EPIDEMIOLOGICAL SCIENCE

Pregnancy and neonatal outcomes in women with axial spondyloarthritis: pooled data analysis from the European Network of Pregnancy Registries in Rheumatology (EuNeP)

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ABSTRACT

Objective To investigate outcome and course of pregnancies in women with axial spondyloarthritis (axSpA) in a pooled data analysis of pregnancy registries in rheumatology.

Methods Prospectively followed women with axSpA, fulfilling ASAS classification criteria and for whom a pregnancy outcome was reported, were eligible for the analysis. Anonymised data of four registries was pooled. Rates of adverse pregnancy outcomes were calculated. Systemic inflammation, disease activity and treatment patterns with tumour necrosis factor inhibitor (TNFi) before, during and after pregnancy were analysed.

Results In a total of 332 pregnancies from 304 axSpA women, 98.8% of the pregnancies resulted in live birth. Mean maternal age was 31 years and disease duration 5 years. Most of these patients received pre-conception counselling (78.4%). Before pregnancy, 53% received TNFi treatment, 27.5% in first and 21.4% in third trimester. Pregnancy and neonatal outcomes were favourable with rates of 2.2% for pre-eclampsia, 4.9% for preterm birth, 3.1% for low birth weight and 9.5% for small for gestational age. Neonates were delivered by caesarean section in 27.7% of pregnancies, of which 47.4% were emergencies. Pooled mean CRP was 4 mg/L before conception peaking in the second trimester at 9.4 mg/L. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was below 4 at all time-points.

Conclusions Pooled rates of most outcomes were better than what had been reported in the literature and within expected rates of those reported for the general population. Pre-conception counselling, planned pregnancies and a tight management in expert centres applying a tailored treatment approach may have contributed to the favourable pregnancy outcomes.

KEY MESSAGES

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Recent meta-analyses showed higher risks of adverse pregnancy outcomes in women with axial spondyloarthritis (axSpA) compared with healthy controls, especially for caesarean section and small for gestational age born neonates.

WHAT THIS STUDY ADDS

⇒ In this first pooled analysis of observational data from four European pregnancy registries in rheumatology, we showed favourable pregnancy outcomes in women with axSpA that were comparable with the general population and lower than rates reported from other axSpA populations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Most of the patients received pre-conception counselling and a tight management of pregnancies with a tailored treatment approach in centres with an expertise on pregnancy management of patients with rheumatic diseases. This may have contributed to the very good outcomes of our study.

⇒ Our findings can reassure women with axSpA in the phase of family planning.

INTRODUCTION

Spondyloarthritis is a chronic rheumatic inflammatory disease that can present with different clinical features, including axial involvement, peripheral signs (enthesitis, arthritis and dactylitis), but also extra-articular manifestations like inflammatory bowel disease, psoriasis and uveitis.[1] When the disease is predominantly axial, patients are diagnosed with axial spondyloarthritis (axSpA).[2]

AxSpA has been historically seen as a predominantly male disease, but recent data show a more balanced sex prevalence.[3] The disease starts in the third decade of life, thus women can be affected in their reproductive years. It is therefore important to understand the influence of axSpA on pregnancy and on the health condition of the mother and the fetus.

Recent meta-analyses showed higher risks of adverse pregnancy outcomes (APOs) in women with axSpA compared with healthy controls.[4–6] They had a greater chance of having a caesarean section (C-section), especially elective C-section,[4 5] and for delivering neonates born small for gestational age (SGA).[4 6] Pooled results of other APOs and foetal complications, for example, pre-eclampsia, preterm birth (PTB), low birth weight (LBW) or congenital abnormalities, were less conclusive.[4–6]

There is only limited information on disease activity levels during pregnancy in patients with axSpA. A review of six studies reported a disease activity increase in almost half of the axSpA pregnancies with a peak in second trimester.[5] In an analysis of 61 prospectively followed women with axSpA, flares occurred in 25% of pregnancies. Stopping treatment with tumour necrosis factor inhibitor (TNFi) at the time of the positive pregnancy test was associated with a three-fold higher flare risk during pregnancy.[7]

Data from the above-mentioned studies mainly derive from claims data analysis, Nordic registries or single-centre (hospital) cohorts. Data from prospectively followed patients with axSpA before, during and after pregnancy are however scarce and were mainly reported from the Norwegian pregnancy registry in rheumatology (RevNatus)[8 9] and the Bern cohort.[7 10]

This study presents results of a pooled analysis using data from four European pregnancy registries with prospectively collected information on women with axSpA before, during and after pregnancy. We focused on the investigation of pregnancy outcomes, on the health of live-born neonates, disease activity and treatment patterns with TNFi.

PATIENTS AND METHODS

Data sources

This cohort study is based on the secondary use of observational data that was initially collected by four European pregnancy registries. Since 2017, the registries EGR2 (France, FR), RePreg (Switzerland, CH), RevNatus (Norway, NO) and Rhekiss (Germany, DE) collaborate in the European Network of Pregnancy Registries in Rheumatology (EuNeP). All registries are multi-centre and enrol women with a rheumatic disease diagnosis, either when they wish to become pregnant or during (early) pregnancy. Data is collected prospectively and nationwide. After enrolment, rheumatologists (in FR also internists, in NO also rheumatology nurses) and patients report information regularly at pre-defined time-points before, during (once per trimester) and after pregnancy, which was described elsewhere.[11]

Relevant variables and their definition were specified by all collaborators in a protocol. Data was extracted by each registry, transferred in an anonymised format via the file-sharing software Seafile (encrypted data via HTTPS/TLS) and pooled into one single dataset after being quality checked.

Study population

Pregnancies were eligible for the analysis if the woman (1) was enrolled and observed in one of the registries, (2) was diagnosed with axSpA before conception and fulfilled the ASAS classification criteria for axSpA,[12] and (3) had a reported pregnancy outcome until the database closing date. Pregnancies with an early pregnancy loss before or at 12 weeks of gestation (WG) were excluded to account for the variation of inclusion criteria regarding WG in the four registries.

Assessments

Selected variables included maternal (age, weight and height, smoking status) and axSpA disease characteristics (disease duration, HLA-B27, extra-articular manifestations, C reactive protein (CRP), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), TNFi exposure), pregnancy (gravidity, multiple pregnancy, pre-eclampsia, delivery mode) and neonatal information (sex, weight, malformations).

