

Pregnancy in patients affected by axial-spondyloarthritis: a narrative review of disease activity and obstetric outcomes

M. Filippini¹, G. Fontana¹, P. Bizzioli¹, F. Crisafulli¹, R. Orabona², S. Zatti², F. Franceschini¹, A. Tincani¹

¹Rheumatology and Clinical Immunology Unit-ERN ReCONNET, Department of Clinical and Experimental Sciences, ASST Spedali Civili, University of Brescia, Italy;

²Obstetrics and Gynecology Unit, ASST Spedali Civili, Brescia, Italy

SUMMARY

Objective. This review aims to summarize the most recent and updated data on pregnancy in patients with axial spondyloarthritis (axSpA), focusing on the recurrence of pregnancy-related complications, the disease activity throughout gestation and the postpartum, and the latest indications for the treatments of future mothers.

Methods. We have conducted a narrative review with an online literature search on Medline and PubMed. We selected only studies written in English published until January 2024, including observational and retrospective studies, meta-analyses, and systematic reviews.

Results. Proper preconception counseling and maternal-fetal monitoring are necessary to ensure the best outcome for both the mother and her baby. Despite the limited and conflicting evidence about the prevalence of adverse pregnancy outcomes in women with axSpA compared to healthy controls, primary findings demonstrate an increased risk of preterm delivery (PTD), low birth weight (LBW), and elective cesarean section (CS). Concerning disease activity, data suggests that 25-80% of women with ankylosing spondylitis experience disease flares during pregnancy, particularly around 20 weeks of gestation. On the contrary, the data on the postpartum disease flare are heterogeneous. The use of biological drugs in pregnancy is safe and effective in controlling disease activity.

Conclusions. Data on pregnancy outcomes in patients with axSpA are scarce and discordant. Probably the difference in maternal disease classification, the evolution of treatment indications, and the differences emerging from study designs can account for these discrepancies. The main evidence shows an increased risk of PTD, LBW, and elective CS (although the latter may reflect cultural influences rather than medical needs due to axSpA itself). The majority of drugs used to treat axSpA, including TNFi, are safe in pregnancy without harming mothers or fetuses. Further data is needed to clarify many controversial aspects in this area.

Key words: Spondyloarthritis, pregnancy, adverse pregnancy outcomes, preterm delivery, disease activity.

Reumatismo, 2024; 76 (3): 211-221

INTRODUCTION

Axial spondyloarthropathy (axSpA) is a chronic inflammatory arthritis primarily impacting the sacroiliac joints and spine (1). Additionally, it can affect peripheral and extra-musculoskeletal structures (2). AxSpA is classified as radiographic axSpA, previously known as ankylosing spondylitis (AS), and non-radiographic axSpA, in which early sacroiliitis is detected by magnetic resonance imaging (1). Despite what was believed in the past, the female/male ratio of the disease occurrence is 1:2 (3),

mainly due to radiographic changes occurring less often in women (4). Usually, symptom onset falls in the second/third decade of life (5), which corresponds to child-bearing age for female patients. Consequently, it is important to investigate their desire for motherhood as soon as the diagnosis is made. Appropriate preconception counseling plays a key role in tailoring the management of each patient with the aim of achieving the best possible outcome (4, 6). Previous research on pregnancy in women with arthritis has demonstrated that active inflammatory disease is related to adverse

Corresponding author:
Angela Tincani
Rheumatology and Clinical
Immunology Unit-ERN ReCONNET,
Department of Clinical and Experimental
Sciences, ASST Spedali Civili,
University of Brescia, Italy
E-mail: angela.tincani@unibs.it

pregnancy outcomes (APOs), especially preterm delivery (PTD) and disease flare (7-9). To reduce these risks, conception should be planned during a period of disease control on stable medications compatible with pregnancy (6, 10). To maintain disease control throughout gestation, it is also essential to have tight monitoring with laboratory, rheumatologic, and obstetric periodic evaluations. If the disease affects organs other than joints, the advice of other specialists could be needed to optimize maternal health and pregnancy outcomes (10). To date, there is scarce and conflicting evidence about the prevalence of APOs in axSpA women compared to the general obstetric population (GOP), making it difficult for rheumatologists and obstetricians to counsel their patients effectively (4, 8, 11-17). The lack of high-quality evidence is due to the shortage of case-control studies and meta-analysis (18), as well as to the characteristics of published studies whose sample sizes are often small (14, 19-21) without shared classification criteria (18). Moreover, available reports often do not detail whether the diagnosis of axSpA relies on radiographic or non-radiographic findings. Another challenge arises from the heterogeneity in clinical practice, social preferences, and cultural influences, particularly concerning breastfeeding and cesarean sections (CS) (22-24). Certainly, the introduction of standardized outcomes and a national disease register will increase the possibility of comparing the data (18). Below, we summarize the available evidence on axSpA and pregnancy.

■ INFERTILITY AND AXIAL SPONDYLOARTHROPATHY

Women with inflammatory arthritis tend to have fewer children than their counterparts (25, 26). This trend may be due to the fact that many of them decide to plan motherhood after the diagnosis of their disease, more often after several years without effective treatments. On the other hand, 13% of women diagnosed with AS choose to avoid pregnancy (27), contributing to a general decline in the birth rate (4, 28). Addi-

tionally, a study revealed that among axSpA women who had a baby, 14.3% reported difficulties in conceiving, despite regular unprotected sexual intercourse, for more than one year without resulting in pregnancy (14).

