Treatment of spondyloarthritis with disease-modifying anti-rheumatic drugs during pregnancy and breastfeeding: comparing the recommendations and guidelines of the principal societies of rheumatology

M. Manara[1*], D. Bruno[2,3*], M. Ferrito[1,4], S. Perniola[2], R.F. Caporali[1,4], E. Gremese[2]

[1]Clinical Rheumatology Unit, ASST G. Pini - CTO, Milan, Italy; [2]Clinical Immunology Unit, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; [3]University of Verona, Italy; [4]Department of Clinical Sciences and Community Health, University of Milan, Italy

**These authors share first authorship*

SUMMARY

Objective. This paper aims to provide an overview of the use of treatments available for axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) during pregnancy and breastfeeding, according to current national recommendations and international guidelines, as well as data on the impact on pregnancy outcomes of paternal exposure to treatment.

Methods. We performed a narrative review of national and international recommendations and guidelines on the reproductive health of patients suffering from rheumatic diseases. The last updated recommendations and guidelines were considered source data.

Results. We reported updated information regarding the treatment of axSpA and PsA with nonsteroidal anti-inflammatory drugs, intra-articular glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs, and targeted synthetic DMARDs during the preconception period, pregnancy, and breastfeeding, as well as data related to paternal exposure. We highlighted any medications that should be discontinued and/or not used in the reproductive age group and also treatments that may be continued, avoiding the withdrawal of drugs that can be used in the different phases, thus preventing the risk of increasing disease activity and flares before, during, and after pregnancy in SpA patients.

Conclusions. The best management of pregnancy in patients with SpA is based on knowledge of updated drug recommendations, a careful and wise evaluation of the risks/benefits of starting or continuing treatment from the SpA diagnosis in a woman of childbearing age through pregnancy and lactation, and sharing therapeutic choices with other healthcare providers (in particular, gynecologists/obstetricians) and the patient.

Key words: *Axial spondyloarthritis, psoriatic arthritis, treatment, pregnancy, breastfeeding, conception.*

Reumatismo, 2024; 76 (3): 222-231

INTRODUCTION

Rheumatic and musculoskeletal diseases (RMDs) may significantly impact quality of life, including aspects related to reproductive health. Over the years, there has been an appreciable effort to define the outcomes of pregnancy in women suffering from RMDs, the compatibility of antirheumatic drugs with conception, pregnancy, and breastfeeding, as well as any potential risk in the case of paternal immunosuppressive drug exposure.

In this scenario, unlike rheumatoid arthritis (RA) (1), there is still limited and controversial data on the course of axial spondyloarthritis (axSpA) during pregnancy (2-4). Spondyloarthritis (SpA), especially in its axial form, has historically been considered a predominantly male disease, but recent data suggests a more balanced prevalence, with a male-to-female ratio of 3:1 for radiographic axSpA (5). Therefore, in the last few years, more attention has been paid to issues related to reproductive health in women with SpA (6).

Corresponding author:
Maria Manara
Clinical Rheumatology Unit,
ASST G. Pini - CTO,
Piazza Cardinal Ferrari 1,
20122 Milano, Italy
E-mail: maria.manara@gmail.com

Understanding the mutual impact that SpA and pregnancy can have on each other is crucial since many affected females are of childbearing age. All decisions regarding medication management should take into consideration both the need to keep the maternal disease under control and the potential side effects of the therapies on the fetus. It is well established that appropriate pregnancy planning, including the optimization of disease control before conception and during pregnancy, is crucial to minimize the chances of adverse pregnancy outcomes (7, 8). Therefore, the choice of treatment should be guided by a careful evaluation of the risk/benefit profile of every patient and should be discussed well before the patient attempts to conceive.

The need for updated guidelines on the use of antirheumatic drugs for the treatment of SpA in pregnancy and breastfeeding is obvious, given the expansion of biologic disease-modifying antirheumatic drugs (bDMARDs) with different modes of action in the last few years, as well as the introduction of targeted synthetic DMARDs (tsDMARDs) in the armamentarium of pharmacological options for SpA (9).

This is the rationale behind the recent update of the 2016 British Society for Rheumatology (BSR) guidelines on prescribing antirheumatic drugs in pregnancy and breastfeeding (10-12), which considers the drugs now potentially available for SpA treatment.

