RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Maternal and infant outcomes in pregnancies of women with axial spondyloarthritis compared with matched controls: results from nationwide health insurance data

Imke Redeker ,[1] Anja Strangfeld ,[1] Johanna Callhoff ,[1] Ursula Marschall,[2] Angela Zink,[1] Xenofon Baraliakos [3]

To cite: Redeker I, Strangfeld A, Callhoff J, *et al*. 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. doi:10.1136/rmdopen-2021-002146

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2021-002146).

Received 7 December 2021
Accepted 4 May 2022

[1]Epidemiology and Health Services Research, German Rheumatism Research Centre, Berlin, Berlin, Germany
[2]BARMER Institute for Health Systems Research, BARMER Statutory Health Insurance, Wuppertal, Germany
[3]Internal Medicine and Rheumatology, Ruhr University Bochum, Bochum, Germany

Correspondence to
Dr Imke Redeker;
Redeker.imke@gmail.com

ABSTRACT

Objectives To investigate pregnancy outcomes in women with axial spondyloarthritis (axSpA) under different pharmacological treatments in comparison with matched controls.

Methods Using health insurance data from 2006 to 2019, pregnancy outcomes of women with axSpA were compared with those of age-matched and calendar year-matched controls without axSpA. Women with axSpA were further stratified by treatment prior to delivery and pregnancy outcomes compared. Adjusted ORs (aORs) with 95% CIs were calculated using generalised estimating equation analyses.

Results A total of 1021 pregnancy outcomes in patients with axSpA were identified (928 deliveries, 80 abortions, 13 ectopic pregnancies) and compared with 10 210 pregnancy outcomes in controls (9488 deliveries, 615 abortions, 147 ectopic pregnancies). Compared with controls, women with axSpA showed higher odds of elective caesarean section (aOR 1.52; 1.25 to 1.85). Among women with axSpA, the risk of preterm birth was higher under non-steroidal anti-inflammatory drugs (NSAIDs) treatment (aOR 2.22; 1.09 to 4.52) than without any anti-inflammatory treatment. The risks of preterm birth (aOR 4.01; 1.93 to 8.34) and small-for-gestational-age (aOR 3.22; 1.34 to 7.73) were increased under NSAIDs treatment in combination with conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), steroids or analgesics. Non-significant increased risks of small-for-gestational-age (aOR 1.68; 0.43 to 6.57) and preterm birth (aOR 1.56; 0.51 to 4.83) were found under biological DMARDs.

Conclusions Women with axSpA have significantly increased odds of caesarean section compared with matched controls. Risks of preterm birth and small-for-gestational-age vary by type of anti-inflammatory treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Axial spondyloarthritis (axSpA) appears to be associated with an increased risk of adverse pregnancy outcomes (such as preterm birth, small-for-gestational-age and pre-eclampsia).
⇒ High heterogeneity among studies and limited data on medication use require further research using large cohorts.

WHAT THIS STUDY ADDS

⇒ Information on the risk of adverse pregnancy outcomes in women with axSpA under different pharmacological treatments in comparison with matched controls without axSpA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Findings of increased risks of preterm birth and small-for-gestational-age among women with axSpA who used non-steroidal anti-inflammatory drugs compared with women with axSpA who did not take any medication may guide future research efforts in understanding how these complications in axSpA pregnancies are related to disease severity and insufficient anti-inflammatory therapy.

INTRODUCTION

In recent years, interest in pregnancy outcomes in axial spondyloarthritis (axSpA), a chronic inflammatory rheumatic disease that predominantly affects the spine and/or sacroiliac joints,[1] has increased as demonstrated by the latest literature reviews and meta-analyses.[2–5] One of their main results is the increased prevalence of caesarean sections (CSs) compared with the general population. Preterm birth also showed a significant trend towards increased prevalence in axSpA pregnancies. Moreover, axSpA appears to be associated with a higher risk of pre-eclampsia and small-for-gestational-age (SGA).

Despite the increased number of studies published in the past decade, the latest literature reviews and meta-analyses highlight the dire need for further research on the outcomes of pregnancy in axSpA due to the large heterogeneity among present studies.[2–4] Moreover, it is pointed out that large cohorts of women with axSpA are required and a special focus should be on pharmacological treatment during pregnancy.

Objectives of this large population-based study were to determine if women with axSpA have worse pregnancy outcomes and if the prevalences of fetal and neonatal complications in axSpA pregnancies are increased compared with matched women without axSpA. Furthermore, this study aimed at investigating pregnancy outcomes in subgroups of women with axSpA under different anti-inflammatory treatment during pregnancy in comparison with matched women without axSpA and in comparison with women with axSpA under no anti-inflammatory treatment during pregnancy.

PATIENTS AND METHODS

Study design

The study was conducted using data of a health insurance fund in Germany (BARMER), which comprise detailed reimbursement-related information on outpatient and inpatient care, pharmacological and non-pharmacological treatment, aids/adaptations and sick leave. BARMER is one of Germany's largest health insurance funds with approximately 9 million members (11% of Germany's population).