In axSpA women, infertility may be due to factors like physical disability (29), pain during intercourse, depression, or fatigue, leading to reduced libido or sexual dysfunction (30).

Other factors negatively impacting fertility include increased maternal age at the onset of the disease and delay in conception due to the need to discontinue specific medications, such as teratogenic drugs (31).

Furthermore, a full dose of nonsteroidal anti-inflammatory drugs (NSAIDs) in the preovulatory phase may prevent the rupture of the follicle wall and the release of the oocyte in a phenomenon called luteinized unruptured follicle syndrome (32, 33).

■ PREGNANCY OUTCOMES IN AXIAL SPONDYLOARTHROPATHY

Pregnancy complications encompass adverse outcomes including miscarriage, stillbirth, PTD, pre-eclampsia (PE), and CS, with significant implications for fetal viability, maternal mortality, and the baby's long-term health (6, 18).

Several studies have demonstrated that women affected by axSpA have a higher rate of APOs compared to the GOP (7, 11, 34), with a prevalence close to 50% of pregnancies (6). In contrast, no increased risk of APOs was found in both a small case-control study (15) and a small prospective cohort (13).

As concerns the miscarriage rate, the data are not consistent. A meta-analysis drawn up in 2020 showed that spontaneous miscarriages occur less frequently in axSpA pregnancies compared to the GOP (18), while a more recent study documented a significantly higher prevalence of miscarriage in 16.7% of cases compared to the GOP (3.2%, $p=0.04$) (6). Such differences could be due to the long period taken into consideration for the collection of data from

women with axSpA or to the difficulty in finding reliable data about the miscarriage rate in the GOP because women who suffer a miscarriage early in pregnancy do not always undergo a medical examination (6). Taking into consideration a third case-control study, a significant difference persists but is less dramatically higher (4.6% in axSpA *versus* 3% in controls). In the same study, the rate of elective abortions was similar between cases and controls (3.2% *versus* 3.1%) (35).

Data are consistent among reviews and meta-analyses about stillbirth, showing a similar prevalence in axSpA pregnancies compared to healthy controls (0,5% *versus* 0,4%) (18, 27).

As concerns PTD, the risk is higher in women with axSpA than in the GOP, according to several systematic reviews and meta-analyses (4, 15, 17, 27, 34, 36-38), up to 2.52 times of the prevalence (6).

In a study based on the German National Health Insurance Data, the percentage of PTD in women with axSpA was higher than in controls, but without statistical significance (35).

Based on a case-control study conducted in the Swedish population, the risk of PTD was increased for both moderate PTD (32-36 weeks) and very preterm (<32 weeks) PTD (17). Another study indicated that risk ratios were similar for medically indicated and spontaneous PTD in pregnancies with axSpA compared with the GOP, but only spontaneous PTD reached statistical significance (12).

Recently, data from the European Network of Pregnancy Registries in Rheumatology reported a lower rate of preterm births among patients with axSpA, prospectively followed during pregnancy, perhaps due to the close monitoring of women in specialized centers that manage patients with rheumatic conditions (39).

The risk of PTD may be associated with various factors, some shared with GOP, such as advanced maternal age (40), and some specific to patients with axSpA, including active disease during pregnancy (7, 17, 34, 41), as well as the higher risk of PE (17, 41), which appeared to be more preva-

lent in cases of AS associated with PTD (27).

A Swedish cohort study performed between 2007 and 2013 observed a decline in PTD among women with axSpA, particularly those medically indicated, reaching a proportion similar to that of the GOP. Various explanations have been proposed to explain the decreased risk of PTD in these subjects, including the increased use of tumor necrosis factor α inhibitors (TNFi) (12).

Given the potential impact on the PTD rate and the healthcare system (42), acknowledging its elevated occurrence in pregnancies with axSpA is essential. Recognizing this higher prevalence is crucial for enhancing patient monitoring, to minimize future risks through prompt identification and treatment of at-risk axSpA women (6).

As concerns PE, it is a serious obstetric complication with potentially fatal consequences for both the mother and baby (43-45). Several risk factors are associated with PE, such as first pregnancy, very low or high maternal age, obesity (44-46), and chronic inflammation (47).

The findings concerning the risk of PE in patients with axSpA are rather controversial. An observational cohort study found no heightened risk of PE in pregnancies with axSpA (48), aligning with earlier research (11, 17, 27, 34). This observation persisted even after adjusting for established PE risk factors, and no associations were noted with antirheumatic treatment or disease activity (48). On the contrary, in a 2022 article, it was found that PE has a prevalence 2.48 times higher in pregnancies with axSpA compared to the GOP [95% confidence interval (CI) 1.61-3.83] (6). Furthermore, the aggregation of data through meta-analysis revealed a high risk of PE in pregnancies with axSpA (36, 37).

In addition, recent studies show a higher prevalence of PE in axSpA pregnancies compared to controls. A Sweden cohort study showed a 1.44 times adjusted risk ratio (12), while a nationwide Irish study reported a 2.48 times greater prevalence compared to the general population (6).

