Current Rheumatology Reports (2019) 21: 16
https://doi.org/10.1007/s11926-019-0816-y

RHEUMATOID ARTHRITIS (L MORELAND, SECTION EDITOR)

Family Planning and Rheumatoid Arthritis

Nicole Hunt[1] · Mehret Birru Talabi[1]

Published online: 6 March 2019

Abstract

Purpose of Review Patients with rheumatoid arthritis (RA) have special family planning considerations that require close coordination with health care providers. While this article focuses on issues inherent to female patients given their potential for pregnancy, we will review pertinent issues related to medication counseling for male patients.

Recent Findings Some women with RA may experience subfertility. Disease activity may decrease for some, but not all pregnant women with RA. Preterm birth is more common among women with RA than among healthy women, which may be explained, in part, by disease activity and/or use of certain medications. Contraception is safe for women with RA.

Summary RA is a chronic, female-predominant inflammatory disease that may affect women and men during their reproductive years. We describe some of these considerations herein and focus on strategies to help providers to clarify and support their patients' reproductive goals.

Keywords Rheumatoid arthritis · Women's health · Family planning · Pregnancy

Introduction

Population estimates suggest that over 2000 women with rheumatoid arthritis (RA) become pregnant in the USA per annum [1]. As treatments continue to improve, and RA becomes a less disabling disease, even more women with RA may consider the potential for pregnancy and childbearing. This review will focus on issues related to fertility, pregnancy, contraception safety, safe medication prescribing during pregnancy and lactation, and pre-pregnancy counseling for individuals with RA.

RA and Fertility

For at least 60 years, women with RA have been observed to have smaller family sizes and higher rates of nulliparity than women without RA [2–6]. Postulated reasons for the family size discrepancy have included clinical factors such as a physical disability that limits sexual activity, subfertility due to highly active disease or the use of certain drugs, higher rates of miscarriage, and patients' personal preferences for family size [7–11].

Several studies suggest that subfertility and nulliparity do indeed contribute to smaller family sizes among a subset of women with RA. Twenty-five percent of women with RA enrolled in the US National Data Bank for Rheumatic Diseases (NDB) who responded to a reproductive health survey ($n = 578$) self-reported infertility [12]. The prospective cohort study, Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA), reported that 42% of women with RA who were trying to conceive experienced prolonged time to pregnancy (TTP) of at least 12 months until conception [9]. In comparison, the US Centers for Disease Control and Prevention (CDC) estimates that 12.1% of all women 15–44 years old have impaired fertility [13].

Reasons for subfertility and nulliparity among RA patients remain unclear. Among patients in the NDB cohort, 19% reported ovulatory dysfunction and 10% reported endometriosis as causes for their infertility; 15% had unexplained infertility [12]. Among women in the PARA cohort who were subfertile, 48% cited unknown causes for the subfertility, and approximately 28% reported ovulatory dysfunction. Medications may also increase the risk of subfertility among RA patients; in the PARA trial, prolonged TTP appeared to be associated with

This article is part of the Topical Collection on *Rheumatoid Arthritis*

✉ Mehret Birru Talabi
birrums@upmc.edu

[1] Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh, 3500 Terrace Street, Pittsburgh, PA 15261, USA

preconception use of NSAIDs or prednisone at doses higher than 7.5 mg daily, even after adjustment for disease activity [9]. At this time, there is no clear association between reduced ovarian reserve as measured through anti-Mullerian hormone levels, and reduced fertility in RA patients [14].

An alternative explanation for smaller family sizes among women with RA may relate to patients' personal preferences and priorities. In one retrospective survey of women with RA, approximately 20% reported that their RA diagnosis had negatively affected their desire to have children [6]. Women cited concerns about their abilities to care for children given physical limitations and fatigue, and fears about whether their medications might affect a developing fetus and/or their diseases might be hereditary. In the NDB cohort, women generally expressed similar concerns; those with more concerns about pregnancy and motherhood trended towards having had fewer pregnancies [12].

While these data collectively suggest that some women may experience subfertility, or may wish to avoid pregnancy because of their diseases, it is important for health care providers to avoid the assumption that women with RA are infertile, subfertile, or uninterested in pursuing pregnancy. Women who erroneously believe that they are subfertile without verification may be more likely to engage in unprotected sex, which could increase the risk for an unintended and/or undesired pregnancy. Thus, women should be counseled to assume that they are fertile RA, pending verification from a reproductive specialist who can confirm, for example, whether prolonged TTP is related to the female patient and not to her (male) partner. In the case of female infertility, assisted reproductive technologies (ART) have been found to be safe and effective among women with RA [15•].

RA and Pregnancy

Disease Activity During Pregnancy

RA disease activity improves for many women during pregnancy—as many as 48–86% of patients experience clinical improvement—according to some studies [16–18]. However, fewer patients may experience disease remission than was previously believed. One prospective study from the UK found that while women trended towards improved disease activity by the third trimester, only 16% achieved complete remission [17]. In the PARA trial, remission rates increased from 17% at preconception to 27% by the third trimester, a difference of only 10%. While women with moderate-to-high disease activity scores in the first trimester experienced a significant drop in scores; their average disease activity scores remained at a moderate level [18].

