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

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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 childbearing 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

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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). Additionally, 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 prevalent 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 population, 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.

Table I - Pregnancy outcomes in axial spondyloarthropathy.

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 spondyloarthropathy; PTD, preterm delivery.

FETAL/NEONATAL OUTCOMES IN AXIAL SPONDYLOARTHROPATHY

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,

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, 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.

Table II - Fetal/neonatal outcomes in axial spondyloarthropathy.

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.

THE IMPACT OF PREGNANCY ON DISEASE ACTIVITY IN AXIAL SPONDYLOARTHROPATHY

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 spondyloarthropathy.

Drugs		Pregnancy	Breastfeeding
Nonsteroidal anti-inflammatory drug (NSAIDs)	Non selective NSAIDs	Allowed in the 1st and 2nd trimesters; intermittent use in the 1st trimester is recommended. Avoid in the 3rd 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

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Paracetamol	Pregnancy	Breastfeeding
Sulphasalazine	Allowed with the intake of 5 mg daily folic acid during the periconceptional period and the first trimester.	Allowed
TNFα 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.

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