All high-risk PE patients should receive low-dose aspirin as prophylaxis until 34-36

gestational weeks (49, 50), and regularly monitor blood pressure and proteinuria, along with fetal and maternal Doppler ultrasounds. Impaired uterine artery Doppler velocimetry at 24-25 weeks of gestation could be associated with an increased risk of hypertensive disorders of pregnancy (51). To date, it is not possible to identify a single cause explaining the increased risk of PE in women with axSpA. Nonetheless, in our opinion, the inflammatory state itself could have an important role.

Premature rupture of membranes was documented in two studies comprising 78 women with axSpA, but no control data were available for comparison (7, 19).

AxSpA women did not show a significant difference in the prevalence of gestational diabetes (6, 7, 11, 18, 27, 35, 52).

As concerns intrauterine growth restriction (IUGR), its incidence was not significantly higher in pregnancies with axSpA compared to controls, with an odds ratio (OR) of 1.17 (95% CI 0.26-5.17) (18).

Most studies showed that axSpA women have an increased prevalence of CS compared to the GOP (11, 17, 18, 34, 36, 52, 53), with almost twice the risk of delivery by CS, according to a recent meta-analysis (18). In contrast, two studies did not observe an increased risk for CS (15, 54), and a recent Irish study even concluded that the prevalence of CS was the only pregnancy outcome that occurred less often in axSpA pregnancies compared to the healthy popu-

lation, although without statistical significance (13.3% versus 18.6%, $p=0,27$) (6). Data regarding the rate of CS during the last few years are not consistent because in some studies it is increasing (55), while in others it is decreasing (12). The CS is an interesting outcome of pregnancy because it can be due to the disease itself but also reflect cultural or obstetric practices (20, 56), although the World Health Organization (WHO) encourages CS to be performed only when medically indicated (11) in order to reduce healthcare costs and gynecological complications (7). Elective CS was more common in axSpA women than in controls, whereas the risk of urgent CS was not significantly different (11, 12, 18, 36). The higher rate of elective CS may have several explanations, including physicians' or maternal concerns about vaginal delivery in women with axSpA or other clinical indications (18). A review showed that the election of CS over spontaneous vaginal delivery could be caused by the presence of active disease (11, 17, 27), PE, prematurity (34), and general comorbidities (17). It is interesting to note that CS was not related to spondyloarthritis, sacroiliitis, or hip arthritis (11, 27).

A summary is shown in Table I.

■ FETAL/NEONATAL OUTCOMES IN AXIAL SPONDYLOARTHRITIS

Data from a meta-analysis showed a trend toward a higher incidence of fetal complications in neonates born to mothers with axSpA, though statistical significance was not observed (18). These adverse outcomes could be attributed to active disease during pregnancy or to the occurrence of pregnancy-related complications, including hypertensive disorders and diabetes (11, 17). Evidence agrees with higher CS and PTD risks in axSpA, but consensus is lacking for the rate of other complications risks, such as small-for-gestational-age (SGA) babies (27, 36).

In a 2021 review (27), only one of the four studies included took into account the rate of SGA babies reporting an increased risk,

Table I - Pregnancy outcomes in axial spondyloarthritis.

Pregnancy outcomes in axSpA	Prevalence compared to healthy controls
Miscarriage	Non-univocal data
Stillbirth	Similar
Pre-term delivery	Increased for both medically and spontaneous PTD, only spontaneous PTD showed statistical significance
Pre-eclampsia	Increased
Cesarean section	Non-univocal data
Premature rupture of membranes	No data for comparison
Gestational diabetes	Similar
Intrauterine growth restriction	Increased

axSpA, axial spondyloarthritis; PTD, preterm delivery.

with an OR of 8.7 (95% CI 1.07-70.72) (54). Other studies recorded a non-significant trend toward an increased risk of SGA in pregnancies with axSpA (12, 15, 34), along with a review reporting an overall OR of 1.66 (95% CI 0.93-2.95). According to a weighted pooled means calculation, the prevalence of SGA was 8.7% in the axSpA pregnancies and 11% in the control group (18). Interestingly, SGA was the sole fetal outcome significantly less common in axSpA pregnancies (5.4% *versus* 11%, $p < 0.01$) in the already quoted Irish study. Additional analysis disclosed an OR of 0.54 (95% CI 0.33-0.89) for SGA following an axSpA pregnancy compared to pregnancies in the GOP (6).

In summary, individual studies' outcomes vary, but when combined, they indicate a non-significant trend toward an increased risk of SGA in pregnancies with axSpA (18). In a systematic review (2020), neonatal intensive care unit (NICU) admission showed an overall OR of 1.55 (95% CI 0.96-2.51), indicating a non-significant trend of increase in axSpA pregnancies compared with the GOP (18). In line with this, another study reported no significant differences between NICU comparing axSpA with the GOP (12.2% *versus* 11.9%, $p = 0.47$) (6). In contrast, a study on infants of mothers with AS showed a risk of NICU admission of around 67%. This may be due to the higher incidence of very low birth weight (LBW) and preterm infants in this cohort, also including twin pregnancies, known to be at risk for PTD and LBW (11). Furthermore, another report demonstrated an increased rate of NICU admissions in the newborn of AS's mother who took medications during pregnancy compared to those who did not (38). Few studies discussed the low 5-minute Apgar score as a pregnancy outcome, showing no increased risk of an Apgar score below 7 at the 5th minute in pregnancies with AS (17, 34). No elevated risk of congenital abnormalities has been shown (18, 35).