Variation in reports of improved disease activity during pregnancy may reflect the retrospective nature of patient reports in some studies, which may be limited by recall bias; alternatively, some studies use patient reports while other studies use objective assessments of disease activity (e.g., Disease Activity Score (DAS)-28 or Health Assessment Questionnaire (HAQ) scores). Serologic status may also contribute to the variation in reports of improved disease activity; in the PARA trial, women who did not have anti-cyclic citrullinated peptide antibodies or rheumatoid factor were more likely to experience an improvement during pregnancy, whereas the disease activity of women with seropositive RA was unchanged during pregnancy [19]. This poses the question whether all of the women who experience "improvement" during pregnancy actually have RA rather than another type of inflammatory arthritis (e.g., spondyloarthritis or sarcoidosis).

Rather than improve, some women may actually experience disease flares, both during pregnancy and in the post-partum period. Some pregnancy-associated flares may be linked to the discontinuation of medical therapies during pregnancy [20]. In the PARA cohort, approximately 40% of women had moderate or severe post-partum flares between 12- and 26-week post-partum [18].

Immunologic causes of fluctuations in disease activity during pregnancy and the post-partum period remain speculative. Immune tolerance during pregnancy facilitates the viability of the fetus despite human leukocyte antigen (HLA) incompatibility between the mother and fetus. A shift from a T helper cell 1 (Th1) immune response towards a T helper cell 2 (Th2) immune response pattern may mediate the decrease in the disease activity experienced by some women [21]. Another possibility may be the role of regulatory T cells, or Tregs, which appear to maintain immunologic self-tolerance and also have been found to facilitate maternal tolerance of a developing fetus [22]. Treg levels among pregnant women with RA increased during pregnancy in one small study and were inversely associated with disease activity in the third trimester and post-partum [23].

Pregnancy Outcomes

Pregnancy outcomes for women with RA are generally favorable, although an increased rate of preterm births (9.2–28%) and small-for-gestational-age (SGA) babies have been observed in both retrospective and prospective cohorts [24–29]. One retrospective trial found that women with active RA at any time during pregnancy had 52% higher incidence of preterm birth as compared with controls; this association remained significant after adjustment for the use of steroids and biologic or non-biologic disease-modifying anti-rheumatic drugs (DMARDs) [27].

While the use of DMARDs did not increase the risk of preterm birth, the use of steroids in any trimester was associated with a two- to fivefold increased risk for preterm birth in the PARA trial and the Organization of Teratology Information Specialists (OTIS) Autoimmune Disease in

Pregnancy Project [27, 30]. Therefore, medication use may not entirely explain the associations between disease activity and preterm birth. Future work is needed to explore the mechanisms by which increased RA disease activity and medications may affect pregnancies of women with RA.

RA and Contraception

In addition to pregnancy prevention, contraception may confer unique benefits to women with RA. For example, contraception may help to delay a desired pregnancy until a time when the patient is using pregnancy-compatible medications and/or her disease is well controlled. In this way, contraception may optimize the timing of pregnancy and thereby may help to improve maternal, fetal, and pregnancy outcomes. Yet, among approximately 2500 reproductive-age women with RA and other rheumatic diseases, we found that only 32% were prescribed contraception over a 2-year timeframe [31]. In contrast, 43% of US women in population-based studies use prescription contraception [32].

These data suggest that some women with RA have unmet contraceptive needs. The reasons for these gaps in contraceptive care are likely multifactorial. Primary care physicians (PCPs) may prefer for subspecialists to manage family planning care for medically complex patients [33], but some rheumatologists do not feel qualified to prescribe contraception. Changes in cervical and breast exam screening recommendations have contributed to fewer annual women's health visits with gynecologists [34–36].

Therefore, it is important for all health care providers who care for female patients with rheumatic diseases to have a general appreciation for the safety and efficacy of the various contraceptive methods. While not explicitly covered herein, it is also important to appreciate that many women select contraceptive methods based on factors other than safety or efficacy, such as reversibility, side effects, convenience, costs, and non-contraceptive benefits.

Contraception Safety and Efficacy

Despite the various myths and misperceptions that exist among patients and providers alike, most forms of contraception are safe for women with RA who wish to avoid pregnancy. First, there is no direct evidence, as extrapolated from other immune-suppressed populations (e.g., HIV), that intrauterine devices (IUDs) are associated with increased risk of pelvic infections [37]. Hormonal contraception is not consistently associated with increased or decreased RA activity in studies. Finally, nulliparity is not a contraindication to IUD and does not increase the risks of uterine perforation or infertility [38, 39]. The Medical Eligibility Criteria for Contraceptive Use (MEC) published by the CDC provides guidance to health care providers who prescribe contraception to women with RA and other chronic medical conditions [40]; MEC recommendations will be summarized herein.

Progestin-only pills and subdermal implants are safe to use without restriction among women with RA. Copper- and levonorgestrel-containing IUDs are also safe to use, but the MEC describes one caveat: women who use immune suppression may require more follow-up to assess for complications such as pelvic infections. It should be noted, however, that longitudinal studies of women with solid organ transplants and HIV have not demonstrated an increased risk of pelvic infections with either the copper or levonorgestrel IUD.

Combined estrogen-progestin hormonal pills, patches, and rings are also considered safe to be used by women with RA, with no apparent risk for thrombosis posed by RA. Estrogen-containing contraception is generally associated with higher thrombotic risk among women who smoke and have migraines with aura [40].