Similarly, the Italian Society of Rheumatology (SIR) has recently released recommendations on the reproductive health of patients suffering from rheumatic diseases (13). The recommendations were developed through a process of adaptation of pre-existing guidelines, which were updated by a systematic literature review according to the Grading of Recommendations Assessment, Development, and Evaluation-ADOLOPMENT methodology (14). As a source for the adaptation process, the American College of Rheumatology (ACR) guideline for the management of reproductive health in RMDs was selected (15).

This paper aims to provide an overview of the use of treatments available for axial and peripheral SpA (namely psoriatic arthritis, PsA) during pregnancy and breastfeeding, according to current national recommendations and international guidelines (10, 13, 15). Data on the impact on pregnancy outcomes of paternal exposure to treatment are also provided.

THE USE OF DISEASE-MODIFYING ANTIRHEUMATIC DRUGS DURING PREGNANCY AMONG WOMEN WITH AXIAL SPONDYLOARTHRITIS

Treatment with nonsteroidal anti-inflammatory drugs

According to the Assessment of SpondyloArthritis International Society-European Alliance of Associations for Rheumatology recommendations for the management of axSpA, the first line of treatment that should be considered for all patients with axSpA is based on physiotherapy, education to correct lifestyles and pharmacological treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) (9). Continuous treatment with NSAIDs should be prescribed to control symptoms and not to prevent radiographic damage, since studies specifically designed to assess the effectiveness of NSAIDs on radiographic damage in axSpA have provided conflicting evidence (16).

Unlike BSR guidelines, SIR recommendations address the potential negative impact of NSAIDs on fertility in women wishing to conceive (10, 13). Therefore, they suggest discussing treatment with NSAIDs since the planning of pregnancy (13). The ACR guidelines "conditionally recommend discontinuation of NSAIDs pre-conception if the patient is having difficulty conceiving (and if disease control would not be compromised) due to the possibility of NSAID-induced unruptured follicle syndrome, a cause of subfertility" (15). Inhibition of prostaglandin synthesis by both selective and non-selective NSAIDs may interfere with follicular rupture and mature ovum release during ovulation, leading to ovulation failure [luteinized unruptured follicle (LUF) syndrome] (17, 18). The increased risk of the LUF syndrome

seems to be higher when women are exposed to selective COX-2 inhibitors than to traditional non-selective NSAIDs in the periovulatory phase, particularly at full doses (19). In a prospective cohort of 245 female patients with RA, preconception use of NSAIDs was negatively associated with pregnancy rate [hazard ratio 0.66 (0.46-0.94)] (20). More recently, a median 2.6-fold increase in time to pregnancy was reported in preconceptionally NSAID-exposed women with axSpA in comparison to women who were not exposed, irrespective of maternal age, smoking, and disease activity (21, 22).

According to the Italian recommendations and ACR guidelines, there is a strong recommendation against the use of NSAIDs during the third trimester of pregnancy since it has been reported to be associated with a significantly increased risk of premature closure of the ductus arteriosus (23). NSAIDs are allowed in the first and second trimesters, with non-selective NSAIDs conditionally recommended over COX-2 inhibitors (10, 13).

Treatment with conventional synthetic disease-modifying anti-rheumatic drugs

In patients with axSpA with an insufficient response to at least two courses of NSAIDs for 2-4 weeks, a second-line treatment should be considered. The choice of the second-line treatment in axSpA should be guided by clinical manifestations: when the clinical picture is characterized mainly by peripheral symptoms, local glucocorticoid injections and sulfasalazine may be considered, while in patients with a purely axial disease, a treatment with conventional synthetic DMARDs (csDMARDs) is not recommended and a bDMARD or tsDMARD should be started (9).

In axSpA patients with mono/oligo-arthritis, enthesitis, or dactylitis, local glucocorticoid injections can be efficacious. On the contrary, the chronic use of systemic glucocorticoids for axSpA is not supported by evidence (9). A recent literature review on musculoskeletal steroid injections in pregnancy did not show an increased risk of adverse side effects to the mother or baby from the maternal use of non-systemic injections of steroids during pregnancy (24).

In patients with axSpA and peripheral arthritis without active axial involvement, sulfasalazine may be considered due to its demonstrated efficacy in this subgroup of patients, while methotrexate did not show adequate efficacy in axSpA (25-27). According to the SIR recommendation, sulfasalazine can be continued during pregnancy.

Treatment with biologic/targeted synthetic disease-modifying antirheumatic drugs

An appreciable effort has been made to better define the use of bDMARDs in the management of patients with axSpA before and during pregnancy. This topic is extensively discussed in both the British and Italian recommendations (10, 13).