A Swedish study found a higher risk of neonatal infection among babies from mothers with axSpA (1.29, 95% CI 1.05-1.59) (12), equal to 1.5 per 100 compared with GOP. Despite increased TNFi use in pregnancy,

Table II - Fetal/neonatal outcomes in axial spondyloarthritis.

Pregnancy outcomes	Comment
Small-for-gestational-age	Increased Non-significant trend
Neonatal intensive care unit admissions	Similar Only two studies showed an increased risk of NICU admissions
Congenital abnormalities	Similar
Neonatal infection	Increased

NICU, neonatal intensive care unit.

infection incidence decreased over time, aligning with studies in other diseases showing no clear association between TNFi use and infant infection (57, 58). A summary is shown in Table II.

■ THE IMPACT OF PREGNANCY ON DISEASE ACTIVITY IN AXIAL SPONDYLOARTHRITIS

Unlike rheumatoid arthritis, which tends to have low activity during pregnancy with a high risk of postpartum flares (59, 60), a scoping review revealed that 25-80% of women with AS experienced disease flares during pregnancy (7, 13, 20, 27, 61). Only a few studies noted improved disease activity (8, 15) or a stable disease course for the majority of patients during gestation (14, 15). A study reported that 72.4% of patients were in stable remission before conception. Despite this, 31.6% experienced heightened disease activity during gestation, while only 18.4% noted improvement (6). Multiple studies (7, 54, 60, 61) and a meta-analysis (18) found flares more common in middle/late pregnancy, peaking around week 20 with increased pain and morning stiffness (13, 62). Active disease at conception and discontinuation of TNFi early in pregnancy are both reported as risk factors for disease flare during pregnancy (27, 54). The relative risk of disease flare for those who stopped TNFi therapy during early pregnancy was 3.08 (95% CI 1.2-7.9) in a study published in 2017 (54).

The reported data on postpartum disease flare (frequency, severity, timing) appear

heterogeneous (10, 33, 63-65), and a wide range rate (30-100%) is recorded (13-15, 20, 21, 61, 66, 67). A study showed an increased remission rate in the postpartum period compared to pregnancy (56.1% versus 40.8%), with flares occurring in 25% of cases (6). Disease activity at conception predicted postpartum flares (4). Flares may be exacerbated by patients discontinuing therapy due to concerns about harming their baby while breastfeeding (10, 68).

In monitoring disease flares, two challenges arise. The first is the difficulty in distinguishing between pregnancy-related changes and inflammatory axSpA symptoms (35, 57). Pregnancy can mimic axSpA symptoms such as early morning stiffness, back pain improving with exercise, and restricted range of motion typical of inflammatory back pain (6). A useful help came from a population study highlighting that active disease and elevated C-reactive protein often peak in the second trimester (61), while pregnancy-related back pain typically occurs in healthy pregnant women during the third trimester (20, 69).

The second challenge is the absence of standardized outcome measures for assessing disease activity in pregnant women with axSpA (6, 70). Indeed, some studies reported the Bath Ankylosing Spondylitis Disease

Activity Index or the Ankylosing Spondylitis Disease Activity Score, while others did not specify the measures, making it difficult to compare different studies (18). However, a clear definition of disease relapse is crucial for making treatment decisions (10).

■ DRUGS AND PREGNANCY IN AXIAL SPONDYLOARTHROPATHY

Medication use in pregnancy varies, possibly reflecting evolving practices and geographical prescribing patterns. For women with axSpA requiring ongoing medication during pregnancy, adjusting treatment before conception is crucial. The withdrawal of incompatible drugs and their replacement with alternatives compatible with pregnancy is fundamental to ensuring the best disease control during pregnancy and minimizing APOs (10).

The British Society for Rheumatology (71, 72), the American College of Rheumatology (73), the European Alliance of Associations for Rheumatology (EULAR) (74), and recently also the Italian Society for Rheumatology (75) have issued guidance and recommendations on the use of different anti-rheumatic drugs during pregnancy and breastfeeding, as outlined in Table III.

Table III - Use of anti-rheumatic drugs during pregnancy and breastfeeding in women with axial spondyloarthritis.