The depot medroxyprogesterone acetate (DMPA) shot may be used with somewhat more caution among women who are at risk for or have a history of non-traumatic fractures (e.g., chronic users of corticosteroids). DMPA leads to transient lower bone mineral density, which could theoretically predispose patients to fractures, although this has not explicitly been studied among women with RA.

In addition to contraceptive safety, the efficacy of various methods may be an important consideration for women at an increased risk of pregnancy complications, such as women who use fetotoxic anti-rheumatic drugs (e.g., methotrexate and mycophenolate mofetil) (Table 1). The relative efficacy of contraceptive methods is presented in Table 2.

Medication Safety in RA During Preconception, Pregnancy, and Lactation

The safety of anti-rheumatic drugs during pregnancy is a major concern for patients and providers alike. The European League Against Rheumatism (EULAR) and the British Society for Rheumatology (BSR) have developed helpful guidelines that may give rheumatologists more confidence in the prescription of pregnancy-compatible medications to patients [41••, 43, 44••]. The American College of Rheumatology has also developed guidelines for medication prescription during pregnancy and lactation that will be published in 2019. Such guidelines are especially valuable since conflicting opinions about medication safety between providers such as obstetricians and rheumatologists [45] may diminish patients' confidence in their treatments.

Social norms and expectations for mothers may prioritize children above the mother's physical functioning and needs [46]; thus, some women may feel that to be "good mothers," they must forgo treatment of their RA during pregnancy. However, as indicated in the sections above, pregnancy outcomes appear to be worse among women with active RA.

Table 1 DMARD safety in preconception and pregnancy based on the EULAR recommendations [41••]

Continue	Discontinue, unsafe	Discontinue, insufficient data
Antimalarials	Methotrexate	Leflunomide
Sulfasalazine	Mycophenolate mofetil	Tofacitinib
Azathioprine	Cyclophosphamide	Abatacept
Ciclosporin		Rituximab
Tacrolimus		Belimumab
Colchicine		Tocilizumab
Intravenous immunoglobulin Glucocorticoids		Ustekinumab
		Anakinra

Thus, women—especially those with active RA at the time of conception—may need to be counseled that discontinuation of safe medications during pregnancy is not necessarily a neutral decision and could potentially affect not only their physical functioning but also the health of their children.

Patients may require additional resources to better conceptualize the safety and compatibility of their medications with pregnancy and lactation. The OTIS "MotherToBaby" website is one such trusted online resource, through which patients may learn more about the compatibility of their medications with pregnancy and lactation [47]. The American College of Rheumatology website also contains helpful patient information about pregnancy, medications, and rheumatic diseases [48].

Pregnancy-Compatible NSAIDs, Non-Biologic DMARDs, and Steroids

The data regarding the safety of using certain drugs during pregnancy may vary. NSAIDs, like sulfasalazine and hydroxychloroquine, do cross the placenta, but are not associated with birth defects. However, NSAIDs should be used with caution as they may increase time to pregnancy among women who are trying to conceive [9], possibly by inhibiting ovulation [49]. NSAIDs have also been linked to increased risk of miscarriages in population studies [50], although these data have been somewhat inconclusive [51]. In the third trimester, they may also cause premature closure of the fetal patent ductus arteriosus [52]. As few studies have evaluated the safety of Cox-2 inhibitors in pregnancy, classical NSAIDs may be preferred for use among pregnant women with RA [53–55].

Hydroxychloroquine is considered compatible with pregnancy. When taken daily at doses of 400 mg or less, it is not associated with increased risk of birth.

Sulfasalazine is also considered safe in pregnancy, with much of its safety data being extrapolated from women with inflammatory bowel diseases [53, 56]. As sulfasalazine is a dihydrofolate reductase inhibitor, folic acid supplementation may be considered for women who use sulfasalazine and who are considering pregnancy. Sulfasalazine was found to cause bloody diarrhea in one infant whose mother used 3 g per day, and thus women should be counseled to consider discontinuation of sulfasalazine if their infants develop intractable diarrhea [57].

At low doses, prednisone or other non-fluorinated steroids are less likely to cross the placenta than fluorinated steroids [58, 59]. While one study of women with RA found that steroid use was associated with preterm birth [9], steroids are also used to prevent preterm birth among women in the general population who are at risk for preterm delivery [60].

Table 2 Efficacy of contraception methods

Highly effective methods	Moderately effective methods	Least effective methods
< 1 pregnancy/100 users/year	6–12 pregnancies/100 users/year	> 18 pregnancies/100 users/year
Irreversible	Combined hormonal contraceptives	Male condoms
Surgical sterilization (male/female)	-Pill	Female condoms
	-Patch	Diaphragms
		Natural family planning
		Sponge
Long-acting reversible contraceptive methods (LARC)	-Vaginal ring	Spermicides
1. Progestin-only subdermal implants	Depot medroxyprogesterone acetate ("Depo shot")	
2. Copper IUD		
3. Levonorgestrel IUD		

Data extrapolated from the Centers for Disease Control and Prevention [42]

Therefore, more investigation is needed on the safety of prednisone among women with RA, although low-dose steroids given orally, intramuscularly, or intraarticularly, are generally felt to be compatible with pregnancy [41••, 43].

