receptor. Anakinra is approved for the treatment of rheumatoid arthritis and cryopyrin-associated periodic syndromes (CAPS). Canakinumab also inhibits IL-1 activity by binding only to IL-1 beta and neutralizing its activity by blocking its interaction with IL-1 receptors. Canakinumab is indicated for the treatment of periodic fever syndromes and systemic juvenile idiopathic arthritis. Rilonacept is indicated for treatment of CAPS and acts by binding IL-1 beta and preventing its interaction with cell surface receptors. Anakinra is considered pregnancy category B[83] and canakinumab and rilonacept are category C.[84] These medications have limited information available for use during pregnancy but may still be used to treat severe and potentially life-threatening disorders throughout pregnancy. A case report of 40 patients receiving anakinra did not show an increased rate of miscarriage or congenital malformation. [7] Additional literature does not support an increased rate of miscarriage, birth defects, or other adverse maternal or fetal outcomes in patients receiving anakinra. [83] One case report demonstrated two-times higher levels of canakinumab in the cord blood and neonatal blood indicating placental transfer. No congenital anomalies were noted upon delivery of the baby.[85] Rilonacept has been shown to cause fetal harm in animal studies at doses lower than what would be expected clinically. [86] Secondary to the limited human data available for use of anakinra, canakinumab, or rilonacept during pregnancy and reports consistent with placental transfer, the risks and benefits of each agent should be considered when deciding to continue during pregnancy. [7,83–85]

Interleukin-6 Inhibitors—Sarilumab and tocilizumab bind to both soluble and membrane bound IL-6 receptors, inhibiting IL-6 mediated signaling. Both agents are approved for treatment of rheumatoid arthritis. Tocilizumab is also indicated for treatment of giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis and cytokine release syndrome. Sarilumab is a newer agent and was not assigned a pregnancy category; however, tocilizumab is considered a pregnancy category C. Both are monoclonal antibodies known to be actively transported across the placenta, with the greatest transfer occurring during the third trimester.[87,88] High-dose sarilumab in animals identified detectable levels in neonates; however, studies have not shown embryotoxicity or teratogenicity. Due to the lack of human data, no recommendation can be made relating to use during pregnancy.[87] Tocilizumab doses greater than 100-fold the dose recommended in humans, demonstrated increased rates of abortion and mortality in animal studies.[79] Furthermore, animal studies have identified that IL-6 inhibition may disrupt cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition.[87,88] Secondary to this information and limited human data it is recommended that tocilizumab be discontinued 10 weeks prior to a planned pregnancy.[79]

Interleukin-12 and 23 Inhibitor—Ustekinumab is a human IgG1κ monoclonal antibody that binds to the p40 protein subunit, disrupting the signaling of IL-12 and IL-23. This agent is approved for treatment of psoriatic arthritis and other non-rheumatologic indications

including psoriasis and Crohn's disease. Ustekinumab has no known placental transfer early in pregnancy, though placental transfer during later trimesters may occur. Based on current human data, there does not appear to be increased rates of miscarriage or congenital malformations; however, due to limited data, no recommendation about its use during pregnancy can be made.[79,89,90]

Interleukin-17 Receptor Inhibitor—Secukinumab is a human IgG1 monoclonal antibody that selectively binds to IL-17A, inhibiting its interaction with the IL-17 receptor. Secukinumab is indicated for the treatment of psoriatic arthritis and ankylosing spondylitis. It is pregnancy category B. There is limited information available in humans; however, placental transfer is more likely to occur during the third trimester.[91] An analysis of the Novartis Global Safety Database found rates of spontaneous abortion in mothers receiving secukinumab to be similar to rates established in a similar population not receiving secukinumab. Unfortunately, this database consists of a small number of pregnancies, many mothers discontinued secukinumab during the first trimester, and many cases have incomplete data.[92] Additional information is needed before further recommendations regarding the use of this medication during pregnancy can be made.[91,92]

Janus Kinase Inhibitors—Baricitinib and tofacitinib are Janus kinase (JAK) inhibitors that modulate the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of Signal Transducers and Activators of Transcription (STATs). Both are approved for treatment of rheumatoid arthritis. Tofacitinib is also indicated for treatment of psoriatic arthritis.