Several studies have focused on the impact of bDMARDs on pregnancy outcomes in women with autoimmune diseases, mainly RA (8, 10, 28-31). Most data are on anti-tumor necrosis factor (TNF)-α drugs, which have revolutionized the management of axSpA (10). Overall, no increase in adverse pregnancy outcomes or severe maternal complications was reported in women with autoimmune diseases exposed to bDMARDs before or during pregnancy compared to those not exposed. Interestingly, the use of bDMARDs by women during pregnancy is not even associated with an increased risk of serious infections in infants during the first year of life (8). Regarding the characteristics of infants from pregnancies exposed and unexposed to biologics, a recent Canadian population-based cohort study did not report an increased risk of preterm delivery and small-for-gestational-age births in pregnancies that were exposed to bDMARDs (28). Although most studies did not stratify pregnancy adverse outcomes based on different TNF inhibitors (TNFi), they did not describe an increased risk of preterm birth, miscarriage, low birth weight, or congenital malformations that were attributable to TNFi exposure (10). Moreover, the available data for several bD-

MARDs exhibit no adverse effects on physical or neurocognitive development in children during the first year of life (8).
Numerous studies examined the outcomes of pregnancies exposed to TNFi during late or early trimesters, generally reporting no significant concerns with late-trimester exposure (10). It is clear that to optimize the therapeutic management of women with axSpa, in order to reduce both the possible adverse pregnancy outcomes and disease activity flares, it is decisive to evaluate the patient's disease activity and stratify the risk of flare based on the inflammatory burden of the disease (8). Based on this, axSpA with a low risk of disease flare on withdrawal of TNFi during pregnancy, could stop infliximab at 20 weeks, adalimumab and golimumab at 28 weeks, and etanercept at 32 weeks of gestation (10). However, they may be continued throughout pregnancy if the axSpA inflammatory burden requires it. In this view, it is important to point out that the timing of drug exposure during pregnancy also impacts the infant vaccination schedule: using the aforementioned therapeutic regimens for TNFi, a full-term infant can have a normal vaccination schedule (8).
The placental transfer rate of certolizumab pegol is minimal due to the lack of the Fc region of the immunoglobulin G1 (IgG1) structure; thus, it is compatible with all three trimesters of pregnancy, without any impact on the vaccination program (10, 32).
Although data on biosimilar use in pregnancy are more limited than for originator bDMARDs, it is conceivable they could have comparable influences (10, 13).
Interleukin (IL)-17 inhibitors (IL-17i) have dramatically changed the scenario of axSpA treatment (9, 33), and currently include secukinumab (human IgG1κ monoclonal antibody that binds to IL-17A) (34), and ixekizumab (humanized monoclonal antibody anti-IL-17A) (35). The IgG1 structure of secukinumab may theoretically imply an increased transplacental passage compared with the IgG4 structure of ixekizumab. Data on IL-17i use in pregnancy are still limited compared to those for TNFi. To date, available studies have reported IL-17i not being teratogenic (10). Three studies of mostly first-trimester pregnancy exposures to both IL-17i did not report any adverse pregnancy outcomes (36, 37). However, there is still insufficient evidence to be confident that they are fully compatible with pregnancy (10). Therefore, it may be appropriate to consider discontinuing the drugs at conception if axSpA is well controlled and reserving their use during pregnancy only in cases of severe maternal disease for which alternative pregnancy-compatible treatments are not available.
The armamentarium of pharmacological options for axSpA also includes Janus kinase inhibitors (JAKi) as tsDMARDs (9). Data on their use in pregnancy remains elusive, relying primarily on case reports, small case series, and data provided by companies (10). Structurally, JAKi are small molecules of low molecular weight capable of crossing the placenta. Although they are characterized by a short half-life, their biological effects could persist for longer (10, 38). Thus, both BSR guidelines and SIR recommendations suggest stopping them at least 2 weeks before planned conception in women suffering from axSpA, as well as other RMDs (10, 13).