For each year between 2006 and 2019, women were identified from the database who (1) were continuously insured over the entire year, (2) were between 18 and 50 years of age and (3) had a diagnosis of axSpA according to International Classification of Diseases, 10th Revision, (ICD-10) code M45 (including both radiographic and non-radiographic axSpA, for which there are no separate codes) documented by an outpatient care facility in at least two quarters or by a hospital in at least one quarter. Pregnancy outcomes were determined adopting an algorithm specifically developed to identify pregnancy outcomes in German health insurance data.[6]

Maternal and infant outcomes in pregnancy

Information on maternal outcomes included live birth, stillbirth, elective termination, ectopic pregnancy, spontaneous abortion, gestational week of delivery, delivery by CS, pre-eclampsia and gestational diabetes. A live birth was defined as preterm if it occurred before gestational week 37 and further defined as extremely preterm if it occurred before week 32. Infant outcomes comprised SGA and congenital malformations. The term SGA was used for a birth in weight and/or size below the 10th percentile for the gestational age based on German reference data.[7] All information on maternal and infant outcomes in pregnancy was gathered from inpatient and outpatient diagnoses according to ICD-10 codes, inpatient and outpatient procedures according to Operation and Procedure Classification System codes, and outpatient services and procedures according to German Uniform Evaluation Standard (EBM—Einheitlicher Bewertungsmaβstab) codes. Congenital malformations encompassed 12 categories, which were adopted from the classification criteria of the European Surveillance of Congenital Anomalies (EUROCAT).[8]

Linking maternal and infant records was possible for the majority of infants (it was not possible for a small number of infants who were co-insured with their fathers while their mothers were self-insured[9]).

The respective codes used to identify and classify pregnancy outcomes are presented in online supplemental table S1 and were adopted from Mikolajczyk *et al*.[10]

Extra-musculoskeletal manifestations and comorbidities

In this analysis, extra-musculoskeletal manifestations (EMMs) comprised inflammatory bowel disease, psoriasis, psoriatic arthritis and anterior uveitis and comorbidities included hypertension, diabetes mellitus and obesity. These were identified based on ICD-10 codes being given in outpatient care prior to delivery, where at least one claim had to be documented.

The respective ICD-10 codes are shown in online supplemental table S1.

Pharmacological treatment

Treatment before and during pregnancy (within 24 to 12 months prior to delivery, up to 12 months prior to delivery and within each trimester) was examined, including non-steroidal anti-inflammatory drugs (NSAIDs), opioids, non-opioid analgesics, steroids, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biological DMARDs (bDMARDs). Information on treatment was gathered using the dispensation date of drug prescriptions in outpatient care and was categorised according to the Anatomical Therapeutic Chemical (ATC) classification, where at least one prescription had to be documented.

The respective ATC codes are shown in online supplemental table S1.

Matched cohort of patients with non-axSpA

A cohort of women without a recorded axSpA diagnosis was matched by maternal age and calendar year of pregnancy outcome in a 1 to 10 ratio from the health insurance data. Only the diagnosis of axSpA (ICD-10 code M45) was excluded among controls, while other diagnoses were not excluded. Women in this cohort of patients with non-axSpA are referred to as controls.

Statistical analysis

Characteristics of patients with axSpA with pregnancy outcomes were examined using descriptive statistics (means, SD and percentages) and compared with controls. Constrained to deliveries of singleton births, ORs and ORs adjusted for obesity, hypertension and diabetes mellitus with 95% CIs for pregnancy outcomes

of women with axSpA versus controls were calculated (maternal age and calendar year of pregnancy outcome were accounted for through matching) using generalised estimating equation analyses, taking the correlated data structure resulting from allowing more than one delivery per woman into account. In sensitivity analyses, pregnancy outcomes were analysed in a subcohort of patients: (1) women with axSpA with a prior diagnosis of rheumatoid arthritis (ICD-10 code M05, M06) were excluded and (2) women with axSpA with at least one EMM present were excluded. Moreover, an analysis including women with multiple births during a single delivery was performed.

In further analyses, women with axSpA were stratified into mutually exclusive groups by their pharmacological treatment prior to delivery. For women with axSpA in each treatment group, ORs of pregnancy outcomes were calculated in comparison with controls and with women with axSpA under no pharmacological treatment during pregnancy. In addition, comparisons among women with axSpA were adjusted for maternal age, obesity and the presence of EMMs.

Data analyses were performed with SAS V.9.4 (SAS Institute).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of the study.

RESULTS

A total of 3,995192 women were between 18 and 50 years of age and had continuous insurance for at least 1 year during the study period of 2006–2019. Of those, 12 763 women received an axSpA diagnosis, among whom 1021 pregnancy outcomes were identified. Deliveries made up the largest part of pregnancy outcomes (n=928; 91%), followed by spontaneous abortions (n=47; 5%), elective abortions (n=33; 3%) and ectopic pregnancies (n=13; 1%). Among the 10 210 pregnancy outcomes in the matched cohort of women with non-axSpA were 9488 deliveries (93%), 299 spontaneous abortions (3%), 316 elective abortions (3%) and 147 ectopic pregnancies (1%) (figure 1).