Outcomes

The primary endpoints of this analysis were several pregnancy and neonatal outcomes. In pregnancies with a live birth, we investigated rates of pre-eclampsia, PTB (birth before 37 WG) and mode of delivery (ie, vaginal delivery or C-section, which was then further stratified into elective and emergency C-section). Neonatal outcomes were analysed for all live-born neonates and comprised rates of LBW (birth weight<2500 g), macrosomia (birth weight>4000 g), SGA (weight <10th percentile in the according WG) and large for gestational age (LGA; weight >90th percentile in the according WG). The growth curves provided by Voigt *et al*[13–15] were used for the calculation of SGA and LGA in all registries, except for RevNatus.[16]

As secondary outcomes, systemic inflammation and disease activity were investigated 6 months before pregnancy, in every trimester and 6 months postpartum. Analyses of the data 6 months before pregnancy were only performed if the patient was enrolled prior to conception. Elevated inflammation and activity were defined as CRP>5 mg/L and BASDAI≥4. Furthermore, TNFi treatment was addressed. A patient was considered to be exposed to TNFi 6 months before pregnancy, in first, second and third trimester, or 6 months after delivery if she has received at least one dosage in the respective time period. Four different mutually exclusive treatment patterns during pregnancy were defined: (1) no TNFi in any of the trimesters, (2) TNFi in every trimester, (3) TNFi solely in first or in first and second trimester, (4) all patterns which are not covered by (1) to (3).

Statistical analyses

Data was descriptively analysed and is presented per registry and as a pooled estimate of all pregnancies across registries. Descriptive statistics include means (SD) or numbers (percentage) as appropriate. Rates of the primary endpoints were calculated by dividing the number of events by the number of pregnancies with live birth (applies to pre-eclampsia, PTB, delivery mode) or the number of live born neonates (LBW, macrosomia, SGA, LGA) and multiplying by 100 to obtain a percentage.

Missing data were not imputed. Pregnancies/neonates with missing data on the respective outcome were not included in the calculation. The tables indicate the number of pregnancies with missing information, the figures pregnancies with available information. Data was analysed with the software package SAS, V.9.4 (SAS Institute, Cary, USA).

Subgroup and sensitivity analyses

To investigate whether the results are affected by the number, order or characteristics of pregnancies or by disease severity, primary and secondary outcomes were investigated in four different subgroups comprising singleton pregnancies, the first reported pregnancy in a patient, the first ever pregnancy in a patient (primigravida) and pregnancies in patients fulfilling the New York classification criteria.[17]

To investigate the influence of medical treatment on the primary outcomes as well as on systemic inflammation and

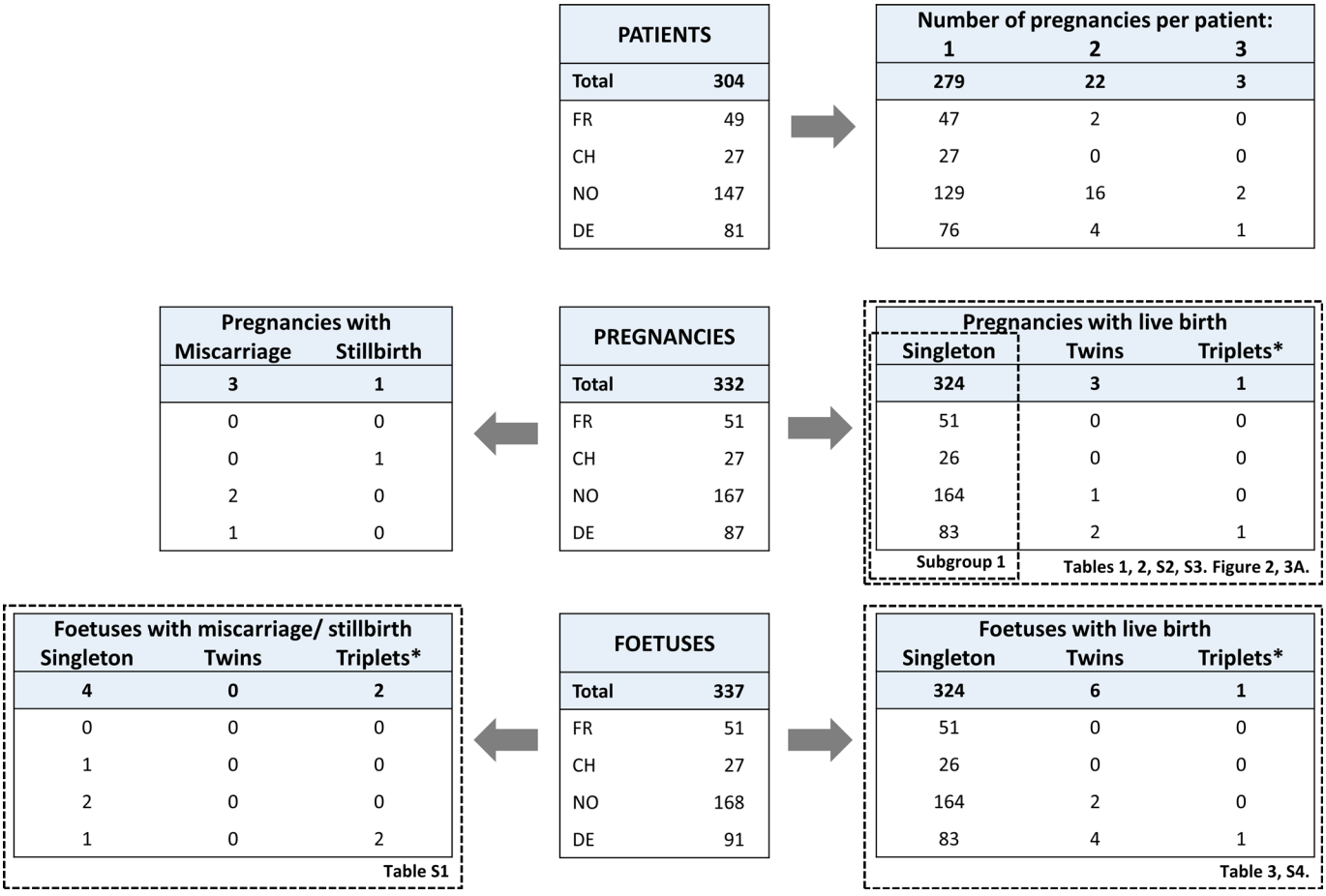


Figure 1 Illustration of number of pregnancies, related number of patients and fetuses, and of pregnancy outcomes for single registries and in combination. *Triplet pregnancy resulted in two aborted foetuses and one live born neonate. The pregnancy itself was counted as live-born pregnancy. CH, Switzerland; DE, Germany; FR, France; NO, Norway.

disease activity, these were further stratified in a sensitivity analysis according to the treatment patterns described above.