Baricitinib has not been assigned a pregnancy category. High dose baricitinib used in animal studies demonstrated reduced fetal birth weights, increased embryo-lethality, and dose-related increases in skeletal malformations. [93]

Tofacitinib is considered pregnancy category C.[94] High dose tofacitinib used in animal studies has demonstrated teratogenicity and feticidal effects.[2] A case series of 27 patients resulted in 7 miscarriages and 1 of 15 fetuses had a congenital malformation.[7] Current recommendations are to discontinue tofacitinib two months prior to a planned pregnancy.[7]

Tumor Necrosis Factor Inhibitors—This class of medication includes adalimumab, certolizumab, etanercept, golimumab, and infliximab, all of which inhibit tumor necrosis factor activity. These agents are used to treat many rheumatic diseases including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis. All of these agents are considered pregnancy category B.[2,79] Of all biologic medications, TNF inhibitors have the most information relating to their use during pregnancy. These agents have not shown increased rates of miscarriage or congenital malformations during the first trimester. There is placental transfer during the second and third trimesters with the greatest transfer during the third trimester via binding to the neonatal Fc receptor.[7,79] However, certolizumab's binding affinity to the neonatal Fc receptor is absent.[2] Therefore, if certolizumab is continued in the third trimester, the blood levels found in the neonate's cord blood are minimal.[2,3,79] Etanercept has a low binding affinity to the neonatal Fc receptor, whereas the complete monoclonal antibodies such as adalimumab, golimumab, and

infliximab have the highest binding affinity.[3] Data suggests that continuation of golimumab during the first trimester is safe, infliximab and adalimumab may be safely continued until week 20 of pregnancy, etanercept may be continued until week 30 or 32, and certolizumab may be continued throughout pregnancy.[2,3,7,79] Treatment with an agent with high affinity to the Fc receptor after gestational week 30 may lead to fetal/cord levels equivalent or greater than maternal levels. In the newborn, IgG has a prolonged half-life and will typically disappear from the child's serum within the first 6 months of life; therefore, it is recommended to avoid live vaccines for the first 6 months after birth.[7]

Breastfeeding

In addition to weighing the risks versus benefits of using medications during pregnancy, the potential risks associated with their use during breastfeeding must also be considered. The current literature analyzing medication use during breastfeeding will be discussed below, focusing on the rheumatic medications reviewed thus far in this article.

Rheumatic medications found to be compatible with breastfeeding include: indomethacin, ibuprofen, diclofenac, naproxen, piroxicam, prednisone, sulfasalazine and TNF inhibitors. Most NSAIDS are excreted in small amounts into breastmilk; however,[95–97] breastfeeding immediately prior to an NSAID dose may help to minimize infant exposure. [58] Prednisone is also present in breastmilk but exposure to the infant is minimized if breastfeeding is performed immediately before or more than 4 hours after a dose.[95]After breastfeeding, sulfasalazine is detected in infants' serum but concentrations have not been detected at high enough concentrations to displace bilirubin from albumin and cause jaundice. This is supported by no reports of kernicterus being identified in the current literature.[72,98] Overall sulfasalazine has been found to be compatible with breastfeeding but adverse effects need to be monitored and use needs to be avoided in ill, premature, or hyperbilirubinemia and glucose-6-phosphate dehydrogenase deficient infants. [58,77,96,98]

Of the biologic agents, tumor necrosis factor inhibitors have the most data available relating to their presence in breast milk. Adalimumab, certolizumab and etanercept may be present in breast milk but at significantly lower concentrations than in the mother's serum.[2,99–101] Despite the potential presence of etanercept and certolizumab in breast milk, these agents were not present in the serum of a small case series of nursing infants. [2,79,99] Infliximab was undetectable in some samples of breast milk and infant serum; however, some infants did have low serum levels of infliximab despite no presence of infliximab in the breast milk.[2] It is unknown if golimumab is present in the breast milk.[79] It is important to note that the poor bioavailability of these large proteins leads to poor absorption and likely will have minimal effect on a nursing infant.[79] These agents are likely compatible with breastfeeding, but the risk-benefit of using these medications in a breastfeeding mother should always be considered and discussed using shared decision-making.[2,79]