Characteristics of women with axSpA and controls are presented in table 1. The mean age at pregnancy outcome was 33 years. Psoriasis was the most prevalent EMM occurring in 7% of women with axSpA within 12 months before the end of pregnancy, followed by uveitis, inflammatory bowel disease and psoriatic arthritis (5.9%, 5.5% and 3.0% respectively). In the cohort of women with non-axSpA, only a small proportion presented with these conditions (table 1). Other comorbidities were also more often present in women with axSpA than in controls. Obesity was present in 17% of women with axSpA and 11% of controls, while hypertension and diabetes mellitus were less prevalent in both groups (8% vs 6% and 6% vs 4%, respectively).

Maternal and infant outcomes

Of the 928 deliveries among women with axSpA, 793 deliveries could be linked to 814 live-born infants (no data were available for infants who were co-insured with their fathers while their mothers were self-insured). Of these 814 live births, 42 were twins and 6 triplets. For controls, 7918 deliveries could be linked to 8034 live births of whom were 380 twins and no triplets. The following results are based on deliveries of singleton births (770 in axSpA and 7688 in matched controls) if not stated otherwise.

A caesarean delivery was more frequent in women with axSpA compared with controls (40% vs 31%), resulting in a significantly increased OR of 1.49 (95% CI 1.27 to 1.75). This increase was mainly attributable to elective CS which were increased in women with axSpA compared with controls (21% vs 14%), while differences in emergency CS were smaller (18% vs 16%). Frequencies of CS stratified by calendar year of delivery are presented in online supplemental table S2. In women with axSpA,

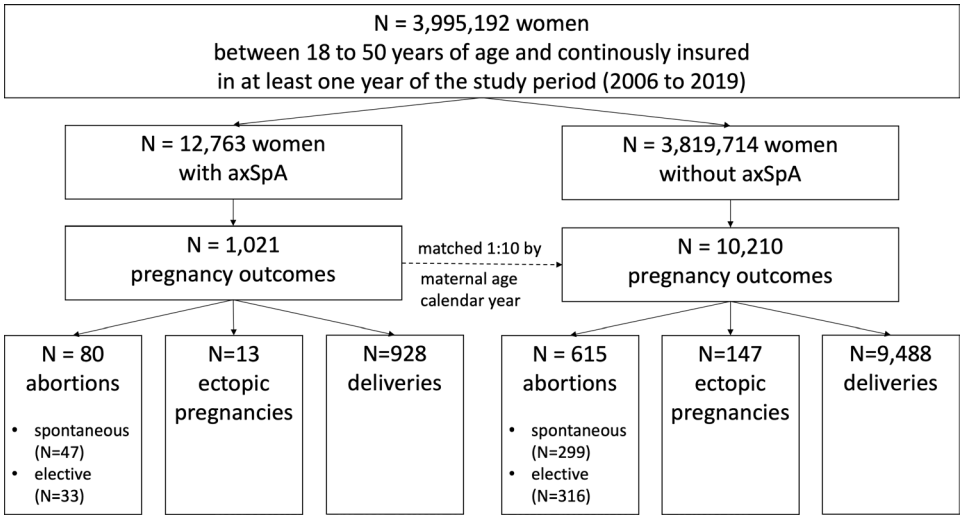

Figure 1 Flowchart of the study design. axSpA, axial spondyloarthritis.

Table 1 Descriptive information related to end-of-pregnancy and on extra-musculoskeletal manifestations and comorbidities of women with axSpA and age-matched and calendar year-matched controls without axSpA

	Women with axSpA	Matched controls
Number of		
deliveries	90.9% (928)	92.5% (9448)
elective terminations	3.2% (33)	3.1% (316)
ectopic pregnancies	1.3% (13)	1.4% (147)
spontaneous abortions	4.6% (47)	2.9% (299)
Age at end of pregnancy*, mean (SD)	33.1 (4.7)	33.1 (4.7)
18–29	23.1% (236)	23.1% (2360)
30–39	67.7% (691)	67.7% (6910)
≥40	9.2% (94)	9.2% (940)
Year of end of pregnancy*		
2006–2009	23.6% (241)	23.6% (2410)
2010–2014	34.2% (349)	34.2% (3490)
2015–2019	42.2% (431)	42.2% (4310)
Extra-musculoskeletal manifestations and comorbidities†		
Psoriasis	6.8% (63)	1.4% (131)
Uveitis	5.9% (55)	0.1% (7)
Inflammatory bowel disease	5.5% (51)	0.8% (73)
Psoriatic arthritis	3.0% (24)	0.1% (7)
Obesity	16.7% (155)	10.9% (1026)
Hypertension	8.3% (77)	5.7% (541)
Diabetes mellitus	6.0% (56)	3.9% (365)

*Matching parameters.
†Prior to end of pregnancy.
axSpA, axial spondyloarthritis.

the frequency of CS has considerably decreased in recent years (53% in 2006 vs 24% in 2019), mainly attributable to a decrease in elective CS. Whereas the frequency of CS in matched controls has varied less over time.