RESULTS

A total of 332 pregnancies from 304 women fulfilling the ASAS classification criteria for axSpA were reported (figure 1). Pregnancies were documented between 2008 and 2020, the majority of them occurred from 2015 onwards (93.6%). The Norwegian registry contributed to half of the pregnancies (50.3%), followed by Germany (26.2%), France (15.4%) and Switzerland (8.1%). Except for three twin and one triplet pregnancies, all pregnancies were singletons. The majority of pregnancies resulted in live births (98.8%). A miscarriage after week 12 was reported for three pregnancies and stillbirth for one pregnancy (online supplemental table 1). Of note, two of the fetuses of the triplet pregnancy died, but the pregnancy itself was counted as pregnancy with a live birth. The following analyses refer to 328 pregnancies with live births in 300 patients. The majority was enrolled in early pregnancy (69.9%). For 99 pregnancies (30.1%), information was also available for the period prior to conception.

Maternal and disease characteristics

At the time of conception, mean maternal age was 31.4 years, the average time between axSpA diagnosis and conception was 5.0 years. Almost half of the patients fulfilled the New York criteria (48%; information was not available from NO). Three-quarter of the pregnancies were HLA-B27 positive (77%), and in one out of ten pregnancies at least one extra-articular manifestation was reported (table 1). Pregnancies in each registry did not differ in maternal age, but in other maternal and axSpA characteristics (online supplemental table 2).

Pregnancy and neonatal outcomes

The great majority of pregnancies were planned (86.5%) and 78.4% received rheumatology counselling prior to conception (table 2). Overall, pre-eclampsia occurred in 2.2% of pregnancies, mean WG at delivery was 39.0% and 4.9% of pregnancies were premature. Almost three-quarters of the infants were delivered vaginally (72.3%). Delivery by C-section ranged between 16.7% in France and 56.5% in Switzerland (online supplemental table 3). Of the pooled data, 47.4% were emergency C-sections (table 2).

Reduced birth weight, namely LBW and SGA, occurred in 3.1% and 9.5%, increased birth weight, namely macrosomia and LGA, in 10.7% of the neonates, respectively (table 3). Rates of these outcomes were comparable between registries (online supplemental table 4). For five neonates, malformations were reported: one neonate was suspected of having a genetic syndrome (intrauterine growth restriction, hypertelorism, hypertyrosinemia), three had minor malformations (cleft lip, hypospadias, hip dysplasia) and no details were available for the last one.

Table 1 Maternal and disease characteristics for pregnancies with live birth as pooled results of the main and subgroup analysis

	Main analysis	Subgroup analysis			
	Pooled total pregnancies	Singleton pregnancies	First pregnancy per registry	First ever pregnancy (primigravida)	NY criteria fulfilled‡
No of pregnancies	328	324	300	132	70
No of patients	300	296	300	132	67
Age in years*	31.4±4.5	31.4±4.5	31.4±4.5	30.3±4.1	32.7±4.4
Weight in kg before WG 20	67.5±14.2	67.3±13.8	67.8±14.3	65.9±11.1	68.6±16.0
BMI in kg/m^2	24.4±5.0	24.3±4.8	24.5±5.0	23.6±3.5	24.5±5.7
BMI≥30 kg/m^2	28 (12.6)	27 (12.3)	27 (13.4)	4 (4.5)	6 (12.8)
Smoking*	18 (7.2)	18 (7.3)	18 (7.9)	6 (6.3)	4 (10.5)
Years since diagnosis*	5.0±4.0	5.0±4.0	4.9±4.1	5.0±3.6	7.1±4.5
Fulfilment of NY criteria	70 (47.6)	69 (47.9)	67 (48.2)	35 (53.0)	70 (100)
HLA-B27 positive	203 (76.6)	201 (76.4)	188 (75.8)	95 (84.1)	51 (77.3)
Extra-articular manifestations†	31 (9.8)	29 (9.3)	27 (9.3)	12 (9.6)	4 (6.2)
Thereof IBD	19 (6.0)	19 (6.1)	16 (5.5)	9 (7.2)	3 (4.6)
Thereof psoriasis	7 (2.2)	6 (1.9)	6 (2.1)	2 (1.6)	0
Thereof uveitis	7 (2.2)	6 (1.9)	7 (2.4)	3 (2.4)	1 (1.5)

Results are given as number (percentage) or mean±SD.
*At the time of conception.
†History of inflammatory bowel disease, psoriasis and/or uveitis.
‡Information was not available from the Norwegian registry.
BMI, body mass index; IBD, inflammatory bowel disease; NY, New York; WG, week of gestation.

Systemic inflammation, disease activity and treatment

Pooled CRP ranged between 4.0 mg/L before conception and 9.4 mg/L in second trimester. Mean postpartum CRP did not reach the low pre-conceptional level (figure 2A). Changes in BASDAI were not as pronounced as for CRP with a pooled mean of 3.0 before conception (figure 2B), and values during pregnancy and postpartum between 3.4 and 3.5. The proportion of patients with elevated inflammation level (CRP>5 mg/L) was highest in second and third trimester with 49% and 46%, respectively (figure 3A). The same pattern was observed for BASDAI≥4 (figure 3B).

