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Temporal trends in adverse pregnancy outcomes in axial spondyloarthritis in Sweden : a cohort study

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Adverse pregnancy outcomes in axial spondyloarthritis: temporal trends in a Swedish nationwide cohort study

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SUMMARY

Background: Existing evidence on the risks associated with pregnancy and childbirth in axial spondyloarthritis (axSpA) is limited and conflicting, with more research needed to guide policy and clinical practice. We aimed to assess risks of adverse pregnancy outcomes in a large cohort of women with axSpA, and to investigate how outcomes varied over time and in relation to anti-rheumatic treatment.

Methods: This register-based cohort study included births in Sweden between April 2007 and December 2020 in women with axSpA and general population comparators, matched 1:10 on year of delivery, maternal age, and parity. We used modified Poisson regression to estimate relative risks of adverse pregnancy outcomes. Models were adjusted for matching factors, maternal height, body-mass index, smoking, educational level, disposable income, and country of birth. We studied how the frequency of certain adverse outcomes, as well as anti-rheumatic treatments, changed over the study period by linear regression and loess plots.

Findings: Among 1580 births in women with axSpA, we found increased risks of preterm birth (risk ratio 1·43 [95% CI 1·13–1·80]), pre-eclampsia (1·44 [1·08–1·92]), elective Caesarean delivery (1·59 [1·37–1·84]), and serious infant infection (1·29 [1·05–1·59]), compared to births in general population comparators. Risks of preterm birth, infant infection, and Caesarean delivery decreased around 0·5 percentage points annually over the study period, while the use of tumour necrosis factor inhibitors during pregnancy increased.

Interpretation: In the light of remaining concerns regarding safety with use of biologics during pregnancy, we saw a reassuring trend where pregnancy outcomes improved over time in the axSpA group concurrent with increased use of biologics. If current rate of improvement is maintained, women with axSpA may eventually not be at increased risk of adverse pregnancy outcomes, when treated in accordance with clinical practice.

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RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed on July 31, 2022 with no date restrictions, using the terms ("axial spondyloarthritis" OR "ankylosing spondylitis") AND "pregnancy", to identify studies on pregnancy outcomes in women with axial spondyloarthritis. Findings from previous observational studies have been inconsistent: from only uneventful pregnancies to increased risks for several adverse outcomes. This heterogeneity is also evident from recent reviews and meta-analyses on the topic. Often, studies were hampered by low sample size or lack of a comparison group, and only a handful studies have tried to find explanations for the increased pregnancy-related risks in the axial spondyloarthritis population.

Added value of this study

In this cohort study of over 1500 births in women with axial spondyloarthritis, the largest to date, we found increased risks of preterm birth, pre-eclampsia, and serious infection in the infant, and a higher proportion of elective Caesarean delivery compared to births in general population comparators. The risks associated with axial spondyloarthritis diminished over time for preterm birth, Caesarean delivery, and infant infection, while the use of tumour necrosis factor inhibitors increased.

Implications of all the available evidence

There is indeed an increased risk of adverse pregnancy outcomes associated with axial spondyloarthritis, and existing evidence supports the notion to strive to minimize disease activity during pregnancy, even if it requires the continued use of biologic anti-rheumatic treatment. Concurrent with increased use of biologics during pregnancy, we saw a reassuring trend where adverse pregnancy outcomes improved over time in the women with axial spondyloarthritis. If current rate of improvement is maintained, women with axial spondyloarthritis may eventually not be at increased risk of adverse pregnancy outcomes, when treated in accordance with clinical practice. This should be reassuring for both patients and practitioners, and may inform women with axial spondyloarthritis in their family planning.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory arthritis typically involving the spine and sacroiliac joints, with debut around childbearing age.[1] While an increased risk of adverse pregnancy and infant outcomes have been reported for pregnancies in women with other rheumatic diseases,[2–5] uncertainty remains around pregnancy-associated risks in axSpA. In recent reviews and meta-analyses, increased risks of Caesarean delivery and preterm birth were reported in axSpA, but consensus is lacking regarding risks of e.g. pre-eclampsia and small-for-gestational-age (SGA).[6–8] This may reflect the high heterogeneity of previous studies, many which were small, without comparison group, or ability to control for confounding.

If consensus on risks is lacking, even less is known about the drivers of adverse pregnancy outcomes in axSpA. Studies in both axSpA and other inflammatory diseases have suggested that disease activity is a risk factor for adverse pregnancy outcomes,[9,10] but also different types of anti-rheumatic treatment have been associated with increased risks.[11–13] Whether treatment is entirely a proxy for disease activity, or if also the treatments themselves affects adverse outcomes, is yet to be established.