Pre-eclampsia (8% vs 6%) and gestational diabetes (12% vs 11%) occurred moderately more often in women with axSpA than in controls without reaching statistical significance, while the occurrence of stillbirth was similar in both groups (0.5% vs 0.4%). Adjusting for obesity, hypertension and diabetes mellitus led to similar results (table 2).

Infants of women with axSpA were more often preterm than controls (7.8% vs 6.2%), resulting in a non-significant increased risk of preterm birth, expressed as an OR of 1.29 (95% CI 0.97 to 1.70). On the other hand, the occurrence of extremely preterm births was comparable in both groups (0.3%) and SGA infants were more prevalent in controls than in women with axSpA (6.2% vs 5.0%).

The increased risk of CS and the higher proportion of preterm birth in women with axSpA compared with controls remained in sensitivity analyses among subcohorts, in which women with axSpA with a prior diagnosis of rheumatoid arthritis (online supplemental table S3) or with EMMs (online supplemental table S4) were excluded. In a further analysis, delivery complications and fetal outcomes were analysed including deliveries of multiple births, that is, 793 deliveries (814 infants) among women with axSpA and 7918 deliveries (8034 infants) among controls (online supplemental table S5). Frequencies and ORs of maternal outcomes were similar to the main analysis in terms of an increased risk of CS. While frequencies of preterm birth and SGA increased in both groups, resulting in a significant higher risk of preterm birth in women with axSpA than controls.

Congenital malformations

Prevalences of congenital malformations in infants of women with axSpA versus controls are shown in table 3. Among the 766 infants of women with axSpA, 8.5% had at least one malformation based on the categories adopted from EUROCAT, while 9.0% had at least one malformation among the 7654 infants of controls. Congenital heart defects by (2.1% in axSpA vs 2.5% in controls) and urinary malformations (2.1% in axSpA vs 1.8% in controls) were most prevalent in both groups.

Pharmacological treatment and pregnancy outcomes

The pharmacological treatment in women with axSpA within 24 to 12 months prior to delivery and up to 12 months prior to delivery is illustrated in figure 2. While around 60% of the women with axSpA received anti-inflammatory treatment within 24 to 12 months prior to delivery, this figure decreased to 45% in the time interval of 12 months prior to delivery, mainly driven by a considerable decrease in treatment with NSAIDs from 49% to 29%. Treatment 12 months prior to delivery with analgesics, steroids or csDMARDs also decreased, although to a smaller degree. Moreover, the proportion of patients treated with bDMARDs (tumour necrosis factor inhibitors for all but four patients) decreased from 12% to 8%.

The pharmacological treatment in women with axSpA stratified by trimester is illustrated in online supplemental figure S1. The proportion of women with axSpA treated with bDMARDs decreased from 4% in the first trimester to 1% in the third trimester, while the proportion with NSAID treatment decreased from 10% in the first trimester to 1% in the third trimester. Treatments with non-opioid analgesics and opioids also reduced to 1% in the third trimester (from 3% and 2% in the first trimester, respectively). Treatment with csDMARDs decreased only slightly (from 3% to 2%) while treatment with steroids increased slightly (from 4.6% to 5.2%).

Women with axSpA were divided into five mutually distinctive groups according to their pharmacological treatment 12 months prior to delivery: (1) no anti-inflammatory treatment, (2) treatment with NSAIDs

Table 2 Prevalences and ORs for pregnancy outcomes in women with axSpA versus age-matched and calendar year-matched controls without axSpA

	Deliveries in women with axSpA n=770	Deliveries in matched controls n=7688	OR (95% CI)	Adjusted OR* (95% CI)
Pre-eclampsia	7.7% (59)	6.2% (479)	1.25 (0.94 to 1.67)	1.10 (0.81 to 1.48)
Gestational diabetes	12.2% (94)	11.1% (850)	1.09 (0.86 to 1.38)	0.82 (0.63 to 1.08)
Caesarean section†	40.3% (310)	31.2% (2399)	**1.49 (1.27 to 1.75)**	**1.42 (1.21 to 1.67)**
Elective	21.3% (162)	14.3% (1088)	**1.58 (1.30 to 1.92)**	**1.52 (1.25 to 1.85)**
Emergency	18.3% (139)	16.1% (1220)	1.19 (0.97 to 1.45)	1.14 (0.93 to 1.40)
Stillbirth	0.5% (4)	0.4% (34)	1.19 (0.42 to 3.34)	1.21 (0.42 to 3.47)
Preterm birth (<gestational week 37)	7.8% (60)	6.2% (473)	1.29 (0.97 to 1.70)	1.22 (0.92 to 1.61)
Gestational week <28	0.3% (2)	0.3% (25)	0.80 (0.19 to 3.38)	0.72 (0.18 to 2.83)
Small for gestational age	5.0% (38)	6.2% (476)	0.78 (0.56 to 1.10)	0.76 (0.54 to 1.06)

Statistical significant associations are shown in bold.
*Adjusted for obesity, hypertension, diabetes mellitus.
†Unspecified for n=100.
‡
axSpA, axial spondyloarthritis.

excluding bDMARDs, csDMARDs, steroids, analgesics, (3) treatment with csDMARDs, steroids or analgesics excluding bDMARDs, NSAIDs, (4) treatment with NSAIDs, csDMARDs, steroids or analgesics excluding bDMARDs, (5) treatment with bDMARDs. Treatment groups reflect both a fixed combination at the same time and successive therapies within 12 months prior to delivery.