THE USE OF DISEASE-MODIFYING ANTIRHEUMATIC DRUGS DURING PREGNANCY AMONG WOMEN WITH PSORIATIC ARTHRITIS

Treatment with conventional synthetic disease-modifying antirheumatic drugs

In patients with PsA, the choice of treatment should be guided by the domains involved, concomitant treatments and/or diseases, and patient's preferences. According to the latest recommendations by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), the first treatment approach should consider NSAIDs, physiotherapy, and glucocorticoid injections for all patients with axial disease, peripheral arthritis, enthesitis and/or dactylitis (39).
In patients with PsA and peripheral arthri-

tis, enthesitis, or dactylitis not responding to this approach and/or psoriasis not responding to topical procedures, a csDMARD should be considered; on the contrary, treatment with csDMARDs is not recommended in patients with axial disease and/or psoriatic nail disease (39).

According to GRAPPA recommendations, the use of csDMARDs (methotrexate, sulfasalazine, or leflunomide) is strongly recommended in PsA patients with peripheral arthritis, due to supportive observational data and universal accessibility (39). However, evidence from randomized controlled trials (RCTs) in support of their use is scarce, as demonstrated by a systematic review of the literature, which showed low-quality evidence concerning the efficacy of methotrexate in PsA (40). For patients with enthesitis or dactylitis, the use of methotrexate is suggested based on the results of a single trial, which did not demonstrate a higher efficacy of etanercept than methotrexate in controlling symptoms related to enthesitis and dactylitis in patients with PsA (41). Skin psoriasis unresponsive to topical agents may be treated with phototherapy, csDMARDs, or bDMARDs; among csDMARDs, methotrexate and cyclosporine may be considered (39).

The teratogenic effect of methotrexate is well known; therefore, all guidelines and recommendations strongly recommend against its use during pregnancy. Methotrexate must be discontinued before conception. ACR guidelines strongly recommend discontinuation within 3 months before conception, and SIR recommendations recommend discontinuation 1-3 months before conception (13, 15).

If the characteristic malformations associated with methotrexate embryopathy have been well described after elective termination of pregnancy with high-dose methotrexate, the teratogenicity of low-dose methotrexate, as prescribed to women with rheumatic disease, is more debated; however, a significantly increased risk of spontaneous abortion has been described in this population (42). Nevertheless, collecting data on this topic could be difficult because, according to published recommendations, most women avoid conception while taking methotrexate.

Leflunomide use is contraindicated during pregnancy; discontinuation of this drug before conception and, if discontinuation has been for less than 24 months, cholestyramine washout until serum levels of metabolite are undetectable are strongly recommended by ACR and BSR guidelines (10, 15). Conversely, cyclosporine is conditionally recommended as compatible for use during pregnancy (13, 15).

Treatment with biologic/targeted synthetic disease-modifying antirheumatic drugs

In patients with PsA not responding to csDMARDs or when csDMARDs are not indicated (as for subjects with axial or nail involvement), a treatment with b/tsDMARDs should be considered. The choice of treatment should be guided by clinical features and should also carefully consider associated extra-articular manifestations or comorbidities, such as uveitis or inflammatory bowel disease (39).

Treatment with TNFi, IL-17i, and JAKi during pregnancy has already been discussed in this paper for axSpA. For the IL-12/23 inhibitor ustekinumab, ACR guidelines conditionally recommend continuing treatment while a woman is trying to conceive but discontinuing once she is found to be pregnant (15). Accordingly, BSR suggests stopping the drug at conception since limited evidence has not shown ustekinumab to be teratogenic, but there remains insufficient evidence to be confident that it is compatible with pregnancy (10). Data from observational studies showed pregnancy outcomes of women with PsA exposed to ustekinumab during the first and second trimesters of pregnancy consistent with the general population and TNFi-exposed pregnancies (43).

No recommendation is given by ACR guidelines regarding the use of apremilast during pregnancy due to the lack of evidence on this topic; however, they underline that small molecules are likely to pass through the placenta (15). SIR recommendations suggest discontinuing apremilast before conceiving (13).

THE USE OF DISEASE-MODIFYING ANTIRHEUMATIC DRUGS DURING BREASTFEEDING AMONG WOMEN WITH AXIAL SPONDYLOARTHRITIS AND PSORIATIC ARTHRITIS

Studies on the excretion of drugs into human breast milk are scarce and mostly based on single-dose or short-term treatment (8). Additionally, even when the passage of a drug into human breast milk is ascertained, studying the effects on the nursing infant remains complicated, considering the many possible confounding factors.