Important developments in SpA over the last decades include the introduction of the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA, capturing patients earlier in the disease course,[14] and the increasing use of biologic therapies, also during pregnancy.[15,16] These factors are likely to influence axSpA outcomes in numerous ways. As one example, in a recent analysis of pooled data from four European rheumatology pregnancy registers (which unfortunately did not include a comparison group), proportions of adverse outcomes in axSpA pregnancies were overall similar to rates reported from the general population.[17] Most patients in this study were included from 2015 onwards, when the use of biologics was increasing also in the pregnant population. Ultimately, these advances can make us question the generalisability of older studies to today's patient population.

To optimally inform, monitor, and treat childbearing women with axSpA, it is of great clinical value to provide robust contemporary data on the impact of axSpA on pregnancy, but this requires large study populations. We used Swedish national registers to study pregnancy outcomes over 14 years in a large cohort of women with axSpA and matched general population comparators, aiming to estimate relative risks of adverse pregnancy outcomes. We place particular focus on how risks have changed over time, and in relation to an altered anti-rheumatic treatment pattern of this patient population during this period.

PATIENTS AND METHODS

Study design and participants

We performed a nationwide, register-based cohort study, comparing the risk of adverse pregnancy outcomes in pregnancies among women with axSpA and general population comparators, matched on year of delivery, maternal age, and parity. Our main data source was the Medical Birth Register (MBR), which includes over 98% of births in Sweden since 1973 and prospectively collects data regarding antenatal care, delivery, and foetal outcomes.[18] The information in MBR was linked to other registers including the National Patient Register (NPR), the Prescribed Drug Register (PDR), and registers with demographic data (appendix p 2). Women with axSpA were identified in NPR as having minimum two visits with a diagnosis of ankylosing spondylitis (AS; International Classification of Diseases [ICD]-10 codes M45 or M08·1) or undifferentiated SpA (uSpA; M46·8 or M46·9) registered after 2001, including one visit to a rheumatology or internal medicine department. High validity of SpA diagnoses in NPR has been described, with a positive predictive value of 80% for an AS diagnosis to fulfil the modified New York criteria, and 89% for uSpA to fulfil any of the commonly used SpA criteria.[19] Additional women with axSpA were identified from the Swedish Rheumatology Quality Register (SRQ), a clinical register longitudinally collecting disease characteristics, disease activity, and anti-rheumatic treatment as registered by the treating rheumatologist, with best coverage among patients on biologic treatments.

All singleton births between April 1, 2007 and December 31, 2020 in women with axSpA were identified in MBR. To ensure exposure during pregnancy, only pregnancies starting at least one calendar year after the second axSpA diagnosis, or inclusion in SRQ, were included. April 2007 was chosen as study start so that all subjects would have prescription data in PDR the year before pregnancy. Each axSpA birth was matched on year of delivery, maternal age (in years), and parity (primiparous/parous) to ten comparator births in women free from chronic inflammatory arthritis at time of birth. These women had previously been randomly selected from the general population as controls in a large register linkage of chronic inflammatory arthritis, matched 5:1 on age and county of residence to women receiving a diagnosis of chronic inflammatory joint disease. The study was approved by the Regional Ethics Review Board in Stockholm (2015/1844-31/2). In accordance with Swedish law, participant consent was not necessary for this register-based study with pseudonymised data.

Outcomes

Data on adverse outcomes were collected from MBR. Outcomes assessed in all births included stillbirth, pre-eclampsia, gestational diabetes, and gestational hypertension. Maternal outcomes assessed in live births included preterm birth and Caesarean delivery. Preterm birth (<37 weeks of gestation) was further classified as moderate or very preterm (32–36 and <32 weeks, respectively), and by mode of onset (spontaneous or medically indicated [i.e. prelabour Caesarean or induction]). Caesarean deliveries were classified as emergency or elective. Infant outcomes included large- and small for gestational age (LGA, SGA), defined as a birthweight of >2 SDs above or below the sex-specific mean for gestational age, Apgar score <7 at 5 minutes, and neonatal or serious (requiring hospitalisation) infant infection during the first year of life. Information on serious infections was collected from NPR. For further details, see appendix (pp 2–4).

Statistical analysis

Modified Poisson regression, with robust standard errors, was applied to estimate risk ratios and 95% confidence intervals (CIs) of adverse outcomes.[20] We also estimated risk differences and 95% CIs using linear regression with robust standard errors. Analyses were adjusted for maternal height, early pregnancy body-mass index (BMI), smoking, highest attained educational level, disposable income, and country of birth (Nordic or non-Nordic), plus the matching factors. Maternal age, height, and BMI were modelled as third-grade polynomials. For sources and parameterisation of variables, see appendix (pp 2–4).