In more than half of the pregnancies, patients were treated with TNFi before conception (52.6%, figure 4). During pregnancy, the proportions were 27.5%, 21.7% and 21.4% in first, second and third trimester, respectively, and raised to 42.3% postpartum. In one-third of pregnancies (32.7%), patients received TNFi at any time between conception and delivery. In 17.8% of pregnancies, TNFi was given in all three trimesters,

Table 2 Pregnancy characteristics, adverse pregnancy outcome and mode of delivery for pregnancies with live birth as pooled results of the main and subgroup analysis

	Main analysis	Subgroup analysis			
	Pooled total pregnancies	Singleton pregnancies	First pregnancy per registry	First ever pregnancy (primigravida)	NY criteria fulfilled*
No of pregnancies	328	324	300	132	70
Pregnancy was planned	218 (86.5)	214 (86.3)	202 (86.3)	101 (93.5)	47 (90.4)
Rheumatologic counselling	196 (78.4)	168 (76.0)	158 (75.6)	72 (77.4)	34 (63.0)
Primigravida	132 (41.0)	131 (41.2)	131 (44.6)	132 (100)	35 (52.2)
Number of fetuses					
Singleton pregnancy	324 (98.8)	324 (100)	296 (98.7)	131 (99.2)	69 (98.6)
Twin pregnancy	3 (0.9)	0	3 (1.0)	1 (0.8)	1 (1.4)
Triplet pregnancy	1 (0.3)	0	1 (0.3)	0	0
Pre-eclampsia	7 (2.2)	7 (2.2)	7 (2.4)	3 (2.3)	0
Gestational week at delivery	39±1.9	39±1.9	39±1.9	39.3±1.8	38.7±2.4
Preterm birth	16 (4.9)	16 (4.9)	15 (5.0)	8 (6.1)	7 (10.0)
Mode of delivery					
Vaginal delivery	224 (72.3)	222 (72.5)	206 (72.8)	91 (75.8)	43 (66.2)
Caesarean section (C-section)	86 (27.7)	84 (27.5)	77 (27.2)	29 (24.2)	22 (33.8)
Thereof elective C-sections	41 (52.6)	40 (52.6)	36 (50.7)	6 (23.1)	13 (68.4)
Thereof emergency C-sections	37 (47.4)	36 (47.4)	35 (49.3)	20 (76.9)	6 (31.6)

Results are given as number (percentage) or mean±SD.
*Information was not available from the Norwegian registry.
NY, New York.

Table 3 Characteristics of live-born neonates (n=331) as pooled results of the main and subgroup analysis

	Main analysis	Subgroup analysis			
	Pooled total pregnancies	Singleton pregnancies	First pregnancy per registry	First ever pregnancy (primigravida)	NY criteria fulfilled*
No of neonates	331	324	303	133	71
Female sex	159 (49.1)	155 (48.9)	140 (47.1)	67 (51.1)	35 (50.7)
Birth weight in g	3370.5±551.9	3382.4±545.4	3378±546.8	3347.4±525.9	3276.9±609.7
Low birth weight (<2500 g)	10 (3.1)	9 (2.9)	8 (2.7)	4 (3.1)	3 (4.3)
Small for gestational age	30 (9.5)	28 (9.0)	29 (10.0)	15 (11.7)	7 (10.1)
Macrosomia (>4000 g)	34 (10.7)	33 (10.6)	32 (11.0)	11 (8.6)	7 (10.1)
Large for gestational age	34 (10.7)	33 (10.6)	32 (11.0)	12 (9.4)	4 (5.8)
Malformations	5 (3.2)	5 (3.3)	5 (3.4)	2 (2.8)	2 (2.9)

Results are given as number (percentage) or mean±SD.
*Information was not available from the Norwegian registry.
NY, New York.

and in 8.9%, TNFi was only given in first or in first and second trimester. In two-thirds of all pregnancies, the patients did not receive any TNFi (67.3%, figure 5). Substantial differences were observed between countries, for example, exposure to TNFi in first trimester was reported for 58% and 37% in Switzerland and France, and for 22% and 20% in Norway and Germany, respectively. Besides TNFi, no other anti-rheumatic therapies were investigated.

Subgroup and sensitivity analyses

The results of the subgroup analyses are presented in tables 1–3 and online supplementary table S5. Primary outcomes were comparable among pooled data and subgroups comprising singleton pregnancies, first reported pregnancy per registry and first ever pregnancy. However, pregnancies of patients fulfilling New York criteria were twice as likely to result in PTB compared with pooled data, and LGA rate was lower.

Whether the patient received no TNFi during pregnancy, or received TNFi throughout pregnancy or in the first trimesters, respectively, did not result in changes of delivery mode and SGA rates. Yet, higher rates of pre-eclampsia, PTB, macrosomia and SGA and lower LBW rates were observed in patients not treated with TNFi during pregnancy than in those who received TNFi. Furthermore, treatment with TNFi during pregnancy resulted in lower rates of patients with elevated inflammation/ disease activity in third trimester.