Treatment with nonsteroidal anti-inflammatory drugs/conventional synthetic disease-modifying antirheumatic drugs

Treatment with NSAIDs, when necessary, is conditionally recommended during breastfeeding (13, 15). Among traditional NSAIDs, the Italian panel suggests preferring ibuprofen, considering its short half-life and the low levels found in maternal milk (13, 44). When a COX-2 inhibitor is necessary, the Italian panel suggests preferring celecoxib (13, 44).

According to SIR recommendations, due to the lack of available evidence, sulfasalazine is conditionally recommended during breastfeeding if clinically needed; the panel suggests maintaining a maximum time interval from drug assumption to breastfeeding (13, 44).

ACR guidelines strongly recommend against the use of leflunomide during breastfeeding and conditionally against the use of methotrexate because, despite the minimal passage of methotrexate into breast milk, the risk of drug accumulation in neonatal tissue cannot be excluded. On the contrary, cyclosporine use is conditionally recommended as compatible with breastfeeding (13, 15).

Treatment with biologic/targeted synthetic disease-modifying antirheumatic drugs

TNFi are fully compatible with breastmilk exposure, although low transfer to breast milk has been detected for infliximab, adalimumab, etanercept, and certolizumab. Therefore, the continuation of TNFi agents is compatible with breastfeeding (10, 13).

Concerning IL-17i, data are much more limited than those on TNFi. However, based on available evidence, maternal treatment with IL-17i is compatible with lactation (10, 13). The same recommendation was given for ustekinumab, which, based on limited evidence, is conditionally recommended for use during breastfeeding (10, 13).

Finally, there is inadequate data to draw conclusions about JAKi and apremilast use in breastfeeding. However, due to their small molecular structure, they should be avoided as they are likely to transfer into breast milk (10, 13). Ongoing development of national registries could help to better define their safety profile, even during breastfeeding.

PATERNAL EXPOSURE TO DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Paternal treatment exposure around the time of conception could impact reproductive outcomes (8). Spermatogenesis takes approximately 74 days to complete its cycle (45). Thus, paternal medication use in the 3 months before conception can potentially lead to detrimental effects on pregnancy and children, primarily affecting spermatogenesis and/or sperm quality.

Treatment with conventional synthetic disease-modifying antirheumatic drugs

Limited data from observational studies suggests that paternal exposure to low-dose methotrexate (≤25 mg/week), leflunomide, or cyclosporine within 3 months of conception is not associated with an increased risk of adverse fetal outcomes. Therefore, paternal use of these drugs is conditionally recommended as compatible with pregnancy by Italian recommendations and BSR guidelines (10, 13). Further data on paternal exposure to methotrexate have been recently reported in a registered study: methotrex-

ate exposure was not associated with congenital anomalies, preterm birth, or small gestational age (46).

Cohort studies on male patients treated with sulfasalazine did not show an increased risk of adverse fetal outcomes, but sulfasalazine was associated with oligospermia, reduced sperm mobility, and abnormal sperm (10). On this basis, SIR recommendations conditionally suggest continuing sulfasalazine as compatible with pregnancy but stopping it if male patients experience difficulty in conceiving (13).

Treatment with biologic/targeted synthetic disease-modifying antirheumatic drugs

Among the therapeutic options for the management of axSpA with b/tsDMARDs, data on paternal exposure are very reassuring. TNFi use was not associated with an increased risk of adverse fetal outcomes (10, 13). Similarly, paternal exposure to secukinumab and ixekizumab did not lead to any adverse drug-related effects (10, 13, 36, 37). No data are available on paternal exposure to ustekinumab (10).

Table I - Summary of the compatibility of drugs used in spondyloarthritis during the preconception period, pregnancy, breastfeeding, and paternal exposure, according to national recommendations and international guidelines.

	Peri-conception	Pregnancy			Breastfeeding	Paternal exposure
		I trimester	II trimester	III trimester		
Local GC injections						
NSAIDs		a	a		b	
Methotrexate	c					
Leflunomide	d					
Sulfasalazine						e
Cyclosporine						
Infliximab				f		
Adalimumab				g		
Golimumab				g		
Etanercept				h		
Certolizumab pegol						
Secukinumab						
Ixekizumab						
Ustekinumab						
Apremilast						
Tofacitinib	i					
Upadacitinib	i					

	Strongly recommended		**Strongly contraindicated**
	Conditionally recommended		Conditionally contraindicated