To explore changes in outcome proportions and treatment patterns over the study period, outcomes with significant relative risks and anti-rheumatic treatment before and during pregnancy were plotted with loess curves by year of delivery, and the average annual change quantified by linear regression. Relative risks of the same outcomes were calculated when dividing the study population into strata by year of delivery (2007–2011, 2012–2016, 2017–2020). Characteristics of women in each stratum, including comorbidities and SpA manifestations, were also investigated.

Preterm birth was selected beforehand as an outcome to study risk factors for in our material. Using separate Poisson regression models, we investigated the associations between preterm birth and measures of disease activity and inflammation. We considered Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Health Assessment Questionnaire–Disability Index (HAQ-DI), and C-reactive protein (CRP) >10 mg/litre as potential predictors. We further investigated whether anti-rheumatic treatments (corticosteroids, conventional systemic disease-modifying anti-rheumatic drugs [csDMARDs], or tumour necrosis factor inhibitors [TNFi]) or non-steroidal anti-inflammatory drugs (NSAIDs) in the year before or during pregnancy (defined as a filled prescription in PDR) were predictive of an increased risk. We also assessed whether manifestations of anterior uveitis, psoriasis, psoriatic arthritis, or inflammatory bowel disease were associated with preterm birth.

Additionally, we explored risk factors for preterm birth already established in the general population. Factors were chosen a priori based on literature and prior knowledge and included maternal age, parity, height, BMI, smoking, educational level, disposable income, pre-eclampsia in current pregnancy, and preterm birth in earlier pregnancy.[21,22] Specifically, we assessed whether the association between these established risk factors and preterm birth differed in axSpA compared to the general population. Modified Poisson regression was applied in axSpA and comparators separately to obtain risk ratios with 95% CIs and p-values for interaction with axSpA in relation to each risk factor.

In sensitivity analyses, to see how risks varied by parity, outcomes with significant results in the main analysis were stratified by first or subsequent birth. To assess whether misclassification of axSpA had affected our results, women with recorded diagnoses of rheumatoid arthritis, psoriatic arthritis, or systemic lupus erythematosus in NPR before pregnancy besides their axSpA diagnosis were excluded.

For the main analysis, where missing data was limited, subjects with missing data (137 [8.7%] in axSpA and 1694 [10.7%] in comparator group), were excluded. However, only 438 women with axSpA had a recorded CRP value in the year before or during pregnancy, and corresponding figures for BASDAI and HAQ-DI was 303 and 350, respectively. Thus, in analyses including disease activity, multiple imputation was performed. Fifty imputed data

sets were created by fully conditional specification among individuals with complete data on other variables. Continuous variables were modelled with linear and quadratic terms and imputed with predictive mean matching. Analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), with graphs produced in R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source
The funding sources had no role in the study design, data collection, analysis, interpretation, or writing of the report.

RESULTS

Between April 1, 2007 and December 31, 2020, 1580 births in women diagnosed with axSpA were recorded in MBR, which we matched with 15792 comparator births (flow diagram describing selection in appendix p 11). Mothers with axSpA were more often born in a Nordic country (1464 [92·7%] vs. 12569 [79·6%] in comparators), but groups were comparable on most background characteristics (table 1).

Pre-eclampsia was more common in births by women with axSpA than comparators (61 [3·9%] vs. 441 [2·8%]), resulting in an adjusted risk ratio of 1·44 (95% CI 1·08–1·92; figure 1, unadjusted estimates in appendix p 5). Caesarean delivery occurred in 382 (24·2%) of axSpA births compared to 2760 (17·5%) of comparator births (1·39 [1·24–1·55]). In particular, there was an increased risk of elective Caesarean delivery (1·59 [1·37–1·84]), whereas the risk of emergency Caesarean delivery was not significantly increased. We also observed an increased risk of preterm birth, with 99 (6·3%) births being preterm in axSpA compared to 682 (4·3%) in comparators (1·43 [1·13–1·80]). Risk ratios were similar for medically indicated and spontaneous preterm birth, but only spontaneous preterm birth reached significance. No increased risk was observed for SGA or LGA birth in axSpA, but for infant infection the risk ratio was 1·29 (1·05–1·59), corresponding to 1·5 more children with infection per 100 women with axSpA (results on the risk difference scale in appendix).

While the proportion of preterm birth remained stable over the study period in comparators, preterm birth among women with axSpA halved, with the most apparent decrease 2007–2013 (figure 2A). Medically indicated births drove the decrease, to levels similar to the general population. Later, spontaneous preterm births also decreased. The rate of Caesarean delivery remained constant among comparators, while it decreased over the study period in axSpA (figure 2B). Infant infection also decreased in axSpA, while the rate of pre-eclampsia remained slightly higher in axSpA births compared to comparators over the study period (figure 2C and D, respectively). Correspondingly, linear regression of these outcomes showed a significant decrease over time in axSpA for preterm birth (average annual decrease 0·4 percentage points), Caesarean delivery (0·6 percentage points), and infant infection (0·6 percentage points), which was not seen for pre-eclampsia or any of the outcomes in comparators. The relative risks of preterm birth, Caesarean delivery, and infant infection also decreased over time when stratifying the study period into three strata (figure 3).