DISCUSSION

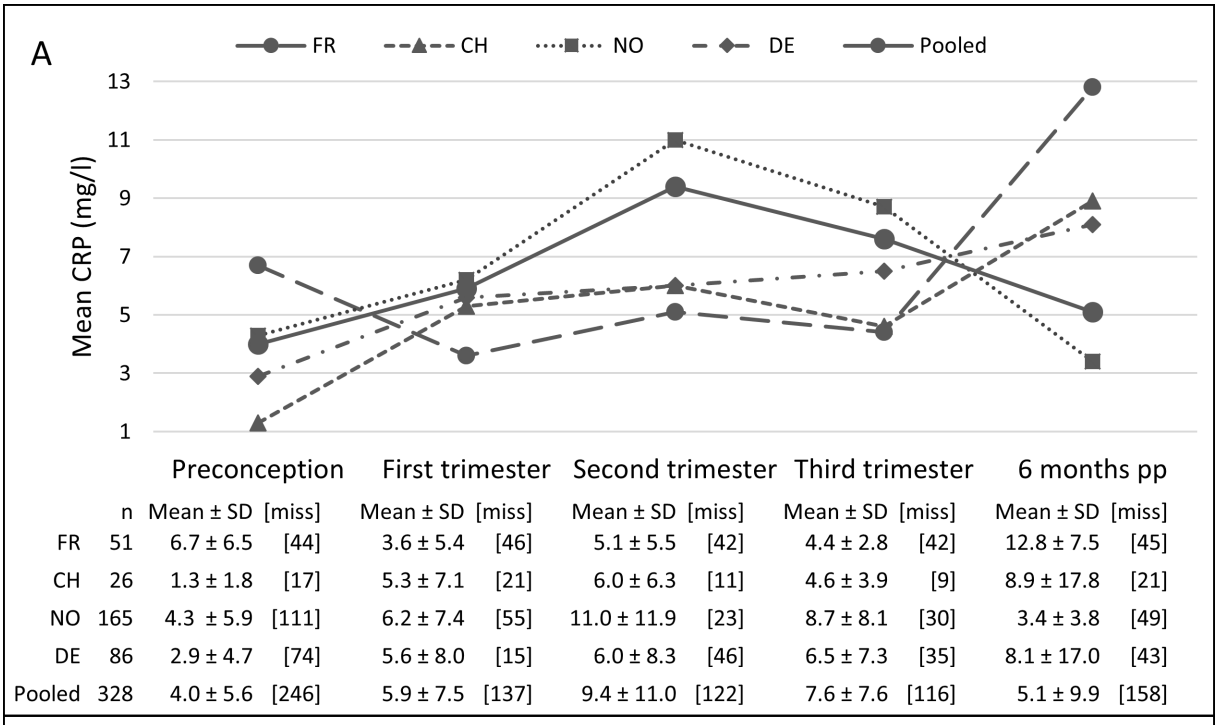
In this pooled analysis of pregnancies in patients with axSpA using observational data from four European pregnancy registries in rheumatology, overall APO rates were very low. This especially refers to pre-eclampsia, PTB, LBW and SGA. Secondary outcomes of this analysis were inflammation/disease activity and treatment with TNFi. Systemic inflammation measured by CRP showed higher levels in second trimester compared with the time before pregnancy and after delivery. These patterns were not as pronounced for disease activity indicated by BASDAI, whose mean values were below 4 throughout pregnancy. With regard to treatment, the majority of patients did not receive TNFi during pregnancy. Before conception, treatment rate was at 53%.

This study investigated rather recent pregnancies, with most deliveries occurring from 2015 onwards, which might reflect both the wider use of very effective treatments (eg, biologics) and also the increased knowledge about pregnancies in this patient groups and therefore changed rheumatology and obstetric routines. The great majority of patients underwent preconception counselling and had a planned pregnancy. Presumably, these women received tight rheumatologic management of their disease at centres specialised in pregnancies of patients with rheumatic conditions and that participate in special pregnancy registries. The low APO rates found herein might therefore not be comparable with older studies or those with retrospective data collection.[4–6] In our study, rates of APO were within the expected rates of the general population despite including singleton and multiple pregnancies in the main analysis as well as more than one pregnancy per patient—both of which can contribute to poorer outcomes.[18 19] These populations were addressed by subgroup analyses, which revealed comparable results.

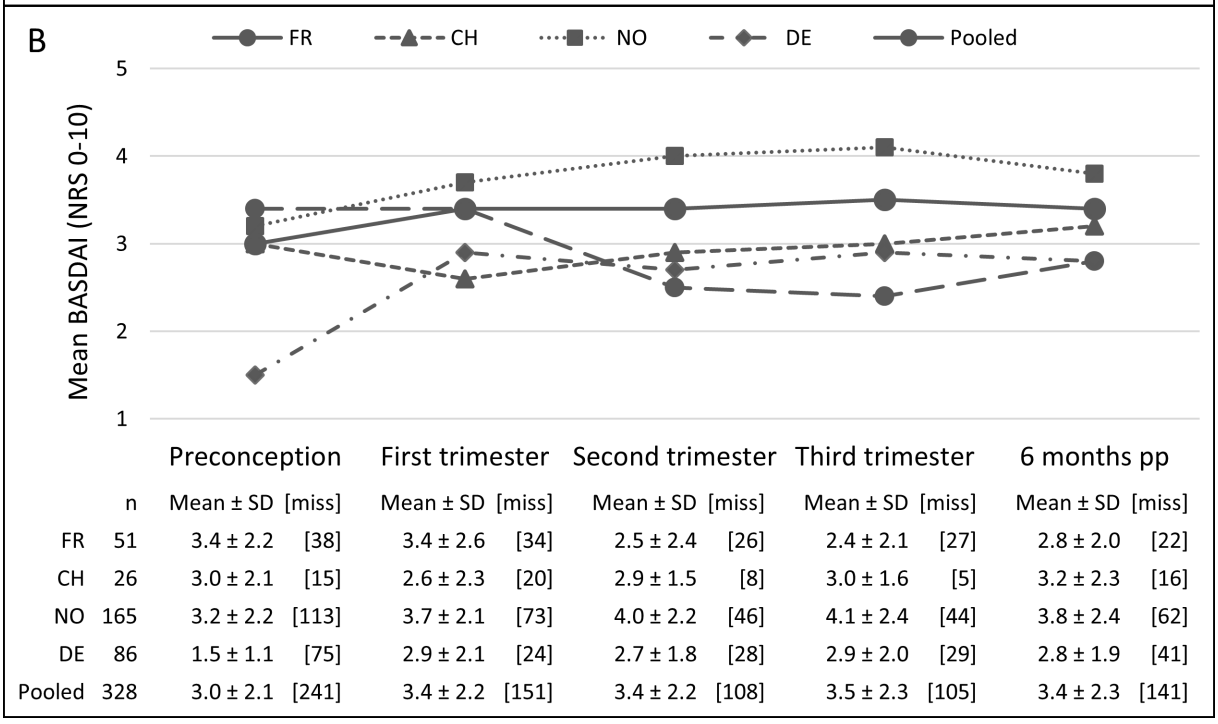
The pooled pre-eclampsia rate in our analysis was 2.2% and varied between 0% and 3.8% depending on country. Rates reported for the general population range from 2.2% to 4.0%,[20] and for patients with axSpA from 1.3% to 7.7%.[21–24] While one meta-analysis of axSpA pregnancies showed no significant association for pre-eclampsia (overall OR 1.3 (95% CI 0.92 to 1.82)) compared with the general population,[5] another showed a risk increase of 59%.[4]

In our data, PTB was reported in 4.9% of the live birth pregnancies (range 0% to 8.1%). This rate is lower than the rate reported for the European general population (8.7% (uncertainty interval 6.3–13.3)).[25] In most of the published data for axSpA, 6.8% to 11.4% of pregnancies were preterm.[10 21–23 26–28] One study reported a rate of only 1.4%[22] and another of 17.3%.[24] Meta-analyses of two, seven and nine studies found controversial outcomes with, on the one hand, significant risk increases for PTB of 64% and 99%[4 6] and, on the other hand, a non-significant result (OR 0.84, 95% CI 0.39 to 1.81),[5] respectively.