While small concentrations of NSAIDs, hydroxychloroquine, and prednisone may be found in breast milk, they generally have not been associated with adverse effects on breastfeeding infants [57, 61, 62]. In general, women may find it reassuring that less drug transfer occurs during breastfeeding than during pregnancy [57].

Pregnancy-Compatible Biologic DMARDs

Tumor necrosis factor-alpha (TNF-α) inhibitors are biologic anti-rheumatic drugs that currently appear to be safe during pregnancy and lactation. TNF-α inhibitors are generally too large to cross the placenta by simple diffusion, and active cross-placental transport does not begin until approximately 16–18 weeks of gestation [63]. Organogenesis is generally complete by 12-week gestation; as the developing fetus is not exposed to TNF-α inhibitors during organogenesis, it is unlikely to develop birth defects related to the medication [64]. Findings from a variety of studies support the theory that pregnancy and fetal outcomes do not differ between users of TNF-α inhibitors and controls [65–68].

However, TNF-α inhibitors can be detectable in the neonatal circulation at least 6 months post-delivery, particularly infliximab and adalimumab [63]; maternal TNF-α inhibitor use currently does not appear to be a predictor for increased neonatal infections [69•]. Given concerns about immunosuppression of the newborn, consensus recommendations generally recommend discontinuation of TNF-α inhibitors in the second or third trimesters; however, when considering discontinuation, providers must account for the individual risks and benefits of a drug, and pharmacologic factors such as its half-life [41••]. As studies suggest that there is minimal transfer of TNF-α inhibitors with lactation, and breastfeeding neonates have not been found to have increased risk of infections, TNF-α inhibitors may be used by lactating mothers [41••, 70]. Live virus vaccines should be avoided among infants exposed to TNF-α inhibitors in the late second or third trimesters (e.g., rotavirus in the USA), but a normal vaccination schedule may otherwise be used [71].

Medications to Avoid or Use with Caution in Pregnancy

Methotrexate should be discontinued at least 3 months prior to pregnancy as it has teratogenic effects and is an abortifacient medication [41••, 43]. Leflunomide also should be avoided in pregnancy, although most of the teratogenicity associated with the drug has been observed in animal and not human studies. As the drug may be sequestered in the bile circulation, a cholestyramine washout can reduce levels of the drug before pregnancy [72].

Newer arthritis therapies, including JAK-2 inhibitors (e.g., tofacitinib), CD-20 inhibitors (e.g., rituximab), CTLA-4 inhibitors (e.g., abatacept), IL-6 blockers (e.g., tocilizumab), and IL-1 blockers (e.g., anakinra), have not been adequately studied to provide strong recommendations towards or against their safety during pregnancy [71]. In exceptional cases, rituximab could be used in early pregnancy, and anakinra could be considered if there is no better alternative for treatment during pregnancy [41••].

Male Considerations

While women are three times more likely than men to develop RA, men still develop RA. As compared to women, most men have a larger age range of fertility and therefore conceptually could have concerns related to medication use, conception, and pregnancy throughout most of their life courses. RA has not clearly been linked to infertility in men, although some RA medications have been linked to subfertility [73••]. Little is known about how men conceptualize risk of medications while attempting to conceive, or what information needs men may have when planning their families.

NSAIDs, hydroxychloroquine, and TNF-α inhibitors do not appear to increase the risk of adverse outcomes in paternally exposed offspring [53, 74–76], although data on NSAID and hydroxychloroquine exposure is limited.

Sulfasalazine has been associated with azoospermia and decreased sperm motility, but these effects appear to be reversible [77], and studies suggest men who actively use sulfasalazine or have had exposure to it may successfully conceive [73••, 78]. No birth defects have been reported in paternally exposed offspring [75]. Men who experience infertility may warrant semen analysis or discontinuation of sulfasalazine.

While some previous guidelines have suggested that methotrexate should be discontinued by fathers in advance of attempting to conceive, recent studies do not suggest that offspring of methotrexate-exposed fathers have higher rates of major birth defects, growth restriction, or preterm birth [75, 79–81]. Paternal discontinuation of leflunomide has also been recommended in the past, although there is little data that suggests that leflunomide is associated with adverse birth outcomes among paternally exposed offspring [73••].

Therefore, given limited data and small sample sizes, sulfasalazine, methotrexate, and leflunomide discontinuation may warrant a discussion with fathers and couples rather than automatic discontinuation, although the potential risks must be discussed in detail.

Pre-Pregnancy Care and Counseling

The American College of Rheumatology recommends that all women with rheumatic diseases should receive risk counseling from their health care providers if contemplating

pregnancy, and diseases should be well controlled on safe anti-rheumatic drugs for at least 3–6 months in advance of pregnancy, in order to optimize clinical outcomes [48]. The pre-pregnancy period provides a critical window of opportunity in which providers may prepare a woman for pregnancy, thereby optimizing future maternal and fetal outcomes.

First, we recommend that health care providers initiate a family planning conversation with all female and male patients of reproductive age at the time of diagnosis of RA and before starting or changing medications with fetotoxic potential. It is important not to make assumptions about a patient's potential for pregnancy because of personal or sociodemographic factors (e.g., sexual orientation, race/ethnicity, marital status, or age). Furthermore, providers should not assume that patients with severe, disabling, or deforming arthritis are not sexually active or are not at risk for unintended pregnancy.