Rheumatic medications found to be incompatible with breastfeeding due to the lack of or limited data include: mycophenolate, methotrexate, leflunomide, colchicine, abatacept, apremilast, rituximab, anakinra, canakinumab, rilonacept, sarilumab, tocilizumab, secukinumab, baricitinib, and tofacitinib. Due to limited information, breastfeeding should be avoided in nursing mothers on mycophenolate.[64,102] Methotrexate is detected in breast

milk in low levels.[52,103] Use of methotrexate is not recommended during breastfeeding, due to side effects (cytopenias) and concern of accumulation in neonatal tissue.[52,96,104] There is no published data on leflunomide levels in breast milk but due to the theoretical risk and long half-life, use of this agent is not recommended while breastfeeding. [48,77] Colchicine is excreted into the breastmilk, but no published data exists for adverse outcomes. However, caution should be exercised and infants should be monitored for any adverse effects if the nursing mother is receiving colchicine therapy.[37] Apremilast is a small molecule and its presence in breast milk is unknown but cannot be excluded.[28] It is unknown if abatacept is secreted in breast milk; therefore, it should not be continued while breastfeeding.[2,78,79] Rituximab is not recommended to be continued while breastfeeding and breastfeeding should not occur within 6 months of the most recent dose of rituximab.[7,79,82] It is unknown if anakinra and canakinumab are secreted in breast milk.[2,7,83,84] One case report of anakinra being continued during lactation did not result in neonatal harm; however, this is not sufficient evidence to ensure the safety of this agent during lactation.[2,7,83] It is unknown if sarilumab or tocilizumab are excreted in human breast milk and there is a lack of data for use during breastfeeding.[79,87,88] Data currently available does not provide insight regarding secukinumab excretion in breast milk; therefore, continuation of this agent while breastfeeding cannot be recommended. [91,92] Baricitinib is present in the breast milk of rats but the clinical relevance of this is unknown.[93] Tofacitinib may be present in breast milk based on its low molecular weight; therefore, it is recommended that tofacitinib not be used when breastfeeding.[2,7,94].

Rheumatic medications with limited data that may be compatible with breastfeeding include: azathioprine, 6-mercaptopurine, hydroxychloroquine, belimumab, ustekinumab. Studies have shown that very low amounts of azathioprine and 6-mercaptopurine appear in breast milk.[105,106] Highest levels of 6-mercaptopurine appear to be present after the first 4 hours of the dose.[107] A study assessing azathioprine use during breastfeeding demonstrated no difference in development, infection, or hospitalization in an infant, whereas a second small study did demonstrate possible risk of neutropenia in infants.(100,106) Hydroxychloroquine is excreted into breast milk in low concentrations but no long term adverse outcomes have been described. [96,108] The anti-B cell agent, belimumab, has an unknown presence in breast milk. Since belimumab is a large protein molecule, absorption is unlikely by the infant due to poor bioavailability. [79–81] There is no data available relating to the presence of ustekinumab in breast milk. If ustekinumab is excreted in breastmilk, since it is a large protein the bioavailability is likely low with poor absorption.[7,89,90]

Discussion

This review summarizes available data about the use of commonly used rheumatologic medications in pregnancy and lactation. It is important to note that due to the ethical implications of performing prospective randomized studies on pregnant women, there is a paucity of data surrounding medication use in this population. Most of the data presented here has been collected from observational studies. Healthcare professionals should regularly discuss pregnancy planning and breastfeeding plans with patients of reproductive age who are on rheumatologic medication so that informed decisions regarding medication use can be made prior to pregnancy and breastfeeding. In the event that

a patient on rheumatologic medication becomes pregnant before such discussion has taken place, we recommend immediate consultation with Rheumatology and OB prior to discontinuing medication, as discontinuation may pose a significant risk for maternal disease flare D[109], which may carry a greater risk to the fetus than continuation of the medication.[110] Discontinuation of medication because of pregnancy in patients with rheumatoid arthritis has been found to be associated with a significantly earlier gestational age at delivery, further underscoring the importance of careful discussion surrounding medication discontinuation.[111]