The proportion of women with axSpA without any anti-rheumatic treatment in the year before pregnancy remained relatively constant over the 14-year study period (figure 4A). The use of TNFi increased from <10% in 2007 to about 40% in 2020, a significant average annual increase of 2 percentage points according to linear regression. The prescription-based use of NSAIDs decreased from 60% to 40% (average annual decrease 1 percentage point). During pregnancy, the proportion of women with no filled prescription of anti-rheumatic drugs decreased from almost 80% in 2007 to around 60% in 2020, coinciding with an increased use of TNFi from about 10% to 25% during pregnancy (figure 4B), with an average annual increase of 1·5 percentage points. Of 216 women who used TNFi during pregnancy, 81 (38%) filled prescriptions after week 14 of pregnancy. Forty-one (51%) of these women delivered in the last two years of the study period.

We found no association between preterm birth and measures of inflammation or disease activity in the year before or during pregnancy, though data was only available for a subset of

the cohort. Neither did type of anti-rheumatic treatment nor presence of SpA manifestations associate with preterm birth (appendix p 7). Established risk factors for preterm birth in the general population were associated with similarly increased risks among women with axSpA (appendix p 12). Statistically significant effect modification was only observed for young maternal age and low educational level, which were associated with preterm birth in axSpA but not in comparators in this material.

As the risks of infant infection and pre-eclampsia were found to be increased, we assessed how these risks related to disease activity, treatment, and SpA manifestations in a post hoc analysis. For infant infection, we found no statistically significant associations with any of the potential risk factors under study (appendix p 8). For pre-eclampsia, a one-unit increase in BASDAI was associated with a risk ratio of 1·50 (95% CI 1·06–2·13). No association was seen with elevated CRP or treatment (appendix p 9).

Stratified by parity, events of pre-eclampsia, Caesarean delivery, and preterm birth were more common among primiparous women, while infant infection was less common (appendix p 13). However, in relation to general population comparators, the relative risks of pre-eclampsia and Caesarean delivery were similar in primiparous and parous women with axSpA. For preterm birth and infant infection, relative risks were higher in parous women. Exclusion of women in the axSpA cohort who were ever diagnosed with rheumatoid arthritis, psoriatic arthritis, or systemic lupus erythematosus (n=135, 86, and 6, respectively) in NPR only lead to minor changes (appendix p 13).

DISCUSSION

This nationwide cohort study on maternal and infant outcomes in over 1500 pregnancies in women with axSpA is to our knowledge the largest of its kind. We found an increased risk of pre-eclampsia, preterm birth, and infant infection compared to general population comparators, and a higher proportion of Caesarean delivery. The risk of SGA birth was not increased. We observed declining rates of preterm birth and Caesarean delivery in axSpA pregnancies but no obvious change in the rate of pre-eclampsia during the study period. The use of TNFi (but not other anti-rheumatic treatments) during pregnancy increased.

The increased risk of preterm birth in axSpA is in agreement with recent systematic reviews and meta-analyses.[6,8,23,24] A higher proportion of Caesarean delivery is reported from most studies on pregnancy outcomes in axSpA, especially elective procedures.[6,7] The low risk of SGA, however, is contrary to estimates from systematic reviews.[6] Estimates there are partly influenced by a previous Swedish study of women with AS using the same data sources as us in an earlier, only slightly overlapping, period, with odds ratio 2·12 (95% CI 1·00–4·50).[13] Our results are instead supported by more recent studies, with rates of SGA in axSpA similar to or lower than the general population.[11,17,25] Of note, Meissner et al. also reported low rates of preterm birth.[17] One explanation to the favourable outcomes observed in that study could be the close monitoring of women in centres specialised in pregnancies in patients with rheumatic conditions.

The decreasing risk of several outcomes over the study period in our axSpA cohort has not been reported before, and we see several potential explanations to this finding. The ASAS classification criteria from 2009 might have led to changes in the axSpA population over time. However, there were generally modest differences in background characteristics when we stratified our cohort by year of delivery, and the ratio of AS vs. uSpA diagnoses remained 1:1. Thus, a change in composition of the cohort is likely not the only explanation to the decrease of adverse events. The use of NSAIDs, corticosteroids, and csDMARDs during pregnancy has remained at low levels while the use of TNFi has increased since around 2010, reflecting increased availability and a change in guidelines to recommend TNFi use during pregnancy.[15,16] One aim of minimizing disease activity in pregnant women is to alleviate the risk that untreated maternal disease poses for the child,[15] and the decrease in adverse outcomes detected in this study could very well be an indication that current treatment guidelines are effective.