Drugs		Pregnancy	Breastfeeding
Nonsteroidal anti-inflammatory drug (NSAIDs)	Non selective NSAIDs	Allowed in the 1 st and 2 nd trimesters; intermittent use in the 1 st trimester is recommended. Avoid in the 3 rd trimester (premature closure of the ductus arteriosus).	Allowed
	Cyclooxygenase-2-selective NSAIDs:	Not recommended because of a lack of data.	Not allowed. Data on celecoxib are available so it could be considered if necessary.
Paracetamol		Allowed	Allowed
Analgesics	Codeine	Allowed, avoid long-term use	Allowed with caution due to the risk of neonatal central nervous system depression
	Tramadol	Allowed during the second/third trimesters if no alternatives (intermittent use)	Allowed (short-term)
Non-fluorinated glucocorticoids (e.g., prednisone, prednisolone and methylprednisolone)		Allowed at minimum effective dose (if possible <20 mg/day).	Allowed

Continue >>>

Paracetamol	Pregnancy	Breastfeeding
Sulphasalazine	Allowed with the intake of 5 mg daily folic acid during the periconceptual period and the first trimester.	Allowed
TNF α inhibitors (TNFi)	Allowed - Certolizumab: no discontinuation - Infliximab: discontinuation at 20 gestational weeks (GW) - Adalimumab and golimumab: discontinuation at 28 GW - Etanercept: discontinuation at 32 GW Infliximab, adalimumab, golimumab and etanercept can be maintained during pregnancy in the case of severe maternal disease. Delayed live vaccines administration in newborns exposed to TNFi (except certolizumab) in utero, with different timing in accordance with the specific drug. Restart TNFi in the post-partum	Allowed
IL17-inhibitors	Precautionally not allowed, except in the case of severe maternal disease in pregnancy without other therapeutic options. Do not administer live virus vaccines to newborns until 6 months of age if IL17-inhibitor is taken in the third trimester.	Allowed
Targeted synthetic DMARDs (JAKi)	Not allowed; discontinue at least 2 weeks before conception.	Not allowed

NSAIDs, nonsteroidal anti-inflammatory drugs; IL, interleukin; DMARDs, disease-modifying antirheumatic drugs; JAKi, Janus kinase inhibitor.

In Table III, we considered the drugs included in the 2022 EULAR recommendations for the treatment of axSpA (76).

There is a focus on using TNFi during pregnancy for disease control and potential fetal effects (77). A recent meta-analysis comparing pregnancy outcomes in women with rheumatological diseases and inflammatory bowel diseases for TNFi users *versus* non-users confirmed no increased rates of complications (78). Furthermore, current guidelines recommend the continuation of TNFi during pregnancy to avoid disease flare (71-75).

A Swedish nationwide study on axSpA pregnancies reported a decreasing risk for pregnancy complications (PTD, infant infection, and CS) from 2007 to 2020 (12). The authors identify as a possible reason for improvement the progressive increased use of biological disease-modifying antirheumatic drugs, improving maternal disease control (12).

It should be considered to delay the administration of live vaccines to newborns of mothers treated with TNFi until the third trimester of pregnancy (except for certolizumab pegol), as suggested by the latest guidelines (72, 75).

Further research is needed to differentiate the influence of pharmacotherapy and disease activity on pregnancy outcomes.

■ MANAGEMENT OF FLARE-UPS DURING PREGNANCY IN AXIAL SPONDYLOARTHROPATHY

Regarding flares with active peripheral involvement, such as arthritis or enthesitis, glucocorticoid injections are an effective option for treating local inflammation, as in non-pregnant patients (74). Another alternative is short-term systemic glucocorticoid (sGC) use with rapid tapering (74) to minimize steroid-related adverse effects like hyperglycemia and bone loss (49). Moreover, second-trimester sGC use is correlated with an elevated risk of PTD, as already described in different diseases. Yet, a prospective study revealed a 38% sGC use in AS women during pregnancy, especially in the case of peripheral joint involvement (11). Considering alternatives, such as sulfasalazine, before sGC for pregnancy flares may be prudent (74).

As described in Table III, the short-term uti-

lization of non-selective NSAIDs is allowed during the first and second trimesters but not during the third trimester due to the risk of premature closure of the ductus arteriosus (71, 72).

Physical therapy and rehabilitation appropriate for pregnancy can also play an important role in reducing drug consumption.

■ BREASTFEEDING IN AXIAL SPONDYLOARTHROPATHY

The WHO encourages breastfeeding for its beneficial role for both the mother and the baby (45). The benefits obtained include a decreased risk of many chronic diseases in breastfed children and a reduced risk of obesity and certain cancers in breastfeeding mothers (79).

Breastfeeding rates in axSpA women vary widely (0.8% to 90%), according to a meta-analysis including four studies (18). An Irish study found lower breastfeeding prevalence in axSpA women (33.7%) compared to the national average (59.9%) (6). A concern is drugs' potential harm to the newborn through breast milk; however, current guidelines show that several medications could be safely used during breastfeeding (71-73, 75) (Table III). Patients need education on medication safety during breastfeeding.

■ CONCLUSIONS

AxSpA is a chronic inflammatory arthritis that affects females during childbearing age, and it is important to investigate the desire for motherhood in disease management.

Preconception counseling plays a key role in developing an individualized plan for pregnancy management to try to improve outcomes for both the mother and the baby. Data on pregnancy outcomes in patients with axSpA are scarce and rather discordant. Probably the difference in maternal disease classification, the evolution of treatment indications, and the difference emerging from study designs (population studies *versus* cohort studies) can account for these discrepancies. Despite these biases, the main evidence showed an increased risk of PTD and elective CS, although the latter

data may reflect cultural influences rather than medical needs due to axSpA itself. As a consequence, an increased rate of LBW is reported.

It is important for physicians and patients to know that flares can occur around 20 weeks of gestation and in the postpartum period, and, in this case, the majority of medications used to treat axSpA, including TNFi, are safe in pregnancy without harming mothers or fetuses.