GC, glucocorticoids; NSAIDs, nonsteroidal anti-inflammatory drugs. [a]NSAIDs are allowed in the 1st and 2nd trimester, with non-selective NSAIDs conditionally recommended over COX-2 inhibitors; [b]NSAIDs are conditionally recommended during breastfeeding, with ibuprofen preferred among non-selective NSAIDs; [c]the Italian Society of Rheumatology (SIR) recommends discontinuation 1-3 months before conception; the American College of Rheumatology guidelines strongly recommend discontinuation within 3 months before conception; the British Society for Rheumatology (BSR) guidelines recommend discontinuation ≥1 month pre-conception; [d]if discontinuation has been for less than 24 months, SIR recommendations recommend starting cholestyramine washout before attempting to conceive. If pregnancy occurs while using Leflunomide, SIR recommendations recommend discontinuing therapy and initiating a washout with cholestyramine; [e]if conception is delayed by >12 months, consider stopping sulfasalazine alongside the investigation of other causes of infertility. Indeed, sulfasalazine was associated with oligospermia, reduced sperm mobility and abnormal sperm; [f]SIR recommendations recommend maintaining therapy during 1st and 2nd trimester. According to BSR guidelines, it could be stopped by 20 weeks if there is a low risk of disease flare. This will allow full-term infants to have a normal vaccination schedule; [g]SIR recommendations recommend maintaining therapy during 1st and 2nd trimesters. According to BSR guidelines, it could be stopped by 28 weeks if there is a low risk of disease flare. This will allow full-term infant to have a normal vaccination schedule; [h]SIR recommendations recommend maintaining therapy during 1st and 2nd trimesters. According to BSR guidelines, it could be stopped by 32 weeks if there is low risk of disease flare. This will allow the full-term infant to have a normal vaccination schedule; [i]discontinuation ≥2 weeks pre-conception.

Finally, paternal exposure to tofacitinib in RA, psoriasis, and ulcerative colitis appears to be safe, not being associated with a greater risk of pregnancy adverse outcomes compared to the general population (10, 13, 47). Data on paternal exposure to baricitinib include eight cases in the clinical trial programs, with six full-term healthy infants and two spontaneous miscarriages (10, 48). Based on the foregoing, available guidelines consider paternal exposure to JAKi to be compatible with conception time (10, 13). No specific data were reported concerning pregnancy outcomes after paternal exposure to apremilast; therefore, SIR conditionally recommends its use as compatible with conception (13).

CONCLUSIONS

Table I summarizes the current knowledge on the use compatibility of drugs during the preconception period, pregnancy, breastfeeding, and paternal exposure in SpA, according to the national recommendations and international guidelines. Certainly, the continuous expansion of treatments for this disease, together with the increase in knowledge and experience about the use of these drugs, will require a continuous updating of the recommendations. While there will always remain a certain degree of uncertainty about the use of some therapies in pregnancy, the updated information provides guidance to rheumatologists and patients to ensure safer prescribing in these scenarios, highlighting any medications that should be discontinued and/or not used in the reproductive age group, but also avoiding the withdrawal of drugs that can be used in the different phases, thus preventing the risk of increasing disease activity and flares before, during, and after pregnancy in SpA patients.

Therefore, the best management of SpA in pregnant patients is based on knowledge of updated drug recommendations, a careful and wise evaluation of the risks/benefits of starting or continuing treatment from SpA diagnosis in a woman of childbearing age through pregnancy and lactation, and sharing therapeutic choices with other healthcare providers (in particular, gynecologists/obstetricians) and the patient.

Contributions

All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

MM has received consulting fees and/or honoraria from UCB, Lilly; RC has received consulting fees and/or honoraria from AbbVie, Amgen, BMS, Celltrion, Fresenius, Galapagos, Janssen, Lilly, Novartis, Pfizer and UCB. The other authors have no conflict of interest to declare.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Funding

None.

Availability of data and materials

Data available from the corresponding author upon request.

REFERENCES

1. Jethwa H, Lam S, Smith C, Giles I. Does rheumatoid arthritis really improve during pregnancy? A systematic review and metaanalysis. J Rheumatol 2019; 46: 245-50.
2. Maguire S, O'Dwyer T, Mockler D, O'Shea F, Wilson F. Pregnancy in axial spondyloarthropathy: a systematic review & meta-analysis. Semin Arthritis Rheum 2020; 50: 1269-79.
3. Lui NL, Haroon N, Carty A, Shen H, Cook RJ, Shanmugarajah S, et al. Effect of pregnancy on ankylosing spondylitis: a case-control study. J Rheumatol 2011; 38: 2442-4.
4. van den Brandt S, Zbinden A, Baeten D, Villiger PM, Østensen M, Förger F. Risk factors for flare and treatment of disease flares during pregnancy in rheumatoid arthritis and axial spondyloarthritis patients. Arthritis Res Ther 2017; 19: 64.
5. Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender Differences in axial spondyloarthritis: women are not so lucky. Curr Rheumatol Rep 2018; 20: 35.