Despite the nationwide cohort, we had limited statistical power to directly test whether individual anti-rheumatic treatments were associated with adverse events, especially when adjusting for other treatments and disease activity. Treatment with TNFi has been associated with adverse pregnancy outcomes in studies of psoriatic arthritis and rheumatoid arthritis, where it was suggested to serve as a proxy for active disease,[26,27] and treatment with NSAIDs and corticosteroids, along with elevated CRP, have previously been associated with preterm birth in axSpA.[9,11,12] We, however, found only minor differences in proportions of preterm birth between those with and without specific treatments, including TNFi, and no relative risks reached significance. Treatment with NSAIDs (vs. no anti-inflammatory treatment) 12 months prior to delivery was associated with a doubled odds of preterm birth in the study by Redeker et al.,[11] but we saw no association between NSAIDs (vs. no NSAIDs) and preterm birth in axSpA. We did not find a significantly increased risk associated with increasing

BASDAI or HAQ-DI or with elevated CRP. We hypothesised that an axSpA diagnosis might lead to effect modification of the association between established risk factors and preterm birth compared to the general population, but found that associations in axSpA and comparators were not significantly different for most factors evaluated. The only exceptions were young maternal age and low educational level, which were associated with increased risks in axSpA but not in comparators. However, these specific factors are usually considered risk factors for preterm birth also in the general population,[22] and thus the lack of association in comparators in our material might be due to chance.

Infant infections, for which we found a significantly increased risk in the entire axSpA cohort, also decreased over time, even though TNFi use increased. Infant infection has been a major concern with exposure of TNFi in utero, but while not studied exclusively in axSpA previously, studies in other diseases have not found a clear association between TNFi use and infant infection.[28,29] In our study, 41 (51%) of the women who used TNFi after week 14 of pregnancy delivered in the last two years of the study period, when the proportion of infant infections was the lowest. We were however not able to conclusively rule out an association between TNFi use and infant infections in our post hoc analysis, where confidence intervals were wide.

An increased risk of pre-eclampsia has been reported from some, but not all, systematic reviews of pregnancy outcomes in axSpA.[6–8] The prevalence of certain risk factors for pre-eclampsia increased over the study period in the women with axSpA (e.g. hypertension, diabetes, obesity), but similar changes were seen in the general population. The risk of pre-eclampsia associated with increasing BASDAI found in the post hoc analysis should be interpreted with caution. While it might be reasonable that higher disease activity confers a higher risk, BASDAI is based on subjective measures such as fatigue and pain, which might be related to symptoms of pre-eclampsia itself. No association was seen with inflammation (CRP >10 mg/litre).

A limitation of this study is the low proportion of pregnancies with data on disease activity necessary to disentangle the effect of active disease from the treatments as such. Exact timing of treatments was also difficult to predict from prescription data. A more precise estimation had been valuable when evaluating the impact of maternal TNFi use on infant infections, as placental transfer mainly takes place in late pregnancy.[30] A limitation of register-based studies in general is the risk of misclassification. We however identified women with axSpA using validated ICD-codes, with an even stricter case-finding algorithm to further improve specificity. We chose to include both AS and uSpA in our definition of axSpA to cover the entire spectra of the condition, but performed restricted analyses excluding women ever receiving a diagnosis of rheumatoid arthritis, psoriatic arthritis, or systemic lupus erythematosus, without markedly changed results.

The use of national register data is a major strength of this study, with excellent coverage of outcomes in MBR and possibility to include births of most Swedish women with axSpA together with general population comparators. Our findings should thus be generalisable to all of Sweden and other countries with similar healthcare settings. The register-based design including prospectively collected data minimises recall and selection bias, and allowed us to adjust for important confounders such as BMI and smoking.

In conclusion, in this large, population-based study, we found that women with axSpA are at increased risk of pre-eclampsia and preterm birth, and a significantly higher proportion deliver by Caesarean section. Of particular interest given concerns for infection risks in relation to TNFi, we also found an increased risk of serious infection in their infants during the first year of life. However, despite the increased use of potent immunomodulatory treatments, the risk of adverse pregnancy outcomes decreased in the axSpA cohort over this period, even approaching the same rates as in the general population. Although we were not able to conclusively test whether pre-natal exposure to maternal TNFi use was directly associated with altered risk for infections in the infant, this should be reassuring for both patients and practitioners, and gives hope that women with axSpA may eventually not be at increased risk of adverse pregnancy outcomes, when treated in accordance with clinical practice.

Contributors

MM and TF have accessed and verified the underlying data. MM performed the statistical analyses and wrote the original draft of the manuscript. All authors contributed to conceptualising and planning the study, interpreting the data and reviewing the manuscript. All authors had full access to all the data in the study. All authors were responsible for the final decision to submit for publication, and have seen and approved the final text.