Table 3 Prevalences of congenital malformations* in infants of women with axSpA versus age-matched and calendar year-matched controls without axSpA

	Infants of women with axSpA n=766	Infants of matched controls n=7654
Malformation	8.5% (65)	9.0% (688)
Nervous system	0.8% (6)	1.0% (75)
Eye	0.5% (4)	0.3% (26)
Ear, face and neck	0.1% (1)	0.2% (14)
Congenital heart defects	2.1% (16)	2.5% (193)
Respiratory system	0.0% (0)	0.1% (9)
Orofacial clefts	0.0% (0)	0.2% (18)
Digestive system	0.4% (3)	0.5% (35)
Genital	0.9% (7)	0.7% (50)
Urinary	2.1% (16)	1.8% (137)
Limb	1.2% (9)	1.7% (133)
Other anomalies/ syndromes	0.8% (6)	0.9% (70)
Chromosomal	0.3% (2)	0.3% (26)

*Based on the categories adopted from the European Surveillance of Congenital Anomalies.
axSpA, axial spondyloarthritis.

Separately for each treatment group, frequencies and (adjusted for maternal age, obesity and EMMs) ORs for pregnancy outcomes were compared with no anti-inflammatory treatment prior to delivery (table 4). Among women with axSpA, the risk of preterm birth was higher for those treated with NSAIDs only (adjusted OR 2.22; 95% CI 1.09 to 4.52) and for those treated with NSAIDS and with csDMARDs, steroids or analgesics (adjusted OR 4.01; 95% CI 1.93 to 8.34) prior to delivery than for those without any anti-inflammatory treatment. Women with axSpA in the latter treatment group also had

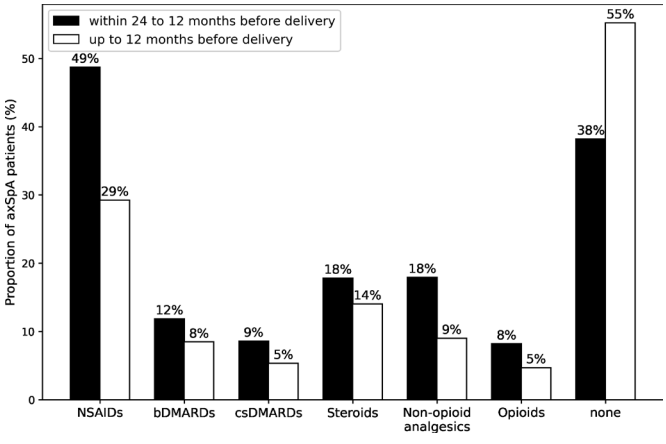

Figure 2 Pharmacological treatment of women with axSpA (n=770) before delivery. axSpA, axial spondyloarthritis; bDMARDs, biological disease-modifying anti-rheumatic drugs; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 4 Frequencies and ORs for pregnancy outcomes in women with axSpA stratified by pharmacological treatment versus no pharmacological treatment during 12 months prior to delivery.