Breastfeeding rates in axSpA women vary widely; patients' education on medication safety during breastfeeding may improve the rate of this practice known to be of the greatest help for the babies.

Further research focusing on reproductive issues in axSpA is certainly needed, as is the introduction of standardized outcomes and national registers of pregnant patients with rheumatic diseases. All these data may help to join and homogenize different experiences.

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

AT, collaboration at different level with UCB, Galapagos, GSK; the other authors declare no conflict of interest.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Funding

None.

Availability of data and materials

Data are available from the corresponding author upon request.

■ REFERENCES

1. Ward MM, Deodhar A, Akl EA, Lui A, Ermann J, Gensler LS, et al. American College of Rheumatology/Spondylitis Association of

- America/Spondyloarthritis Research and Treatment Network 2015 recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2016; 68: 282-98.
2. Sammaritano LR. Pregnancy in rheumatic disease patients. *J Clin Rheumatol* 2013; 19: 259-66.
 3. Lee W, Reveille JD, Weisman MH, et al. Women with ankylosing spondylitis: a review. *Arthritis Rheum* 2008; 59: 449-54.
 4. Ostensen M, Ostensen H. Ankylosing spondylitis—the female aspect. *J Rheumatol* 1998; 25: 120-4.
 5. Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet* 2017; 390: 73-84.
 6. Maguire S, Wilson F, Gallagher P, Ms Mohamed M, Maher S, O’Shea F. What to expect when women with axial spondyloarthritis are expecting: prevalence of complications of pregnancies in women with axial spondyloarthritis. *Semin Arthritis Rheum* 2022; 54: 151993.
 7. Zbinden A, van den Brandt S, Østensen M, Villiger PM, Förger F. Risk for adverse pregnancy outcome in axial spondyloarthritis and rheumatoid arthritis: disease activity matters. *Rheumatology* 2018; 57: 1235-42.
 8. 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.
 9. Ostensen M, Husby G. Pregnancy and rheumatic disease. A review of recent studies in rheumatoid arthritis and ankylosing spondylitis. *Klin Wochenschr* 1984; 62: 891-5.
 10. Giles I, Yee CS, Gordon C. Stratifying management of rheumatic disease for pregnancy and breastfeeding. *Nat Rev Rheumatol* 2019; 15: 391-402.
 11. Smith CJFF, Bandoli G, Kavanaugh A, Chambers CD. Birth outcomes and disease activity during pregnancy in a prospective cohort of women with psoriatic arthritis and ankylosing spondylitis. *Arthritis Care Res* 2020; 72: 1029-37.
 12. Morin M, Frisell T, Stephansson O, Hellgren K. Temporal trends in adverse pregnancy outcomes in axial spondyloarthritis in Sweden: a cohort study. *Lancet Rheumatol* 2023; 5: e121-9.
 13. Ostensen M, Husby G. A prospective clinical study of the effect of pregnancy on rheumatoid arthritis and ankylosing spondylitis. *Arthritis Rheum* 1983; 26: 1155-9.
 14. Ostensen M, Romberg O, Husby G. Ankylosing spondylitis and motherhood. *Arthritis Rheum* 1982; 25: 140-3.
 15. Timur H, Tokmak A, Türkmen GG, İnal HA, Uygur D, Danişman N. Pregnancy outcome in patients with ankylosing spondylitis. *J Matern Fetal Neonatal Med* 2016; 29: 2470-4.
 16. Ursin K, Lydersen S, Skomsvoll JF, Wallenius M. Disease activity during and after pregnancy in women with axial spondyloarthritis: a prospective multicentre study. *Rheumatology* 2018; 57: 1064-71.
 17. Jakobsson GL, Stephansson O, Askling J, Jakobsson LTH. Pregnancy outcomes in patients with ankylosing spondylitis: a nationwide register study. *Ann Rheum Dis* 2016; 75: 1838-42.
 18. Maguire S, O’Dwyer T, Mockler D, O’Shea F, Wilson F. Pregnancy in axial spondyloarthritis: a systematic review & meta-analysis. *Semin Arthritis Rheum* 2020; 50: 1269-79.
 19. Zhou Q, Bian X, Liu J. Management of pregnancy with ankylosing spondylitis. *Chin Med Sci J* 2012; 27: 46-9.
 20. Förger F, Ostensen M, Schumacher A, Villiger P. Impact of pregnancy on health related quality of life evaluated prospectively in pregnant women with rheumatic diseases by the SF-36 health survey. *Ann Rheum Dis* 2005; 64: 1494-9.
 21. Förger F, Villiger PM, Ostensen M. Pregnancy in patients with ankylosing spondylitis: do regulatory T cells play a role?. *Arthritis Rheum* 2009; 61: 279-83.
 22. Boerma T, Ronsmans C, Melesse DY, Barros AJD, Barros FC, Juan L, et al. Global epidemiology of use of and disparities in caesarean sections. *Lancet* 2018; 392: 1341-8.
 23. Rito AI, Buoncristiano M, Spinelli A, Salanave B, Kunešová M, Hejgaard T, et al. Association between characteristics at birth, breastfeeding and obesity in 22 countries: the WHO European Childhood Obesity Surveillance Initiative - COSI 2015/2017. *Obes Facts* 2019; 12: 226-43.
 24. Ibanez G, Martin N, Denantes M, Saurel-Cubizolles MJ, Ringa V, Magnier AM. Prevalence of breastfeeding in industrialized countries. *Rev Epidemiol Sante Publique* 2012; 60: 305-20.
 25. Østensen M, Andreoli L, Brucato A, Cetin I, Chambers C, Clowse MEB, et al. State of the art: Reproduction and pregnancy in rheumatic diseases. *Autoimmun Rev* 2015; 14: 376-86.
 26. Clowse MEB, 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: 668-74.
 27. Mokbel A, Lawson DO, Farrokhyar F. Pregnancy outcomes in women with ankylosing spondylitis: a scoping literature and methodological review. *Clin Rheumatol* 2021; 40: 3465-80.
 28. Keeling SO, Oswald AE. Pregnancy and rheumatic disease: “by the book” or “by the doc”. *Clin Rheumatol* 2009; 28: 1-9.
 29. Helland Y, Dagfinrud H, Kvien TK. Perceived influence of health status on sexual activity in RA patients: associations with demographic and disease-related variables. *Scand J Rheumatol* 2008; 37: 194-9.
 30. Khnaba D, Rostom S, Lahlou R, Bahiri R, Abouqal R, Hajjaj-Hassouni N. Sexual dysfunction and its determinants in Moroccan