We recommend that health care providers use open-ended questions to initiate family planning conversations. In prior work, we have recommended starting with the following question: (1) "Tell me a bit about your life and where pregnancy fits in your plans. I ask because I'd like to work with you to try to make sure things turn out the way you'd like them to" [82]. Other evidence-based questions have been developed to help to initiate family planning questions, including One Key Question© ("Would you like to become pregnant in the next year?"), or the PATH questions (e.g., "Do you think you might like to have (more) children at some point?") [83–85].

During the initial conversation, health care providers should determine whether the patient has childbearing potential (e.g., no prior surgical sterilization) and discuss the outcomes of prior pregnancies. As discussed in the earlier sections, women with greater disease activity are at increased risk of subfertility and adverse pregnancy and fetal outcomes; thus, providers should carefully assess patients' current disease activity and extent of extra-articular organ involvement (e.g., pulmonary fibrosis).

Women with RA who wish to become pregnant may be reassured that many women with RA have successful pregnancies, particularly when their diseases are well controlled at the time of conception [82, 86, 87]. Women who clearly wish to avoid pregnancy may be referred to a PCP or gynecologist for contraception. Importantly, women who are at high risk of pregnancy complications—particularly those women who may have a disease-associated complication (e.g., pulmonary fibrosis) or use teratogenic medications—may require a more urgent referral to avoid unintended, undesired, and complicated pregnancies.

At least 30% of women have complex feelings and emotions about pregnancy and therefore may not explicitly express that they wish to avoid or to pursue pregnancy [88]. These patients, if sexually active with men, are at risk for unintended pregnancy if they do not use contraception. We would caution against advising such patients to use fetotoxic medications so as to avoid inadvertent fetal exposure to teratogenic medications. We would also consider preemptively prescribing folic acid supplementation. Referral to an obstetrician-gynecologist for additional care and counseling may also be appropriate.

Conclusions

Although women with RA face unique challenges related to their reproductive health, many have safe and successful pregnancies, particularly when their RA is well controlled with pregnancy-compatible medications. Health care providers have more access to data now than ever, which may help patients with RA make well-informed reproductive decisions that are aligned with their values and priorities. Some women with RA will experience subfertility; rheumatologists may inform women with RA that ART appears to be a safe and well-tolerated option. Other women may choose to limit their family sizes due to fears about how their RA and medications may affect a developing fetus or their ability to rear their children; counseling women about the safety and compatibility of certain drugs with pregnancy and lactation is critical. Women can be advised that most forms of contraception are generally safe if they wish to avoid pregnancy. Reproductive health needs of male patients require future study and exploration. Health care providers face an important responsibility in helping to provide quality family planning care and counseling for all reproductive-age patients with rheumatic diseases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Golding A, Haque UJ, Giles JT. Rheumatoid arthritis and reproduction. Rheum Dis Clin N Am. 2007;33(2):319–43 vi-vii.