6. Meissner Y, Strangfeld A, Molto A, Forger F, Wallenius M, Costedoat-Chalumeau N, et al. Pregnancy and neonatal outcomes in women with axial spondyloarthritis: pooled data analysis from the European Network of Pregnancy Registries in Rheumatology (EuNeP). Ann Rheum Dis 2022; 81: 1524-33.
7. Smith CJF, Förger F, Bandoli G, Chambers CD. Factors associated with preterm delivery among women with rheumatoid arthritis and women with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2019; 71: 1019-27.
8. Götestam 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: 795-810.
9. Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis 2023; 82: 19-34.
10. Russell MD, Dey M, Flint J, Davie P, Allen A, Crossley A, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford) 2023; 62: e48-88.
11. 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 (Oxford) 2016; 55: 1693-7.
12. 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 (Oxford) 2016; 55: 1698-702.
13. ISS. La salute riproduttiva nei pazienti con malattie reumatologiche. Available from: https://www.iss.it/-/salute-riproduttiva-in-pazienti-con-malattie-reumatologiche. Accessed on: 7/01/2024.
14. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE evidence to decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol 2017; 81: 101-10.
15. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Rheumatol 2020; 72: 529-56.
16. Wang R, Bathon JM, Ward MM. Nonsteroidal antiinflammatory drugs as potential disease-modifying medications in axial spondyloarthritis. Arthritis Rheumatol 2020; 72: 518-28.
17. Stone S, Khamashta MA, Nelson-Piercy C. Nonsteroidal anti-inflammatory drugs and reversible female infertility: is there a link?. Drug Saf 2002; 25: 545-51.
18. Pall M, Fridén BE, Brännström M. Induction of delayed follicular rupture in the human by the selective COX-2 inhibitor rofecoxib: a randomized double-blind study. Hum Reprod 2001; 16: 1323-8.
19. Micu MC, Micu R, Ostensen M. Luteinized unruptured follicle syndrome increased by inactive disease and selective cyclooxygenase 2 inhibitors in women with inflammatory arthropathies. Arthritis Care Res (Hoboken) 2011; 63: 1334-8.
20. Brouwer J, Hazes JMW, Laven JSE, Dolhain RJEM. Fertility in women with rheumatoid arthritis: influence of disease activity and medication. Ann Rheum Dis 2015; 74: 1836-41.
21. Maguire S, Molto A. Pregnancy & neonatal outcomes in spondyloarthritis. Best Pract Res Clin Rheumatol 2023; 37: 101868.
22. Hamroun S, Couderc M, Flipo RM, Sellam J, Richez C, Dernis E, et al. Op0153 Preconceptional nsaid treatment is associated with longer time-to-conception in women with spondyloarthritis: analysis of the prospective Gr2 cohort. Ann Rheum Dis 2022; 81: 99.
23. 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: 824-9.
24. Filippini C, Saran S, Chari B. Musculoskeletal steroid injections in pregnancy: a review. Skeletal Radiol 2023; 52: 1465-73.
25. Chen J, Lin S, Liu C. Sulfasalazine for ankylosing spondylitis. Cochrane Database Syst Rev 2014; 11: CD004800.
26. Khanna Sharma S, Kadiyala V, Naidu G, Dhir V. A randomized controlled trial to study the efficacy of sulfasalazine for axial disease in ankylosing spondylitis. Int J Rheum Dis 2018; 21: 308-14.
27. Chen J, Veras MMS, Liu C, Lin J. Methotrexate for ankylosing spondylitis. Cochrane Database Syst Rev 2013; 2: CD004524.
28. Tsao NW, Sayre EC, Hanley G, Sadatsafavi M, Lynd LD, Marra CA, et al. Risk of preterm delivery and small-for-gestational-age births in women with autoimmune disease using biologics before or during pregnancy: a population-based cohort study. Ann Rheum Dis 2018; 77: 869-74.
29. Beltagy A, Aghamajidi A, Trespidi L, Ossola W, Meroni PL. Biologics during pregnancy and breastfeeding among women with rheumatic diseases: safety clinical evidence on the road. Front Pharmacol 2021; 12: 621247.