- women with rheumatoid arthritis. *Pan Afr Med J* 2016; 24: 16.
31. Hansen KR, Knowlton NS, Thyer AC, Charleston JS, Soules MR, Klein NA. A new model of reproductive aging: the decline in ovarian non-growing follicle number from birth to menopause. *Hum Reprod* 2008; 23: 699-708.
 32. Østensen M. Sexual and reproductive health in rheumatic disease. *Nat Rev Rheumatol* 2017; 13: 485-93.
 33. Eudy AM, Siega-Riz AM, Engel SM, Franceschini N, Green Howard A, Clowse MED, et al. Effect of pregnancy on disease flares in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2018; 77: 855-60.
 34. Mørk S, Voss A, Möller S, Bliddal M. Spondyloarthritis and outcomes in pregnancy and labor: a nationwide register-based cohort study. *Arthritis Care Res* 2021; 73: 282-8.
 35. Redeker I, Strangfeld A, Callhoff J, Marschall U, Zink A, Baraliakos X. Maternal and infant outcomes in pregnancies of women with axial spondyloarthritis compared with matched controls: results from nationwide health insurance data. *RMD Open* 2022; 8: e002146.
 36. Hamroun S, Hamroun A, Bigna JJ, Allado E, Förger F, Molto A. Fertility and pregnancy outcomes in women with spondyloarthritis: a systematic review and meta-analysis. *Rheumatology* 2022; 61: 1314-27.
 37. Bernardy C, Baillet A, Gaudin P, Romand X. Comment on the article by Maguire et al. pregnancy in axial spondyloarthropathy: a systematic review & meta-analysis. *Semin Arthritis Rheum* 2022; 52: 151845.
 38. Unal C, Fadiloglu E, Tanacan A, Zaim OC, Bek-sac MS. Retrospective evaluation of pregnancies with ankylosing spondylitis in a tertiary center in Turkey. *Int J Rheum Dis* 2020; 23: 101-5.
 39. 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.
 40. Fuchs F, Monet B, Ducruet T, Chaillet N, Audibert F. Effect of maternal age on the risk of preterm birth: a large cohort study. *PLoS One* 2018; 13: e0191002.
 41. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008; 371: 75-84.
 42. Vogel JP, Chawanpaiboon S, Moller AB, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. *Best Pract Res Clin Obstet Gynaecol* 2018; 52: 3-12.
 43. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertension* 2018; 72: 24-43.
 44. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet* 2016; 387: 999-1011.
 45. Redman CWG, Sargent IL. Immunology of pre-eclampsia. *Am J Reprod Immunol* 2010; 63: 534-43.
 46. Wadström H, Eriksson JK, Neovius M, Askling J. How good is the coverage and how accurate are exposure data in the Swedish Biologics Register (ARTIS)? *Scand J Rheumatol* 2015; 44: 22-8.
 47. Ibfelt EH, Jensen DV, Hetland ML. The Danish nationwide clinical register for patients with rheumatoid arthritis: DANBIO. *Clin Epidemiol* 2016; 8: 737-42.
 48. Pape Secher AE, Granath F, Glinthborg B, Rom A, Hetland ML, Hellgren K. Risk of pre-eclampsia and impact of disease activity and anti-rheumatic treatment in women with rheumatoid arthritis, axial spondylarthritis and psoriatic arthritis: a collaborative matched cohort study from Sweden and Denmark. *RMD Open* 2022; 8: e002445.
 49. Andreoli L, Bertias 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: 476-85.
 50. Onno Teng YK, Bredewold EOW, Rabelink TJ, Huizinga TWJ, Jeroen Eikenboom HC, Limper M. An evidence-based approach to pre-pregnancy counselling for patients with systemic lupus erythematosus. *Rheumatology* 2018; 57: 1707-20.
 51. Espinoza J, Kusanovic JP, Bahado-Singh R, Gervasi MT, Romero R, Lee W, et al. Should bilateral uterine artery notching be used in the risk assessment for preeclampsia, small-for-gestational-age, and gestational hypertension?. *J Ultrasound Med* 2010; 29: 1103-15.
 52. Park EH, Lee JS, Kim Y, Lee SM, Jun JK, Lee EB, et al. Pregnancy outcomes in Korean women with ankylosing spondylitis. *Korean J Intern Med* 2021; 36: 721-30.
 53. 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: 2310-4.
 54. 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.
 55. Declercq E, Menacker F, MacDorman M. Maternal risk profiles and the primary cesarean rate in the United States, 1991-2002. *Am J Public Health* 2006; 96: 867-72.