2. Hargreaves ER. A survey of rheumatoid arthritis in West Cornwall; a report to the empire rheumatism council. Ann Rheum Dis. 1958;17(1):61–75.
3. Kay A, Bach F. Subfertility before and after the development of rheumatoid arthritis in women. Ann Rheum Dis. 1965;24:169–73.
4. Wallenius M, Skomsvoll JF, Irgens LM, Salvesen KA, Nordvag BY, Koldingsnes W, et al. Parity in patients with chronic inflammatory arthritides childless at time of diagnosis. Scand J Rheumatol. 2012;41(3):202–7.
5. Wallenius M, Salvesen KA, Daltveit AK, Skomsvoll JF. Secular trends of pregnancies in women with inflammatory connective tissue disease. Acta Obstet Gynecol Scand. 2015;94(11):1195–202.
6. Katz PP. Childbearing decisions and family size among women with rheumatoid arthritis. Arthritis Rheum. 2006;55(2):217–23.
7. Walldorf J, Brunne S, Gittinger FS, Michl P. Family planning in inflammatory bowel disease: childlessness and disease-related concerns among female patients. Eur J Gastroenterol Hepatol. 2018;30(3):310–5.
8. Skomsvoll JF, Ostensen M, Baste V, Irgens LM. Number of births, interpregnancy interval, and subsequent pregnancy rate after a diagnosis of inflammatory rheumatic disease in Norwegian women. J Rheumatol. 2001;28(10):2310–4.
9. Brouwer J, Hazes JM, Laven JS, Dolhain RJ. Fertility in women with rheumatoid arthritis: influence of disease activity and medication. Ann Rheum Dis. 2015;74(10):1836–41.
10. Ostensen M. Rheumatoid arthritis: the effect of RA and medication on female fertility. Nat Rev Rheumatol. 2014;10(9):518–9.
11. Leroy C, Rigot JM, Leroy M, Decanter C, Le Mapihan K, Parent AS, et al. Immunosuppressive drugs and fertility. Orphanet J Rare Dis. 2015;10:136.
12. Clowse ME, Chakravarty E, Costenbader KH, Chambers C, Michaud K. Effects of infertility, pregnancy loss, and patient concerns on family size of women with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res. 2012;64(5):668–74.
13. NCHS. Key statistics from the National Survey of Family Growth. In. Centers for Disease Control and Prevention: Atlanta; 2016.
14. Brouwer J, Laven JS, Hazes JM, Schipper I, Dolhain RJ. Levels of serum anti-Mullerian hormone, a marker for ovarian reserve, in women with rheumatoid arthritis. Arthritis Care Res. 2013;65(9):1534–8.
15.• Brouwer J, Fleurbaaij R, Hazes JMW, Dolhain R, Laven JSE. Subfertility in women with rheumatoid arthritis and the outcome of fertility assessments. Arthritis Care Res (Hoboken). 2017;69(8):1142–9. **While subfertility is an issue for some women with RA, this paper helps to demonstrate that assisted reproductive technologies are effective for these women.**
16. Ostensen M, Fuhrer L, Mathieu R, Seitz M, Villiger PM. A prospective study of pregnant patients with rheumatoid arthritis and ankylosing spondylitis using validated clinical instruments. Ann Rheum Dis. 2004;63(10):1212–7.
17. Barrett JH, Brennan P, Fiddler M, Silman AJ. Does rheumatoid arthritis remit during pregnancy and relapse postpartum? Results from a nationwide study in the United Kingdom performed prospectively from late pregnancy. Arthritis Rheum. 1999;42(6):1219–27.
18. de Man YA, Dolhain RJ, van de Geijn FE, Willemsen SP, Hazes JM. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum. 2008;59(9):1241–8.
19. de Man YA, Bakker-Jonges LE, Goorbergh CM, Tillemans SP, Hooijkaas H, Hazes JM, et al. Women with rheumatoid arthritis negative for anti-cyclic citrullinated peptide and rheumatoid factor are more likely to improve during pregnancy, whereas in autoantibody-positive women autoantibody levels are not influenced by pregnancy. Ann Rheum Dis. 2010;69(2):420–3.
20. van den Brandt S, Zbinden A, Baeten D, Villiger PM, Ostensen M, Forger F. Risk factors for flare and treatment of disease flares during pregnancy in rheumatoid arthritis and axial spondyloarthritis patients. Arthritis Res Ther. 2017;19(1):64.
21. Kahn DA, Baltimore D. Pregnancy induces a fetal antigen-specific maternal T regulatory cell response that contributes to tolerance. Proc Natl Acad Sci U S A. 2010;107(20):9299–304.
22. Corthay A. How do regulatory T cells work? Scand J Immunol. 2009;70(4):326–36.
23. Forger F, Marcoli N, Gadola S, Moller B, Villiger PM, Ostensen M. Pregnancy induces numerical and functional changes of CD4+ CD25 high regulatory T cells in patients with rheumatoid arthritis. Ann Rheum Dis. 2008;67(7):984–90.
24. Norgaard M, Larsson H, Pedersen L, Granath F, Askling J, Kieler H, et al. Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. J Intern Med. 2010;268(4):329–37.
25. Langen ES, Chakravarty EF, Liaquat M, El-Sayed YY, Druzin ML. High rate of preterm birth in pregnancies complicated by rheumatoid arthritis. Am J Perinatol. 2014;31(1):9–14.
26. Wallenius M, Skomsvoll JF, Irgens LM, Salvesen KA, Nordvag BY, Koldingsnes W, et al. Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth. Arthritis Rheum. 2011;63(6):1534–42.
27. Smith CJF, Forger F, Bandoli G, Chambers CD. Factors associated with preterm delivery among women with rheumatoid arthritis and juvenile idiopathic arthritis. Arthritis Care Res. 2018.
28. Bharti B, Lee SJ, Lindsay SP, Wingard DL, Jones KL, Lemus H, et al. Disease severity and pregnancy outcomes in women with rheumatoid arthritis: results from the Organization of Teratology Information Specialists Autoimmune Diseases in pregnancy project. J Rheumatol. 2015;42(8):1376–82.
29. Rom AL, Wu CS, Olsen J, Kjaergaard H, Jawaheer D, Hetland ML, et al. Fetal growth and preterm birth in children exposed to maternal or paternal rheumatoid arthritis: a nationwide cohort study. Arthritis Rheum. 2014;66(12):3265–73.
30. de Man YA, Hazes JM, van der Heide H, Willemsen SP, de Groot CJ, Steegers EA, et al. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. Arthritis Rheum. 2009;60(11):3196–206.
31. Birru Talabi M, Clowse MEB, Blalock SJ, Moreland L, Siripong N, Borrero S. Contraception use among reproductive-age women with rheumatic diseases. Arthritis Care Res. 2018.
32. Daniels KDJ, Jones J. Current contraceptive status among women aged 15–44: United States, 2011–2013. In: NCHS Data Brief. Hyattsville: National Center for Health Statistics; 2015. p. 1–8.
33. Toomey D, Waldron B. Family planning and inflammatory bowel disease: the patient and the practitioner. Fam Pract. 2013;30(1):64–8.
34. U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force Recommendation Statement; Final Recommendations. Ann Intern Med. 151:716–26.
35. Qaseem A, Humphrey LL, Harris R, Starkey M, Denberg TD. Clinical Guidelines Committee of the American College of P: screening pelvic examination in adult women: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2014;161(1):67–72.
36. Moyer VA. Force USPST: screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;156(12):880–91. W312.
37. Tepper NK, Curtis KM, Nanda K, Jamieson DJ. Safety of intrauterine devices among women with HIV: a systematic review. Contraception. 2016;94(6):713–24.
38. Heinemann K, Reed S, Moehner S, Minh TD. Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine

devices in the European Active Surveillance Study on Intrauterine Devices. Contraception. 2015;91(4):274–9.
39. Hubacher D, Lara-Ricalde R, Taylor DJ, Guerra-Infante F, Guzman-Rodriguez R. Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women. N Engl J Med. 2001;345(8):561–7.
40. Curtis KJT, Tepper NK, Zapata L, Horton L, Jamieson DJ, Whiteman MK. U.S. Medical Eligibility Criteria for contraceptive use. In: Centers for Disease Control and Prevention: Morbidity and Mortality Weekly Report; 2016.
41.•• Gotestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75(5):795–810. **This is a very important set of guidelines to help providers weigh the risks and benefits of anti-rheumatic drug use in anticipation of or during pregnancy. Guidelines from the American College of Rheumatology are forthcoming in 2019.**
42. CDC. Effectiveness of family planning methods. 2018.
43. Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology. 2016;55(9):1693–7.
44.•• Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part II: analgesics and other drugs used in rheumatology practice. Rheumatology. 2016;55(9):1698–702. **This is another important set of guidelines to help providers safely prescribe anti-rheumatic drugs before, during, or after pregnancy**.
45. Panchal S, Khare M, Moorthy A, Samanta A. Catch me if you can: a national survey of rheumatologists and obstetricians on the use of DMARDs during pregnancy. Rheumatol Int. 2013;33(2):347–53.
46. Hays S. The cultural contradictions of motherhood. New Haven: Yale University Press; 1998.
47. Mother to Baby. https://mothertobaby.org.
48. Pregnancy and rheumatic disease. http://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Living-Well-with-Rheumatic-Disease/Pregnancy-Rheumatic-Disease#sthash.JxTY5YE4.dpuf.
49. Duffy DM. Novel contraceptive targets to inhibit ovulation: the prostaglandin E2 pathway. Hum Reprod Update. 2015;21(5):652–70.
50. Nakhai-Pour HR, Broy P, Sheehy O, Berard A. Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion. CMAJ. 2011;183(15):1713–20.
51. Dathe K, Fietz AK, Pritchard LW, Padberg S, Hultzsch S, Meixner K, et al. No evidence of adverse pregnancy outcome after exposure to ibuprofen in the first trimester - evaluation of the national Embryotox cohort. Reprod Toxicol. 2018;79:32–8.
52. Koren G, Florescu A, Costei AM, Boskovic R, Moretti ME. Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. Ann Pharmacother. 2006;40(5):824–9.
53. Viktil KK, Engeland A, Furu K. Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150, 000 pregnant women and expectant fathers. Scand J Rheumatol. 2012;41(3):196–201.
54. Palmsten K, Hernandez-Diaz S, Kuriya B, Solomon DH, Setoguchi S. Use of disease-modifying antirheumatic drugs during pregnancy and risk of preeclampsia. Arthritis Care Res. 2012;64(11):1730–8.
55. Ostensen ME, Skomsvoll JF. Anti-inflammatory pharmacotherapy during pregnancy. Expert Opin Pharmacother. 2004;5(3):571–80.
56. Norgard B, Pedersen L, Christensen LA, Sorensen HT. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish nationwide cohort study. Am J Gastroenterol. 2007;102(7):1406–13.
57. AAP. Transfer of drugs and other chemicals into human milk. Pediatrics. 2001;108(3):776–89.
58. Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. Arch Intern Med. 2000;160(5):610–9.
59. Kemp MW, Newnham JP, Challis JG, Jobe AH, Stock SJ. The clinical use of corticosteroids in pregnancy. Hum Reprod Update. 2016;22(2):240–59.
60. American College of O, Gynecologists: ACOG Committee Opinion number 313, September 2005. The importance of preconception care in the continuum of women's health care. Obstet Gynecol. 2005;106(3):665–6.
61. Ostensen M. Piroxicam in human breast milk. Eur J Clin Pharmacol. 1983;25(6):829–30.
62. Noviani M, Wasserman S, Clowse ME. Breastfeeding in mothers with systemic lupus erythematosus. Lupus. 2016;25(9):973–9.
63. Mahadevan U, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2013;11(3):286–92 quiz e224.
64. Clowse ME. The use of anti-TNFalpha medications for rheumatologic disease in pregnancy. Int J Women's Health. 2010;2:199–209.
65. Hoxha A, Calligaro A, Di Poi E, Peccatori S, Favaro M, Del Ross T, et al. Pregnancy and foetal outcomes following anti-tumor necrosis factor alpha therapy: a prospective multicentre study. Joint Bone Spine. 2017;84(2):169–73.
66. Clowse MEB, Scheuerle AE, Chambers C, Afzali A, Kimball AB, Cush JJ, et al. Pregnancy outcomes after exposure to Certolizumab pegol: updated results from a pharmacovigilance safety database. Arthritis Rheum. 2018;70(9):1399–407.
67. Diav-Citrin O, Otcheretianski-Volodarsky A, Shechtman S, Ornoy A. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. Reprod Toxicol. 2014;43:78–84.
68. Weber-Schoendorfer C, Oppermann M, Wacker E, Bernard N, network of French pharmacovigilance c, Beghin D, et al. Pregnancy outcome after TNF-alpha inhibitor therapy during the first trimester: a prospective multicentre cohort study. Br J Clin Pharmacol. 2015;80(4):727–39.
69.• Vinet E, De Moura C, Pineau CA, Abrahamowicz M, Curtis JR, Bernatsky S. Serious Infections in rheumatoid arthritis offspring exposed to tumor necrosis factor inhibitors: a cohort study. Arthritis Rheumatol. 2018;70(10):1565–71. **This study shows that infection risk is generally low among neonates exposed to TNF-alpha inhibitors *in utero*, although there may be an increased risk of infections from infliximab**.
70. Clowse ME, Forger F, Hwang C, Thorp J, Dolhain RJ, van Tubergen A, et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. Ann Rheum Dis. 2017;76(11):1890–6.
71. Andreoli L, Bertsias GK, Agmon-Levin N, Brown S, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis. 2017;76(3):476–85.
72. Chambers CD, Johnson DL, Robinson LK, Braddock SR, Xu R, Lopez-Jimenez J, et al. Birth outcomes in women who have taken leflunomide during pregnancy. Arthritis Rheum. 2010;62(5):1494–503.
73.•• Mouyis M, Flint JD, Giles IP. Safety of anti-rheumatic drugs in men trying to conceive: a systematic review and analysis of published evidence. Semin Arthritis Rheum. 2018. **This is one of the first**