30. Puchner A, Gröchenig HP, Sautner J, Helmy-Bader Y, Juch H, Reinisch S, et al. Immunosuppressives and biologics during pregnancy and lactation : a consensus report issued by the Austrian Societies of Gastroenterology and Hepatology and Rheumatology and Rehabilitation. Wien Klin Wochenschr 2019; 131: 29-44.
31. Allen KD, Kiefer MK, Butnariu M, Afzali A. Pregnant women with immune mediated inflammatory diseases who discontinue biologics have higher rates of disease flare. Arch Gynecol Obstet 2022; 306: 1929-37.
32. Porter C, Armstrong-Fisher S, Kopotsha T, Smith B, Baker T, Kevorkian L, et al. Certolizumab pegol does not bind the neonatal Fc receptor (FcRn): consequences for FcRn-mediated in vitro transcytosis and ex vivo human placental transfer. J Reprod Immunol 2016; 116: 7-12.
33. Atzeni F, Carriero A, Boccassini L, D'Angelo S. Anti-IL-17 agents in the treatment of axial spondyloarthritis. Immunotargets Ther 2021; 10: 141-53.
34. Frieder J, Kivelevitch D, Menter A. Secukinumab: a review of the anti-IL-17A biologic for the treatment of psoriasis. Ther Adv Chronic Dis 2018; 9: 5-21.
35. Blauvelt A. Ixekizumab: a new anti-IL-17A monoclonal antibody therapy for moderate-to severe plaque psoriasis. Expert Opin Biol Ther 2016; 16: 255-63.
36. Warren RB, Reich K, Langley RG, Strober B, Gladman D, Deodhar A, et al. Secukinumab in pregnancy: outcomes in psoriasis, psoriatic arthritis and ankylosing spondylitis from the global safety database. Br J Dermatol 2018; 179: 1205-7.
37. Meroni M, Generali E, Guidelli GM, Parodi M, Cutolo M, Selmi C. THU0319 overall safety of 7-week secukinumab exposure during pregnancy in women with psoriatic arthritis. Ann Rheum Dis 2018; 77: 377-8.
38. Dowty ME, Lin J, Ryder TF, Wang W, Walker GS, Vaz A, et al. The pharmacokinetics, metabolism, and clearance mechanisms of tofacitinib, a janus kinase inhibitor, in humans. Drug Metab Dispos 2014; 42: 759-73.
39. Coates LC, Soriano ER, Corp N, Bertheussen H, Callis Duffin K, Campanholo CB, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. Nat Rev Rheumatol 2022; 18: 465-79.
40. Wilsdon TD, Whittle SL, Thynne TR, Mangoni AA. Methotrexate for psoriatic arthritis. Cochrane Database Syst Rev 2019; 1: CD012722.
41. Mease PJ, Gladman DD, Collier DH, Ritchlin CT, Helliwell PS, Liu L, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase III trial. Arthritis Rheumatol 2019; 71: 1112-24.
42. Weber-Schoendorfer C, Diav-Citrin O. Methotrexate in pregnancy: still many unanswered questions. RMD Open 2023; 9: e002899.
43. Mahadevan U, Naureckas S, Tikhonov I, Wang Y, Lin CB, Geldhof A, et al. Pregnancy outcomes following periconceptional or gestational exposure to ustekinumab: review of cases reported to the manufacturers global safety database. Aliment Pharmacol Ther 2022; 56: 477-90.
44. Drugs and Lactation Database (LactMed®). Bethesda, MD, USA: National Institute of Child Health and Human Development; 2006.
45. Griswold MD. Spermatogenesis: the commitment to meiosis. Physiol Rev 2016; 96: 1-17.
46. Zarén P, Turesson C, Giwercman A. Methotrexate use among men—association with fertility and the perinatal health of their children: a Swedish nationwide register study. Fertil Steril 2023; 120: 661-9.
47. Mahadevan U, Dubinsky MC, Su C, Lawendy N, Jones TV, Marren A, et al. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. Inflamm Bowel Dis 2018; 24: 2494-500.
48. Costanzo G, Firinu D, Losa F, Deidda M, Barca MP, Del Giacco S. Baricitinib exposure during pregnancy in rheumatoid arthritis. Ther Adv Musculoskelet Dis 2020; 12: 1759720X19899296.