56. Thuillier C, Roy S, Peyronnet V, Quibel T, Nlandu A, Rozenberg P. Impact of recommended changes in labor management for prevention of the primary cesarean delivery. *Am J Obstet Gynecol* 2018; 218: 341.e1-e9.
57. Tsao NW, Rebic N, Lynd LD, De Vera MA. Maternal and neonatal outcomes associated with biologic exposure before and during pregnancy in women with inflammatory systemic diseases: a systematic review and meta-analysis of observational studies. *Rheumatology* 2020; 59: 1808-17.
58. Bröms G, Kieler H, Ekblom A, Gissler M, Hellgren K, Leinonen MK. Paediatric infections in the first 3 years of life after maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther* 2020; 52: 843-54.
59. 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.
60. Ursin K, Lydersen S, Skomsvoll JF, Wallenius M. Psoriatic arthritis disease activity during and after pregnancy: a prospective multicenter study. *Arthritis Care Res* 2019; 71: 1092-100.
61. Østensen 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: 1212-7.
62. Tham M, Schlör GR, Yerly D, Mueller C, Surbek D, Villiger PM, et al. Reduced pro-inflammatory profile of $\gamma\delta$ T cells in pregnant patients with rheumatoid arthritis. *Arthritis Res Ther* 2016; 18: 26.
63. de Man YA, Dolhain RJEM, van de Geijn FE, Willemsen SP, Hazes JMW. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum* 2008; 59: 1241-8.
64. Lockshin MD, Reinitz E, Druzin ML, Murrman M, Estes D. Lupus pregnancy. Case-control prospective study demonstrating absence of lupus exacerbation during or after pregnancy. *Am J Med* 1984; 77: 893-8.
65. Ostensen M. The effect of pregnancy on ankylosing spondylitis, psoriatic arthritis, and juvenile rheumatoid arthritis. *Am J Reprod Immunol* 1992; 28: 235-7.
66. Østensen M, Förger F, Nelson JL, Schuhmacher A, Hebisch G, Villiger PM. Pregnancy in patients with rheumatic disease: anti-inflammatory cytokines increase in pregnancy and decrease post partum. *Ann Rheum Dis* 2005; 64: 839-44.
67. Ostensen M. The influence of pregnancy on blood parameters in patients with rheumatic disease. *Scand J Rheumatol* 1984; 13: 203-8.
68. Nalli C, Manfredi L, Fredi M, Crisafulli F, Bertocchi S, amilya Khizroeva J, et al. Managing puerperium in patients with systemic autoimmune diseases: an update. *Expert Rev Clin Immunol* 2022; 18: 391-9.
69. Hainline B. Low-back pain in pregnancy. *Adv Neurol* 1994; 64: 65-76.
70. Andreoli L, Gerardi MC, Fernandes M, Bortoluzzi A, Bellando-Randone S, Brucato A, et al. Disease activity assessment of rheumatic diseases during pregnancy: a comprehensive review of indices used in clinical studies. *Autoimmun Rev* 2019; 18: 164-76.
71. 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* 2023; 62: e48-88.
72. Schreiber K, Frishman M, Russell MD, Dey M, Flint J, Allen A, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: comorbidity medications used in rheumatology practice. *Rheumatology* 2023; 62: e89-104.
73. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, D 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.
74. Skorpen CG, 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.
75. SIR. Recommendations of the Italian Society of Rheumatology on the reproductive health of patients with rheumatological diseases, available on the website of the Italian National Institute of Health. Available from: https://www.reumatologia.it/obj/files/lineeguida/LG_C006_SIR_SRMR.pdf. [Material in Italian].
76. 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.
77. Lindström U, Olofsson T, Wedrén S, Qirjazo I, Askling J. Biological treatment of ankylosing spondylitis: a nationwide study of treatment trajectories on a patient level in clinical practice», *Arthritis Res. Ther.*, vol. 21, fasc. 1, p. 128, mag. 2019, doi: 10.1186/s13075-019-1908-9.
78. Komaki F, Komaki Y, Micic D, Ido A, Sakuraba A. Outcome of pregnancy and neonatal complications with anti-tumor necrosis factor- α use in females with immune mediated diseases; a systematic review and meta-analysis. *J Autoimmun* 2017; 76: 38-52.
79. Binns C, Lee M, Low WY. The long-term public health benefits of breastfeeding. *Asia Pac J Public Health* 2016; 28: 7-14.