	No treatment (n=416 deliveries)	Treatment with NSAIDs* (n=125 deliveries)			Treatment with csDMARDs, steroids or analgesics† (n=93 deliveries)			Treatment with NSAIDs and csDMARDs, steroids or analgesics‡ (n=73 deliveries)			Treatment with bDMARDs (n=63 deliveries)		
		axSpA	OR (95% CI)	Adjusted OR§ (95% CI)	axSpA	OR (95% CI)	Adjusted OR[d]§ (95% CI)	axSpA	OR (95% CI)	Adjusted OR§ (95% CI)	axSpA	OR (95% CI)	Adjusted OR§ (95% CI)
Pre-eclampsia¶	8.7% (36)	4.0% (5)	0.46 (0.18 to 1.20)	0.42 (0.15 to 1.17)	4.3% (4)	0.46 (0.15 to 1.38)	0.50 (0.17 to 1.51)	6.8% (5)	0.74 (0.29 to 1.88)	0.60 (0.23 to 1.54)	14.3% (9)	1.77 (0.80 to 3.89)	2.09 (0.82 to 5.31)
Gestational diabetes¶	12.5% (52)	10.4 (13)	0.83 (0.44 to 1.60)	0.74 (0.33 to 1.63)	11.8% (11)	0.96 (0.48 to 1.92)	0.64 (0.24 to 1.74)	9.6% (7)	0.71 (0.30, 1.69)	0.67 (0.23 to 1.91)	17.5% (11)	1.52 (0.75to 3.10)	0.78 (0.26 to 2.33)
Caesarean section¶	41.8% (174)	36.0% (45)	0.77 (0.51 to 1.14)	0.76 (0.51 to 1.14)	34.4% (32)	0.72 (0.45 to 1.16)	0.70 (0.43 to 1.12)	39.7% (29)	0.89 (0.55 to 1.44)	0.85 (0.51 to 1.41)	47.6% (30)	1.37 (0.80 to 2.34)	1.20 (0.68 to 2.12)
Elective Caesarean section¶	22.0% (91)	17.2% (21)	0.72 (0.45 to 1.14)	0.74 (0.46 to 1.18)	23.1% (21)	0.97 (0.58 to 1.64)	0.96 (0.56 to 1.63)	20.8% (15)	0.91 (0.45 to 1.83)	0.93 (0.44 to 1.96)	22.2% (14)	1.10 (0.59 to 2.05)	1.03 (0.53 to 2.01)
Emergency Caesarean section¶	19.4% (80)	17.2% (21)	0.85 (0.52 to 1.42)	0.84 (0.50 to 1.40)	9.9% (9)	0.46 (0.22 to 0.95)	0.45 (0.21 to 0.95)	18.1% (13)	0.91 (0.47 to 1.76)	0.82 (0.41 to 1.63)	25.4% (16)	1.44 (0.78 to 2.67)	1.25 (0.65 to 2.39)
Preterm birth (<week 37)**	5.0% (21)	10.5% (13)	**2.21 (1.07 to 4.56)**	**2.22 (1.09 to 4.52)**	10.0% (9)	2.09 (0.92 to 4.74)	1.93 (0.87 to 4.26)	17.8% (13)	**4.06 (1.93 to 8.55)**	**4.01 (1.93 to 8.34)**	6.3% (4)	1.28 (0.43 to 3.80)	1.56 (0.51 to 4.83)
Small for gestational age**	3.6% (15)	5.6% (7)	1.60 (0.63 to 4.02)	1.62 (0.64 to 4.08)	5.6% (5)	1.57 (0.56 to 4.44)	1.64 (0.56 to 4.80)	11.0% (8)	**3.29 (1.34 to 8.07)**	**3.22 (1.34 to 7.73)**	4.8% (3)	1.34 (0.37 to 4.77)	1.68 (0.43 to 6.57)

Statistical significant associations are shown in bold.
*Excluding bDMARDs, csDMARDs, steroids and analgesics.
†Excluding bDMARDs and NSAIDs.
‡Excluding bDMARDs.
§Adjustment for maternal age, obesity and extra-musculoskeletal manifestations.
¶Based on deliveries.
**Based on infants.
axSpA, axial spondyloarthritis; b/csDMARDs, biological/conventional synthetic disease-modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs.

a significantly increased risk of SGA (adjusted OR 3.22; 95% CI 1.34 to 7.73) compared with women with axSpA without anti-inflammatory treatment. Moreover, non-significant increased risks of preterm birth (adjusted OR 1.56; 95% CI 0.51 to 4.83) and SGA (adjusted OR 1.68; 95% CI 0.43 to 6.57) in women with axSpA under treatment with bDMARDs were found (table 4). Prevalences of congenital malformations in infants of women with axSpA stratified by pharmacological treatment during 12 months prior to delivery are illustrated in online supplemental table S6.

Compared with controls, the risk of preterm birth was increased in women with axSpA treated with NSAIDS only (OR 1.88; 95% CI 1.05 to 3.36) and in women with axSpA treated with NSAIDS and with csDMARDs, steroids or analgesics (OR 3.96; 95% CI 2.17 to 7.21). Women with axSpA in the latter treatment group also had a higher risk of SGA (OR 2.38; 95% CI 1.16 to 4.88), whereas women with axSpA treated with bDMARDs or without anti-inflammatory treatment had no significantly increased risks of preterm birth or SGA in comparison with women without axSpA (online supplemental table S7). The odds of elective CS were significantly higher in women with axSpA under no anti-inflammatory treatment (OR 1.65; 95% CI 1.28 to 2.12) and in women with axSpA treated with csDMARDs, steroids or analgesics (OR 1.81; 95% CI 1.11 to 2.96) than in controls, while the risk of emergency CS was increased in women with axSpA under treatment with bDMARDs (OR 1.85; 95% CI 1.04 to 3.28). Moreover, the risk of pre-eclampsia was increased in women with axSpA under treatment with bDMARDs (OR 2.51; 95% CI 1.24 to 5.09) and in women with axSpA under no anti-inflammatory treatment (OR 1.45; 95% CI 1.01 to 2.08) compared with controls.

DISCUSSION

In this large nationwide study on pregnancy outcomes, we show that women with axSpA have significantly increased odds of CS compared with matched controls. We further stratified our analyses by pharmacological treatment during the 12 months prior to delivery, showing an increased risk of preterm delivery in women with axSpA treated with NSAIDs only compared with women with axSpA without any anti-inflammatory treatment. The risk of preterm delivery was also higher in women with axSpA treated with NSAIDs and csDMARDs, steroids or analgesics. Women with axSpA in this treatment group also had an increased risk of SGA. Among women with axSpA under treatment with bDMARDs we found non-significant higher risks of SGA and preterm delivery compared with women with axSpA without any anti-inflammatory treatment.