Declaration of interests

We declare no competing interests.

Data sharing

Data in this study comes from Swedish national registers and are only available via the register-holding authorities themselves, after ethical review.

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TABLES AND FIGURES

Table 1. Maternal characteristics in singleton pregnancies in women with axSpA and comparators, matched on year of delivery, maternal age, and parity.

	axSpA births (n=1580)	Comparator births (n=15792)
Maternal age, years*		
19–24	76 (4·8)	760 (4·8)
25–29	387 (24·5)	3870 (24·5)
30–34	657 (41·6)	6570 (41·6)
≥35	460 (29·1)	4592 (29·1)
Year of delivery*		
2007–2011	338 (21·4)	3380 (21·4)
2012–2016	609 (38·5)	6089 (38·6)
2017–2020	633 (40·1)	6323 (40·0)
Parity*		
Primiparous	642 (40·6)	6414 (40·6)
Parous	938 (59·4)	9378 (59·4)
Maternal country of birth		
Nordic country	1464 (92·7)	12569 (79·6)
Non-Nordic country	116 (7·3)	3221 (20·4)
Missing	0 (0·0)	2 (<0·1)
Maternal BMI (early pregnancy)		
<18.5	32 (2·0)	300 (1·9)
18·5–24·9	879 (55·6)	8699 (55·1)
25–29·9	352 (22·3)	3851 (24·4)
≥30	216 (13·7)	2005 (12·7)
Missing	101 (6·4)	937 (5·9)
Maternal height, cm		
<160	156 (9·9)	1921 (12·2)
160–164	374 (23·7)	3839 (24·3)
165–169	496 (31·4)	4433 (28·1)
≥170	494 (31·3)	5021 (31·8)
Missing	60 (3·8)	578 (3·7)
Smoking (early pregnancy)		
Smoker	77 (4·9)	655 (4·1)
Non-smoker	1423 (90·1)	14334 (90·8)
Missing	80 (5·1)	803 (5·1)
Maternal education†		
9 years or less	89 (5·6)	1174 (7·4)
10–12 years	540 (34·2)	5145 (32·6)
>12 years	946 (59·9)	9005 (57·0)
Missing	5 (0·3)	468 (3·0)
Disposable income		
Quartile 1	333 (21·1)	3956 (25·1)
Quartile 2	411 (26·0)	3878 (24·6)
Quartile 3	426 (27·0)	3863 (24·5)
Quartile 4	409 (25·9)	3880 (24·6)
Missing	1 (0·1)	215 (1·4)

Maternal comorbidities‡		
Diabetes	41 (2·6)	234 (1·5)
Hypertension	30 (1·9)	182 (1·2)
Thyroid disease	126 (8·0)	1044 (6·6)
Ankylosing spondylitis diagnosis	770 (48·7)	..
SpA manifestations§		
Anterior uveitis	289 (18·3)	..
Psoriatic arthritis	86 (5·4)	..
Psoriasis	53 (3·4)	..
Inflammatory bowel disease	87 (5·5)	..
Other rheumatic diagnoses‡		
Rheumatoid arthritis	135 (8·5)	..
Systemic lupus erythematosus	6 (0·4)	..

Data are n (%). Sources and definitions of variables are found in appendix pp 2–4. SEK=Swedish Krona. *Matching variables. †In calendar year before pregnancy. ‡Before pregnancy. §Before delivery.

	axSpA births n (%)	Comparator births n (%)	Adj. RR* (95% CI)
Maternal outcomes			
Among all births			
Pre-eclampsia	61 (3·9)	441 (2·8)	1·44 (1·08–1·92)
Gestational diabetes	33 (2·1)	320 (2·0)	1·23 (0·84–1·82)
Gestational hypertension	32 (2·0)	316 (2·0)	0·94 (0·64–1·38)
Stillbirth	0 (0·0)	64 (0·4)	
Among live births			
Caesarean delivery	382 (24·2)	2760 (17·5)	1·39 (1·24–1·55)
Elective	236 (14·9)	1496 (9·5)	1·59 (1·37–1·84)
Emergency	146 (9·2)	1264 (8·0)	1·15 (0·96–1·37)
Preterm birth	99 (6·3)	682 (4·3)	1·43 (1·13–1·80)
Moderately preterm birth	92 (5·8)	575 (3·7)	1·55 (1·22–1·96)
Very preterm birth	7 (0·4)	107 (0·7)	0·64 (0·26–1·58)
Medically indicated	30 (1·9)	206 (1·3)	1·44 (0·93–2·22)
Spontaneous	69 (4·4)	472 (3·0)	1·44 (1·09–1·90)
Infant outcomes (live births)			
5-min Apgar score <7	20 (1·3)	287 (1·8)	0·69 (0·41–1·15)
Small for gestational age†	25 (1·6)	352 (2·2)	0·77 (0·51–1·16)
Large for gestational age†	61 (3·9)	582 (3·7)	1·02 (0·77–1·34)
Infant infection	105 (6·6)	795 (5·1)	1·29 (1·05–1·59)