When possible, patients should work with their rheumatologist to plan pregnancy when their rheumatologic disease is under good control. Studies show that patients with preconception lupus activity have a six-fold increase in gestational loss [112] and that active disease is a predictor of SLE flare (p=0.002) and fetal loss (p=0.018) [113], emphasizing the importance of achieving remission prior to conception. In women with RA, higher disease severity early in pregnancy correlated with risk of preterm delivery and SGA.[114] General consensus is that the rheumatologic disease should be under good control for at least 6 months prior to conception, preferably on a regimen that is compatible with pregnancy.[115]

A multidisciplinary care team consisting of Maternal Fetal Medicine, Obstetrics, rheumatology, primary care, pharmacy, and any other pertinent subspecialists is vital to promoting good outcomes for pregnant patients with rheumatologic disease. [116,117] Because high quality evidence regarding rheumatologic medication use in pregnancy is often lacking and the care of the pregnant patient is often nuanced and emotionally charged, we recommend the use of shared decision-making to promote informed choices that carefully balance the risk and benefit to the mother and baby while preserving respect for patient autonomy.

Acknowledgments

No financial support or funding was received for this study.

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Table 1:

Biologic Disease-Modifying Antirheumatic Drugs in Pregnancy

Drug	Mechanism of Action	Rheumatologic uses	Pregnancy Category	Data Available	Placental Transfer	Lactation
Abatacept [2,78,79]	Selective T cell co-stimulation modulator	• rheumatoid arthritis • juvenile idiopathic arthritis • psoriatic arthritis	C	• No increased risk in animal studies when exposed to maximum recommended human dose. • At extremely elevated doses there were alterations in immune function. • Recommended to discontinue 10 weeks prior to conception • A case series of 152 patients resulted in increased rates of miscarriage and congenital malformations when used in combination with MTX • Registry for monitoring use in pregnancy (1–877-311–8972)	• Crosses the placenta but animal studies have not revealed congenital abnormalities	• Unknown if secreted in breast milk; therefore, considered contraindicated
Adalimumab [2,3,7]	TNF inhibitor	• Rheumatoid arthritis • Juvenile idiopathic arthritis • Ankylosing spondylitis • Psoriatic arthritis	B	• No increased rate of miscarriages or congenital malformations when used during first trimester. • Placental transfer during 2nd and 3rd trimester • If continued in the 3rd trimester, the result is therapeutic levels in the newborn's cord blood.	• Greatest during 3rd trimester • IgG1 molecules are actively transported from maternal circulation to the fetal circulation via binding to the neonatal Fc receptor. • Binding affinity to the neonatal Fc receptor is highest for complete monoclonal antibodies.	• Presence detected at 0.1% to 1%, no effect on milk production or adverse effects
Apremilast [28]	Phospodiesterasae-4 inhibitor	• Psoriatic arthritis	C	• Dose related abortions have been reported in animal studies	• Rate of placental transfer is unknown	• Presence in breast milk is unknown but cannot be excluded
Anakinra [2,7,83]	IL-1 inhibitor	• Rheumatoid arthritis • Cryopyrin associated periodic syndromes	B	• No harm was demonstrated in animal studies even at doses 25 times the maximum recommended human dose. • In one report of use during pregnancy, placenta retention was the only abnormality. • Limited data reported relating to safety if continued during pregnancy.	• Has been shown to pass through placenta.	• Due to limited data its use is not recommended.
Baricitinib [93]	JAK inhibitor	• Rheumatoid arthritis	-	• High doses in animals resulted in reduced fetal body weights, increased embryo-lethality, and does related increases in skeletal malformations	• Unknown	• Present in animal breast milk but clinically relevance in humans is unknown
Belimumab [7,80,81]	Reduces B-cell activity	• Systemic lupus erythematosus	C	• One case report demonstrated healthy pregnancy with mild Epstein's anomaly in baby. • No evidence in animal models of embryotoxicity or fetal malformations with exposure 9 times the exposure at the maximum recommended human dose. • Registry for monitoring use prior to or	• Actively transported across the placenta during the third trimester and may affect immune response in the in utero-exposed infant.	• No data; however, large protein molecule; therefore, absorption unlikely due to low bioavailability.