Our study confirms one of the main findings of latest reviews and meta-analyses regarding the increased odds of CS.[2–4] Both elective and emergency CS were more common in women with axSpA than in controls. However, our explanatory analyses by treatment group showed that the risk of emergency CS in comparison with controls was only increased in women with axSpA under treatment with bDMARDs, who were more likely than controls to deliver by emergency CS. Pre-eclampsia may be the driving factor, the risk of which was increased for women with axSpA under treatment with bDMARDs compared with controls (online supplemental table S7). Moreover, the odds of elective CS were increased in women with axSpA without anti-inflammatory treatment. Considering pharmacological treatment as a surrogate marker for disease severity suggests that reasons for increased elective CS may be attributed to the disease itself with its diagnosis affecting the decision to recommend CS.[11 12]

While the proportion of preterm births in women with axSpA was comparable with national statistics (7.8% vs 8.4%,[13]), it was lower in controls (6.2%) without reaching statistical significance found in previous studies.[11 12] Disease severity may be an important explanatory factor for the higher proportion, supporting an association between systemic inflammation and preterm birth, which has been previously suggested.[11 12 14 15]

Spontaneous abortions were not investigated in several pregnancy studies of women with axSpA.[3] In our study, the proportion of spontaneous abortions of 2.9% in controls was in line with 3.3% reported in a multicentre study in Germany,[16] while it was higher in women with axSpA (4.6%). The proportions of elective abortions were comparable between women with axSpA and controls (3.2% vs 3.1%). Furthermore, the proportion of stillbirths in women with axSpA was comparable with controls (0.5% vs 0.4%), which is in line with national statistics (0.4%[13]) and was also reported in the latest reviews and meta-analyses.[2–4] There was also no difference observed for gestational diabetes, consistent with previous results.[2–4]

Altogether congenital malformations were comparable between infants from axSpA pregnancies (8.5%) and from control pregnancies (9.0%). These proportions are higher than the 6.5% reported in literature,[17] which is likely due to our less restrictive adaptation of the classification criteria of EUROCAT.

A large proportion of women with axSpA did not receive any anti-inflammatory treatment before (40%) and during (55%) pregnancy. A possible explanation may be that such cases were most probably the lighter axSpA cases. The only adverse outcomes seen (SGA and preterm birth) among women with axSpA were in those who used NSAIDs compared with those who did not take any anti-inflammatory medication. An explanation may be that the use of NSAIDs increase the risk for adverse outcomes in axSpA, which warrants further investigation in this topic. By contrast, higher risks of adverse outcomes were seen for bDMARD use when compared with no medication use, although in a non-significant manner.

A major strength of this study was the practically population-based design, comprising a nationwide cohort of women with axSpA insured in one of

Germany's largest statutory health insurance funds. Women with axSpA in specialist and non-specialist care were included, thus limiting the risk of selection bias and providing information from a real-life setting, which adds to generalisability of our findings. Furthermore, the large database allowed for generating a large sample size of women with axSpA and selecting a group of women without axSpA as comparator. Another advantage of the large cohort was that analyses could be stratified by pharmacological treatment during pregnancy. To the best of our knowledge, this is the first study comparing pregnancy outcomes of women with axSpA under bDMARDs with women with axSpA who did not take any anti-inflammatory medication as well as with matched non-axSpA controls, which has in general been hampered so far by small populations. Another strength is that information on abortions was available, which is often missing in studies using birth register data that only capture third trimester losses.[2]

It should be acknowledged that the use of administrative data has its own limitations since they are not primarily collected for scientific purposes. However, pregnancy outcomes in this study were identified adopting an algorithm that has been previously validated in German health insurance data.[6] Regarding the diagnosis of axSpA, we have previously validated it by surveying a random sample, stratified by age and sex, of patients with an axSpA diagnosis recorded in the BARMER health insurance data and found that 85% of these patients confirmed their diagnosis.[18] Another drawback is the lack of information on disease activity and severity of axSpA, which may be contributing to pregnancy outcomes. Pharmacological treatment the year prior to delivery and the presence of comorbidities and EMMs may be regarded as a surrogate marker. However, it should be noted that frequency or dose of the medications were not taken into consideration in relation to conception and pregnancy. It should also be noted that we lacked data on maternal smoking and adjusting for it was thus not feasible but has been investigated elsewhere resulting in minor differences.[12] Moreover, information on parity and prior history of preterm birth or pre-eclampsia, which may all affect pregnancy outcomes, was not available. However, women could have more than one birth between 2006 and 2019. The resulting correlated data structure was taken into account in the analysis. Due to low frequencies for certain pregnancy outcomes, interpreting these results warrant some caution.