In our analysis, the pooled rate of neonates with LBW was 3.1% (range 2.1% to 8.7%), which is quite low compared with the prevalence of LBW in Europe of 7.0 (uncertainty range 6.8–7.1) per 100 live births.[29] Rates of LBW reported by other axSpA studies from different countries vary widely between 3.9% and 22.0%.[22 23 28] One out of ten neonates in our analysis was born SGA. In the French and Swiss data, the SGA prevalence was higher than the expected 10% (17.0% and 21.7%, respectively), which may be caused by the reference cohort as German national growth curves were used.[14 15] Other axSpA cohorts reported rates between 3.1% and 16.4%.[10 21 22 26 28] Two meta-analyses estimated a pooled 2-fold and 2.4-fold increased risk of SGA born infants to women with axSpA in comparison to healthy pregnant women, respectively.[4 6]



	n	Preconception Mean ± SD	[miss]	First trimester Mean ± SD	[miss]	Second trimester Mean ± SD	[miss]	Third trimester Mean ± SD	[miss]	6 months pp Mean ± SD	[miss]
FR	51	6.7 ± 6.5	[44]	3.6 ± 5.4	[46]	5.1 ± 5.5	[42]	4.4 ± 2.8	[42]	12.8 ± 7.5	[45]
CH	26	1.3 ± 1.8	[17]	5.3 ± 7.1	[21]	6.0 ± 6.3	[11]	4.6 ± 3.9	[9]	8.9 ± 17.8	[21]
NO	165	4.3 ± 5.9	[111]	6.2 ± 7.4	[55]	11.0 ± 11.9	[23]	8.7 ± 8.1	[30]	3.4 ± 3.8	[49]
DE	86	2.9 ± 4.7	[74]	5.6 ± 8.0	[15]	6.0 ± 8.3	[46]	6.5 ± 7.3	[35]	8.1 ± 17.0	[43]
Pooled	328	4.0 ± 5.6	[246]	5.9 ± 7.5	[137]	9.4 ± 11.0	[122]	7.6 ± 7.6	[116]	5.1 ± 9.9	[158]