Drug	Mechanism of Action	Rheumatologic uses	Pregnancy Category	Data Available	Placental Transfer	Lactation
				during pregnancy (http://pregnancyregistry.gsk.com/belimumab.html or www.bprgsk.com)		
Canakinumab [84,85]	IL-1 inhibitor	• Cryopyrin-associated periodic syndromes • Familial Mediterranean fever • Hyperimmune D syndrome • Mevalonate kinase deficiency • Tumor necrosis factor receptor associated periodic syndrome	C	• Fetal skeletal development delay in animal models at doses 23-fold the maximum recommended human dose and greater; there was no embryotoxicity or fetal malformations. • No human studies	• A case report in a patient with Muckle Wells Syndrome, demonstrated 2 times higher levels of canakinumab in the cord blood and neonatal blood indicating active placental transfer. The baby was delivered, and no congenital anomalies were identified.	• Unknown if secreted into breast milk.
Certolizumab [2,7]	TNF inhibitor	• Ankylosing spondylitis • Axial spondyloarthritis • Psoriatic arthritis • Rheumatoid arthritis	B	• No increased rate of miscarriages or congenital malformations when used during first trimester. • Possible placental transfer during 2nd and 3rd trimester. • If continued in the 3rd trimester, the result is below detection to minimal levels of certolizumab can be found in the neonate's cord blood.	• Greatest during 3rd trimester • IgG1 molecules are actively transported from maternal circulation to the fetal circulation via binding to the neonatal Fc receptor. • Binding affinity to the neonatal Fc receptor is absent with Certolizumab.	• Unknown if secreted into breast milk. • (see other TNF information)
Etanercept [2,7]	TNF inhibitor	• Ankylosing spondylitis • Psoriatic arthritis • Rheumatoid arthritis • Juvenile idiopathic arthritis	B	• No increased rate of miscarriages or congenital malformations when used during first trimester. • Placental transfer during 2nd and 3rd trimester. • If continued in the 3rd trimester, the result is very low levels of etanercept can be found in the neonate's cord blood.	• Greatest during 3rd trimester • IgG1 molecules are actively transported from maternal circulation to the fetal circulation via binding to the neonatal Fc receptor. • Binding affinity to the neonatal Fc receptor is low.	• Undetectable in one infant (12 weeks old), despite being present in the breast milk.
Golimumab [2,7]	TNF inhibitor	• Ankylosing spondylitis • Psoriatic arthritis • Rheumatoid arthritis	B	• No increased rate of miscarriages or congenital malformations when used during first trimester. • Placental transfer during 2nd and 3rd trimester • If continued in the 3rd trimester, the result is therapeutic levels in the newborn's cord blood.	• Greatest during 3rd trimester • IgG1 molecules are actively transported from maternal circulation to the fetal circulation via binding to the neonatal Fc receptor. • Binding affinity to the neonatal Fc receptor is highest for complete monoclonal antibodies.	• Unknown if secreted into breast milk. • (see other TNF information)
Infliximab [2,7]	TNF inhibitor	• Ankylosing spondylitis • Psoriatic arthritis • Rheumatoid arthritis	B	• No increased rate of miscarriages or congenital malformations when used during first trimester. • Placental transfer during 2nd and 3rd trimester	• Greatest during 3rd trimester • IgG1 molecules are actively transported from maternal circulation to the	• Undetectable in breast milk samples and serum of 3 infants.