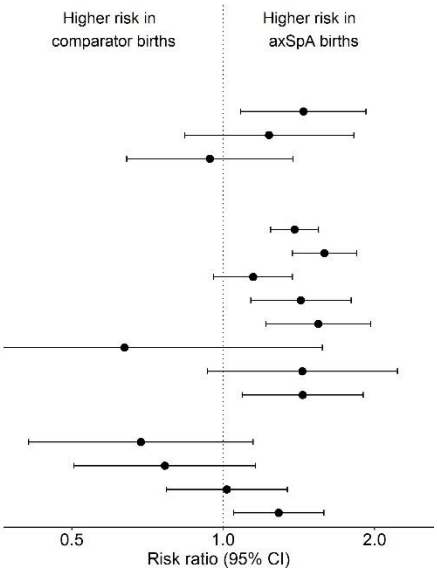

Figure 1. Relative risks of adverse pregnancy outcomes among births in women with axSpA (n=1580) and matched comparator births (n=15792).

Relative risks from modified Poisson regression. Comparators were matched 1:10 on year of delivery, maternal age, and parity. *Adjusted for matching factors and maternal country of birth, height, body-mass index, smoking in early pregnancy, educational level, and disposable income in the year before pregnancy. Unadjusted estimates and risk differences in appendix (pp 5–6). †1 axSpA birth and 13 comparator births were missing data for small and large for gestational age.

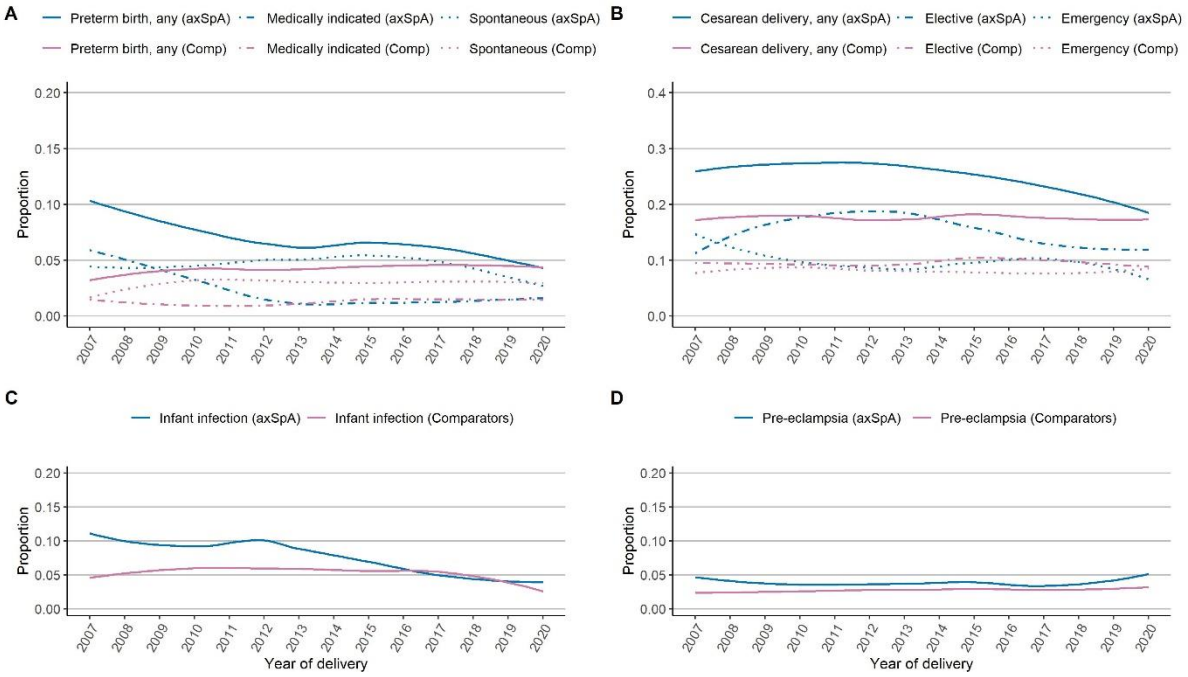

Figure 2. Proportion of adverse pregnancy outcomes per year of delivery in women with axSpA and general population comparators.

Proportion of (A) preterm birth, (B) Caesarean delivery, (C) infant infection, and (D) pregnancies complicated by pre-eclampsia, by year of delivery. Lines are loess curves. Comp=general population comparators.