In conclusion, using data of a large cohort of women with axSpA, we have provided evidence for increased odds of receiving CS compared with matched controls. Among women with axSpA, higher risks of preterm birth and SGA were found among those who used NSAIDs compared with those who did not take any anti-inflammatory medication, while non-significant higher risks of adverse outcomes were seen for bDMARD use when compared with no medication use. Our findings may support future research efforts in the influence of pharmacotherapy before and during pregnancy on disease activity and pregnancy outcome to understand how complications in axSpA pregnancies are related to disease severity.

Twitter Johanna Callhoff @callhoffj

Acknowledgements We would like to thank the statutory health insurance fund BARMER for providing data for this study.

Contributors IR is responsible for the overall content as guarantor. IR, XB contributed to study concept and design. IR, AS, JC, UM, AZ, XB contributed to acquisition, analysis or interpretation of data. IR, XB contributed to drafting of the manuscript. IR, AS, JC, UM, AZ, XB contributed to critical revision of the manuscript and approval of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests XB has received honoraria for talks, advisory boards, paid consultancies, and grants for studies from AbbVie, Amgen, Bristol-Myers Squibb, Celltrion, Celgene, Chugai, Gilead, Janssen, Lilly, MSD, Novartis, Pfizer, Sandoz, UCB. AS has received speaking fees from Bristol-Myers Squibb, Celltrion, MSD, Pfizer and Roche. UM is an employee of BARMER. AZ has received speaking fees from AbbVie, Janssen, Pfizer, Roche and Sanofi-Aventis.

Patient consent for publication Not applicable.

Ethics approval Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data are owned by the statutory health insurance fund BARMER and are not publicly available.

ORCID iDs
Imke Redeker http://orcid.org/0000-0003-3377-2683
Anja Strangfeld http://orcid.org/0000-0002-6233-022X
Johanna Callhoff http://orcid.org/0000-0002-3923-2728
Xenofon Baraliakos http://orcid.org/0000-0002-9475-9362

REFERENCES

1 Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet* 2017;390:73–84.
2 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.
3 Hamroun S, Hamroun A, Bigna J-J, *et al*. Fertility and pregnancy outcomes in women with spondyloarthritis: a systematic review and meta-analysis. *Rheumatology* 2022;61:1314–27.
4 Maguire S, O'Dwyer T, Mockler D, *et al*. Pregnancy in axial spondyloarthropathy: A systematic review & meta-analysis. *Semin Arthritis Rheum* 2020;50:1269–79.
5 Giovannopoulou E, Gkasdaris G, Kapetanakis S. And pregnancy: a literature review. *Curr Rheumatol Rev* 2017;13:162–9.
6 Wentzell N, Schink T, Haug U, *et al*. Optimizing an algorithm for the identification and classification of pregnancy outcomes in German claims data. *Pharmacoepidemiol Drug Saf* 2018;27:1005–10.
7 Kehl S, Dötsch J, Hecher K, *et al*. Intrauterine Growth Restriction. Guideline of the German Society of Gynecology and Obstetrics (S2k-Level, AWMF Registry No. 015/080, October 2016). *Geburtshilfe Frauenheilkd* 2017;77:1157–73.

8 EUROCAT. *EUROCAT guide 1.4: instruction for the registration of congenital anomalies. 2013 last update version 22*. University of Ulster: EUROCAT central registry, 2021.
9 Garbe E, Suling M, Kloss S, *et al*. Linkage of mother-baby pairs in the German Pharmacoepidemiological research database. *Pharmacoepidemiol Drug Saf* 2011;20:258–64.
10 Mikolajczyk RT, Kraut AA, Garbe E. Evaluation of pregnancy outcome records in the German Pharmacoepidemiological research database (GePaRD). *Pharmacoepidemiol Drug Saf* 2013;22:873–80.
11 Mørk S, Voss A, Möller S, *et al*. Spondyloarthritis and outcomes in pregnancy and labor: a nationwide Register-Based cohort study. *Arthritis Care Res* 2021;73:282–8.
12 Jakobsson GL, Stephansson O, Askling J, *et al*. Pregnancy outcomes in patients with ankylosing spondylitis: a nationwide register study. *Ann Rheum Dis* 2016;75:1838–42.
13 IfaQuFiGGAQ 2020.
14 Zbinden A, van den Brandt S, Østensen M, *et al*. Risk for adverse pregnancy outcome in axial spondyloarthritis and rheumatoid arthritis: disease activity matters. *Rheumatology* 2018;57:1235–42.
15 Goldenberg RL, Culhane JF, Iams JD, *et al*. Epidemiology and causes of preterm birth. *Lancet* 2008;371:75–84.
16 Berle P, Weiss E. [Rate of spontaneous abortion in relation to the time of fetal viability assessment]. *Geburtshilfe Frauenheilkd* 1990;50:959–63.
17 Queißer-Wahrendorf A. Angeborene körperliche Anomalien: Epidemiologie. In: Hoffmann GF, Lentze MJ, Spranger J, *et al*, eds. *Pädiatrie: Grundlagen und praxis*. Berlin, Heidelberg: Springer, 2015: 1–7.
18 Redeker I, Hoffmann F, Callhoff J, *et al*. Determinants of psychological well-being in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. *Ann Rheum Dis* 2018;77:1017–24.