Drug	Mechanism of Action	Rheumatologic uses	Pregnancy Category	Data Available	Placental Transfer	Lactation
				• If continued in the 3rd trimester, the result is therapeutic levels in the newborn's cord blood.	fetal circulation via binding to the neonatal Fc receptor. • Binding affinity to the neonatal Fc receptor is highest for complete monoclonal antibodies.	
Rilonacept [86]	IL-1 inhibitor	• Cryopyrin Associated Periodic Syndromes	C	• Fetal harm occurred during animal studies at exposure that was below that expected clinically	• Unknown	• Unknown
Rituximab [2,7]	Binds the CD20 antigen activating B-cell cytotoxicity	• Rheumatoid arthritis • Granulomatosis with polyangiitis	C	• Documented spontaneous and therapeutic abortions and premature births. • Congenital abnormalities have included a clubfoot, ventral septal defect, patent foramen ovale, and patent ductus arteriosus. • Hematologic abnormalities and increased risk of infection noted.	• Reduction of B cells has been noted in offspring. • Potentially increasing risk of infection and/or hematologic abnormalities.	• Unknown if secreted into breast milk.
Sarilumab [87]	IL-6 inhibitor	• Rheumatoid arthritis	-	• In animal studies it was not embryotoxic or teratogenic with exposure up to 84 times the maximum recommended human dose and it did not impact growth or development up to one month after birth; however, sarilumab was detected in the serum of neonates. *Pregnancy exposure registry: 1–877-311–8972.	• Monoclonal antibodies are actively transported across the placenta during the 3rd trimester • Detected in animal neonate's serum 1 month after birth	• Unknown if secreted into breast milk.
Secukinumab [91,92]	IL-17 inhibitor	• Ankylosing spondylitis • Psoriatic arthritis	B	• No adverse development effects or embryo-fetal toxicity were observed in animals at doses 30 times those recommended in humans • Data from Novartis global safety database showed: 238 pregnancies, rates of spontaneous abortions were in line with established rates for this population; however, most patients stopped secukinumab during the 1st trimester	• Humanized monoclonal antibody with the majority of placental transfer during the 3rd trimester	• Unknown if excreted in breast milk.
Tocilizumab [79,88]	IL-6 inhibitor	• Rheumatoid arthritis • Giant cell arteritis • Polyarticular JIA • Systemic JIA • Cytokine release syndrome	C	• No teratogenicity demonstrated in animal models at any dose. • Increased risk of abortion rates and fetal mortality at doses >100-fold the dose used in humans. *Pregnancy exposure registry: 1–877-311–8972.	• Monoclonal antibodies are transported across the placenta in a linear fashion, with the largest amount transferred during the 3rd trimester.	• Unknown if secreted into breast milk; however, IgG is excreted in human milk; therefore, it is expected that it could be present. Breastfeeding is not recommended while using this medication.
Tofacitinib [2,7,94]	JAK inhibitor	• Psoriatic arthritis • Rheumatoid arthritis	C	• Teratogenicity and feticidal effect at much higher levels than the maximum recommended dose in humans have been reported in animal studies. *Pregnancy exposure registry: 1–877-311–8972.	---------	• No data but due to its low molecular weight passage into breast milk possible. Should not be used when breastfeeding.

Drug	Mechanism of Action	Rheumatologic uses	Pregnancy Category	Data Available	Placental Transfer	Lactation
Ustekinumab [7,89,90]	IL-12/23 inhibitor	• Psoriatic arthritis	B	• Limited data but based on what is known there is no increased rate of miscarriage or congenital malformation in animal studies at doses 100 times the maximum recommended human dose. *Pregnancy exposure registry: 1–877-311–8972.	• Does not cross the placenta early in pregnancy but may cross later in pregnancy.	• No data; however, large protein molecule; therefore, absorption unlikely due to low bioavailability.

Table 2:

Disease-Modifying Antirheumatic Drugs in pregnancy

Drug	Mechanism of Action	Rheumatologic Uses	Pregnancy Category	Data Available	Placental Transfer	Lactation
Azathioprine 31,106,107,118	Purine synthesis inhibitor	• Systemic lupus erythematosus • Rheumatoid Arthritis	D	• Human studies suggest azathioprine exposure is not associated with increased risk of congenital malformations • Initial studies found that it can cause lower birth weight, gestational age and prematurity but not fetal malformations. Recent studies have not found these same risks • Risk vs. benefit must occur for disease state and possible medication adverse events	• Azathioprine and 6-mp cross the placenta in low concentrations • 6-mp is not converted to active form thioinosinic acid in the fetus due to a lack of fetal inosine pyrophosphorylase enxyme	• Very small amounts have been detected in breastmilk and negligible amounts in neonates • Highest levels appear to be first 4 hours after consumption
Hydroxychloroquine 44,45,108–		• Systemic lupus erythematosus • Rheumatoid arthritis • Sjogren's syndrome	- (C previously)	• Human pregnancies resulting in live births have been reported in the literature and no increase in the rate of birth defect has been demonstrated • Male fertility: decreases sperm count, full count will recover ~ 2 months after stopping therapy (life cycle of sperm is 74 days)	• Placental transfer occurs	• Excreted into breast milk in low concentrations • No long-term outcomes have been described
Leflunomide 48–50	Pyrimidine synthesis inhibitors	• Rheumatoid arthritis • Psoriatic arthritis • Takyasu arteritis • Giant cell arteritis	X	• Teratogenicity and embryo-lethality occurred in animals administered leflunomide at doses lower than the human exposure • Human studies have demonstrated minor and major abnormalities in the fetus	• Placental transfer occurs	• No studies available • Women should discontinue breastfeeding during treatment
Methotrexate 52,55,56,96,119,120	Purine synthesis inhibitor	• Rheumatoid arthritis • Psoriatic arthritis • Systemic lupus erythematosus • Vasculitis • Inflammatory myositis	**X**	• Known teratogenic effect; fetal death and congenital malformations • Use in first trimester has shown malformation (head, face, limbs and bones), poor growth, developmental delays, and intellectual disabilities. • Some studies have shown heart defects and oral clefts (less evidence available) • Currently there is a lack of studies on the safety of methotrexate and male reproduction	• Placental transfer modulated by protein pumps	• Detected concentrations in breast milk • Due to side effects and concerns for accumulation use is contraindicated
Mycophenolate 64,65,67	Nucleotide synthesis inhibitor	• Systemic lupus erythematosus • Systemic sclerosis • Myopathies • Bechet's disease	D	• Human data demonstrates increased risk of congenital malformations (ear, eye, and lip/palate abnormalities), anomalies (distal limb heart, esophagus, kidney, and nervous system) and first trimester pregnancy loss • The incidence of anomalies and the miscarriage rate reported in National	• Placental transfer occurs but it has not been well characterized	• Unknown if secreted into breast milk • Use should be avoided

Drug	Mechanism of Action	Rheumatologic Uses	Pregnancy Category	Data Available	Placental Transfer	Lactation
				Transplantation Pregnancy Registry (NTPR) is 23% and 49%, respectively		
NSAIDS [58,95,96]	Cyclooxegenase enzyme inhibitor	• Rheumatoid arthritis • Psoriatic arthritis • Ankylosing spondylitis	B	• Large studies have not found an increased risk of congenital abnormalities, prematurity or preterm birth Some studies have shown increased risk of miscarriages and spontaneous abortion • Not recommended in 3rd trimester due to increased risk of premature closure of ductus arteriosus	• -	• Indomethacin, ibuprofen, diclofenac, naproxen, and piroxicam are considered compatible • Short acting agents preferred • Breastfeeding immediately before dose is preferred
Corticosteroids [19,20,95]	Anti-inflammatory and immunosuppressive through numerous mechanism	• Most rheumatologic conditions	-	• Prednisone, cortisone, or hydrocodone ideal formulations due to rapid onset and minimal placental transfer Betamethasone and dexamethasone cross placenta with similar maternal and fetal complications; should not be used • Possible increased risk of cleft lip/ palate but recent studies have not found same risk	• Minimal placental transfer with prednisone, cortisone and hydrocortisone • Betamethasone and dexamethasone cross placental with similar maternal and fetal concentrations	• Found to be safe during breastfeeding • Ingestion by the infant is <0.1% of maternal dose • Exposure is minimized by breastfeeding immediately before or 4 hours after ingestion
Sulfasalazine [2,72]	Unknown	• Rheumatoid arthritis • Psoriatic arthritis	B	• Rat and rabbit studies with doses up to 6 times higher than that of human doses resulted in no fetal harm • Studies have not found increased risk of congenital abnormalities, low birth weight, miscarriages or prematurity • Male fertility: reversible sperm count occurs while on therapy but could decrease chance of children long term	• Sulfasalazine and its metabolite (sulfapyridine) pass through placenta	• Active metabolite detected in breast milk at 30–60% of maternal serum • Use with caution ill, premature, or hyperbilirubinemia and glucose-6-phosphate dehydrogenase deficient infants
Colchicine [37]	Prevents microtubule formation	• Gout • Familial Mediterranean fever • Behcet's	C	• No adequate well controlled studies in humans; however published animal studies demonstrated embryo fetal toxicity, teratogenicity, and altered postnatal development at exposures within or above clinical therapeutic range • More recent studies have found no increased risk of miscarriages or major fetal malformations while being treated for FMF. • No specific data available for gout	• Crosses the placenta	• Excreted in breastmilk; limited information suggests infants receive < 10% of maternal weight-adjusted dose