	Year of delivery	axSpA births n (%)	Comparator births n (%)	Adj. RR* (95% CI)
Among all births				
Pre-eclampsia	2007–2011	12 (3·6)	88 (2·6)	1·26 (0·67–2·34)
	2012–2016	23 (3·8)	168 (2·8)	1·47 (0·91–2·37)
	2017–2020	26 (4·1)	185 (2·9)	1·51 (0·99–2·30)
Among live births				
Caesarean delivery	2007–2011	93 (27·5)	616 (18·3)	1·49 (1·22–1·81)
	2012–2016	154 (25·3)	1077 (17·8)	1·44 (1·22–1·69)
	2017–2020	135 (21·3)	1067 (16·9)	1·29 (1·08–1·52)
Preterm birth	2007–2011	30 (8·9)	131 (3·9)	1·85 (1·19–2·88)
	2012–2016	37 (6·1)	267 (4·4)	1·40 (0·97–2·01)
	2017–2020	32 (5·1)	284 (4·5)	1·28 (0·88–1·88)
Infant infection	2007–2011	33 (9·8)	183 (5·4)	1·56 (1·06–2·30)
	2012–2016	46 (7·6)	356 (5·9)	1·25 (0·92–1·69)
	2017–2020	26 (4·1)	256 (4·1)	1·10 (0·74–1·64)

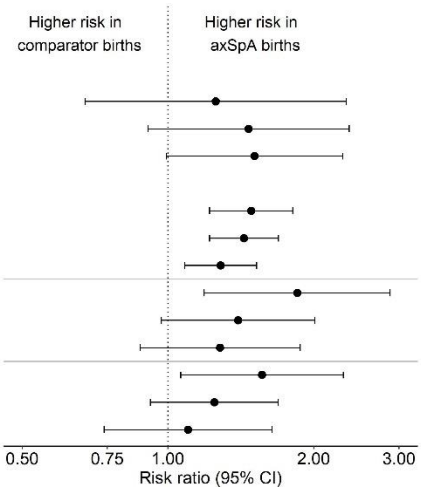

Figure 3. Number of events and relative risks of selected outcomes by year of delivery in three strata.

Relative risks from modified Poisson regression. *Adjusted for matching factors and maternal country of birth, height, body-mass index, smoking in early pregnancy, educational level, and disposable income in the year before pregnancy.

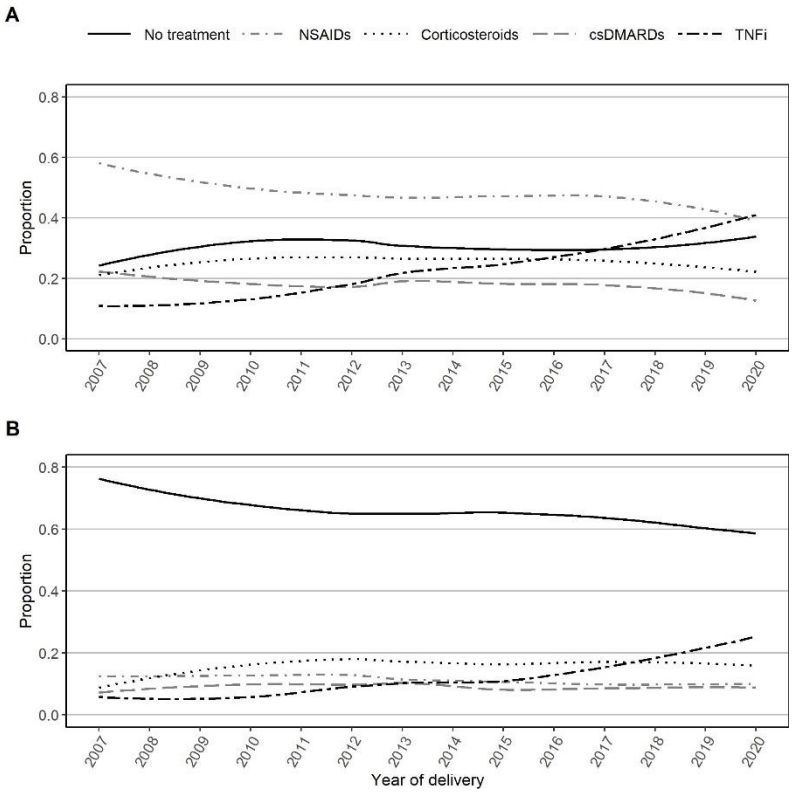

Figure 4. Proportion of births in women with axSpA on NSAIDs and anti-rheumatic treatments by year of delivery.

Proportion of births with treatment (A) in the year before pregnancy and (B) any time during pregnancy, depicted by loess curves. NSAIDs=non-steroidal anti-inflammatory drugs. csDMARDs=conventional systemic disease-modifying anti-rheumatic drugs. TNFi=tumour necrosis factor inhibitors.