reviews available to help providers to counsel men with rheumatic diseases about medications in anticipation of pregnancy.

74. Larsen MD, Friedman S, Magnussen B, Norgard BM. Birth outcomes in children fathered by men treated with anti-TNF-alpha agents before conception. Am J Gastroenterol. 2016;111(11):1608–13.
75. Wallenius M, Lie E, Daltveit AK, Salvesen KA, Skomsvoll JF, Kalstad S, et al. No excess risks in offspring with paternal preconception exposure to disease-modifying antirheumatic drugs. Arthritis Rheum. 2015;67(1):296–301.
76. Clowse ME, Wolf DC, Forger F, Cush JJ, Golembesky A, Shaughnessy L, et al. Pregnancy outcomes in subjects exposed to Certolizumab pegol. J Rheumatol. 2015;42(12):2270–8.
77. O'Morain C, Smethurst P, Dore CJ, Levi AJ. Reversible male infertility due to sulphasalazine: studies in man and rat. Gut. 1984;25(10):1078–84.
78. Riley SA, Lecarpentier J, Mani V, Goodman MJ, Mandal BK, Turnberg LA. Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution. Gut. 1987;28(8):1008–12.
79. Weber-Schoendorfer C, Hoeltzenbein M, Wacker E, Meister R, Schaefer C. No evidence for an increased risk of adverse pregnancy outcome after paternal low-dose methotrexate: an observational cohort study. Rheumatology (Oxford). 2014;53(4):757–63.
80. Eck LK, Jensen TB, Mastrogiannis D, Torp-Pedersen A, Askaa B, Nielsen TK, et al. Risk of adverse pregnancy outcome after paternal exposure to methotrexate within 90 days before pregnancy. Obstet Gynecol. 2017;129(4):707–14.
81. Winter RW, Larsen MD, Magnussen B, Friedman S, Kammerlander H, Norgard BM. Birth outcomes after preconception paternal exposure to methotrexate: a nationwide cohort study. Reprod Toxicol. 2017;74:219–23.
82. Birru Talabi M, Clowse MEB, Schwarz EB, Callegari LS, Moreland L, Borrero S. Family planning counseling for women with rheumatic diseases. Arthritis Care Res. 2018;70(2):169–74.
83. Bellanca HK, Hunter MS. ONE KEY QUESTION(R): preventive reproductive health is part of high quality primary care. Contraception. 2013;88(1):3–6.
84. Geist C, Aiken AR, Sanders JN, Everett BG, Myers K, Cason P, et al. Beyond intent: exploring the association of contraceptive choice with questions about pregnancy attitudes, timing and how important is pregnancy prevention (PATH) questions. Contraception. 2018.
85. Callegari LS, Aiken AR, Dehlendorf C, Cason P, Borrero S. Addressing potential pitfalls of reproductive life planning with patient-centered counseling. Am J Obstet Gynecol. 2017;216(2):129–34.
86. Kavanaugh A, Cush JJ, Ahmed MS, Bermas BL, Chakravarty E, Chambers C, et al. Proceedings from the American College of Rheumatology Reproductive Health Summit: the management of fertility, pregnancy, and lactation in women with autoimmune and systemic inflammatory diseases. Arthritis Care Res. 2015;67(3):313–25.
87. Clowse ME. Managing contraception and pregnancy in the rheumatologic diseases. Best Pract Res Clin Rheumatol. 2010;24(3):373–85.
88. Borrero S, Nikolajski C, Steinberg JR, Freedman L, Akers AY, Ibrahim S. Schwarz EB: "It just happens": a qualitative study exploring low-income women's perspectives on pregnancy intention and planning. Contraception. 2015;91(2):150–6.