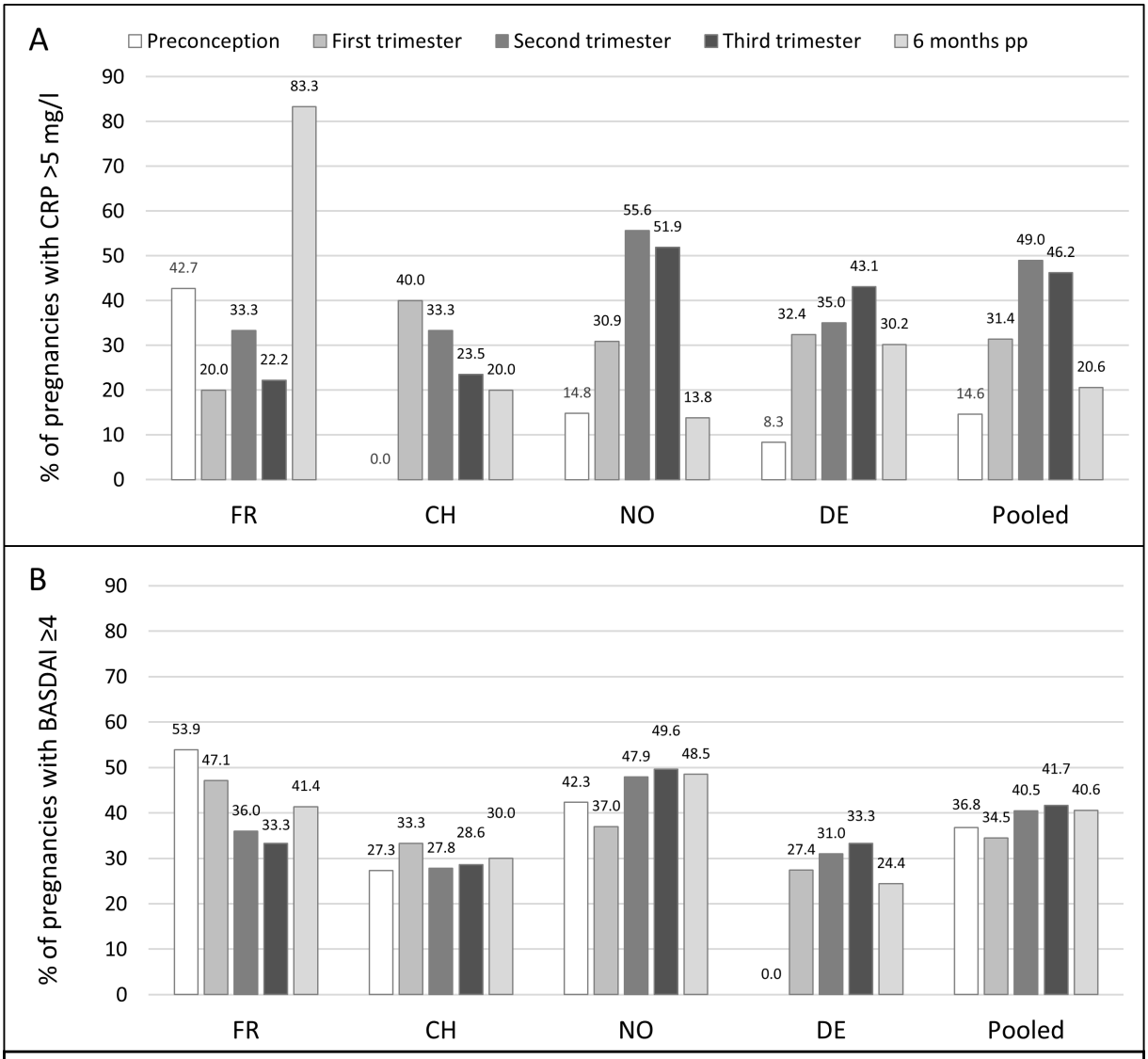


	n	Preconception Mean ± SD	[miss]	First trimester Mean ± SD	[miss]	Second trimester Mean ± SD	[miss]	Third trimester Mean ± SD	[miss]	6 months pp Mean ± SD	[miss]
FR	51	3.4 ± 2.2	[38]	3.4 ± 2.6	[34]	2.5 ± 2.4	[26]	2.4 ± 2.1	[27]	2.8 ± 2.0	[22]
CH	26	3.0 ± 2.1	[15]	2.6 ± 2.3	[20]	2.9 ± 1.5	[8]	3.0 ± 1.6	[5]	3.2 ± 2.3	[16]
NO	165	3.2 ± 2.2	[113]	3.7 ± 2.1	[73]	4.0 ± 2.2	[46]	4.1 ± 2.4	[44]	3.8 ± 2.4	[62]
DE	86	1.5 ± 1.1	[75]	2.9 ± 2.1	[24]	2.7 ± 1.8	[28]	2.9 ± 2.0	[29]	2.8 ± 1.9	[41]
Pooled	328	3.0 ± 2.1	[241]	3.4 ± 2.2	[151]	3.4 ± 2.2	[108]	3.5 ± 2.3	[105]	3.4 ± 2.3	[141]

Figure 2 Systemic inflammation and disease activity before, during and after pregnancy in pregnancies with live births. Mean values±SD deviation (number of pregnancies with missing information) of CRP (A) and BASDAI (B) are shown. Means are given for pregnancies with available information as pooled results for all pregnancies with live birth (n=328) and stratified by registry. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CH, Switzerland; CRP, C reactive protein; DE, Germany; FR, France; miss, number of pregnancies with missing information on CRP (figure A) and BASDAI (figure B); N, number of pregnancies with live birth; NO, Norway; pp, postpartum.

In this pooled study, 27.7% of the neonates were delivered by C-section (range 16.7%–56.5%), and 47.4% of the procedures were due to emergency reasons (range 20.0%–61.5%). Studies in other axSpA populations similarly reported widely varying values ranging from 23.4% to 55%.[10 21–23 26 30] Differences in delivery mode may be caused by a variety of reasons such as disease activity and treatment modalities, appear to be strongly affected by country-specific or even hospital-specific factors and are ultimately at the discretion of the physician and patient. However, most previous studies that have compared delivery mode in women with and without axSpA, found a significantly increased risk of C-section in axSpA, which was confirmed by two meta-analyses.[4 5]

For systemic inflammation, pooled levels were low with the highest peak of CRP in second trimester. Means were mainly triggered by the Norwegian registry, which contributed to about

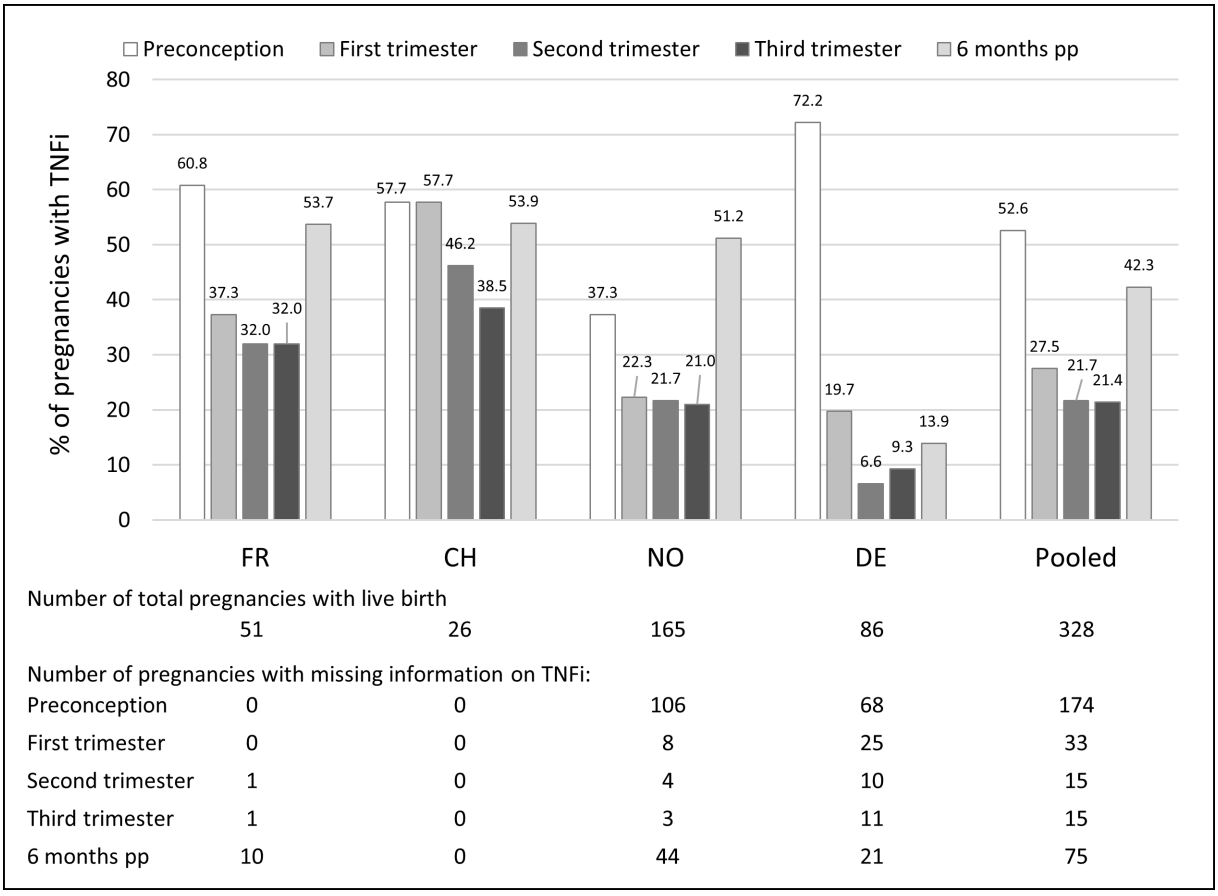


	FR	CH	NO	DE	Pooled
Number of total pregnancies with live birth	51	26	165	86	328
Number of pregnancies with missing information on CRP | BASDAI					
Preconception	44 | 38	46 | 34	42 | 26	42 | 27	45 | 22
First trimester	17 | 15	21 | 20	11 | 8	9 | 5	21 | 16
Second trimester	111 | 113	55 | 73	23 | 46	30 | 44	49 | 62
Third trimester	74 | 75	15 | 24	46 | 28	35 | 29	43 | 41
6 months pp	246 | 241	137 | 151	122 | 108	116 | 105	158 | 141

Figure 3 Percentages of patients with elevated systemic inflammation and disease activity before, during and after pregnancy in pregnancies with live births. Percentages of pregnancies with elevated CRP>5 mg/L (A) and BASDAI≥4 (B) are shown. Percentages are given for pregnancies with available information as pooled results for all pregnancies with live births (n=328) and stratified by registry. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CH, Switzerland; CRP, C reactive protein; DE, Germany; FR, France; NO, Norway; pp, postpartum.

50% of the available data. However, almost half of the patients had elevated CRP levels in second and third trimester. This pattern was not found for the disease activity measured with the BASDAI. This could be explained by the fact that pregnancy is a state of low-grade inflammation with elevation of CRP in the ultra-high sensitivity range.[31] In normal pregnancy, CRP slowly increases reaching levels in the range of 1000 ng/mL around term. However, usually, these pregnancy-related ultra-low CRP levels are not captured by normal tests. In a previous prospective analysis of patients with axSpA, 44% had elevated CRP levels in second trimester which were related to disease activity and not to changes due to pregnancy.[10] We assume that this is also the case in this study. Of note, unlike systemic lupus erythematosus, there is no pregnancy-specific disease activity instrument for axSpA.

While half of the patients were treated with TNFi before conception, the rate declined to 28% in first and 21% in third trimester. The lower proportion of patients using TNFi during



	FR	CH	NO	DE	Pooled
Number of total pregnancies with live birth	51	26	165	86	328
Number of pregnancies with missing information on TNFi:					
Preconception	0	0	106	68	174
First trimester	0	0	8	25	33
Second trimester	1	0	4	10	15
Third trimester	1	0	3	11	15
6 months pp	10	0	44	21	75

Figure 4 Treatment with TNFi before, during and after pregnancy for pregnancies with live birth. Percentages are given for pregnancies with available information as pooled results for all pregnancies with live birth (n=328) and stratified by registry. CH, Switzerland; DE, Germany; FR, France; NO, Norway; pp, postpartum; TNFi, tumour necrosis factor inhibitor.

third trimester reflects treatment recommendations that advise TNFi discontinuation in the last trimester of pregnancy, except for Fc-free TNFi.[32 33] After birth, TNFi use increased again, but we cannot conclude from our data whether the drug was initiated because of an increase in disease activity or prophylactically to prevent disease flares. Stratifying patients by TNFi treatment,

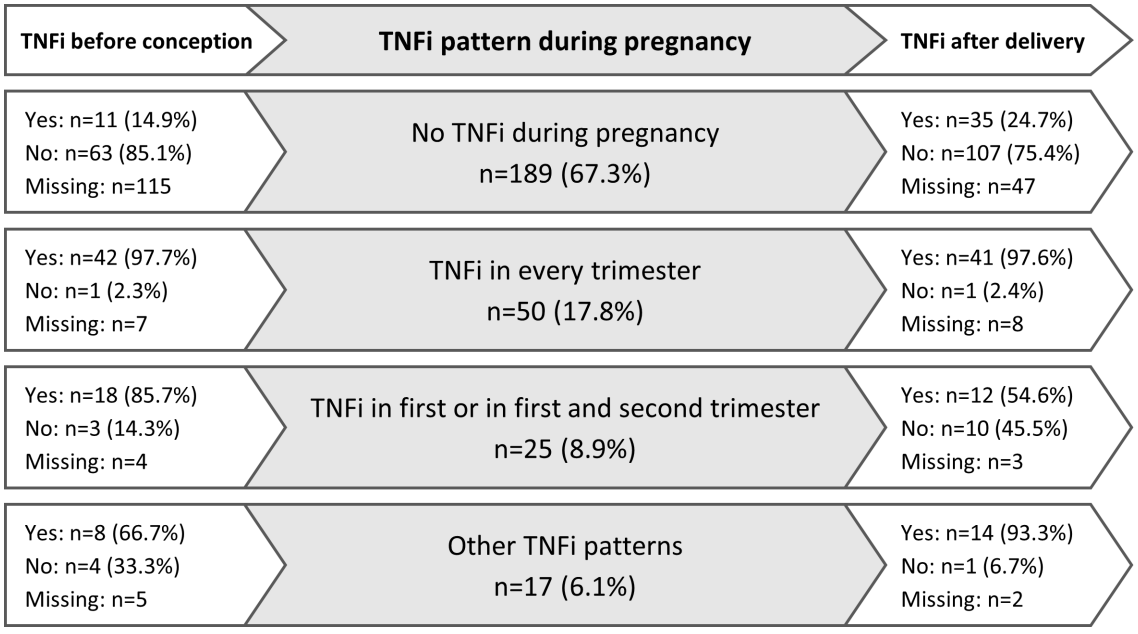


Figure 5 Treatment patterns with TNFi during pregnancy for pregnancies with available information in all three trimesters (n=281). Treatment with TNFi during pregnancy was categorised into different patterns. The figure additionally shows if patients of each pattern received TNFi before conception and after birth. TNFi, tumour necrosis factor inhibitor.

we saw lower pre-eclampsia, PTB and LGA rates in women receiving TNFi during pregnancy and a lower percentage of patients with elevated inflammation/disease activity in third trimester.

This study has several strengths and limitations. Strengths are that we investigated recent pregnancies. Even though, data collection started in 2008, most of the pregnancies were reported between 2015 and 2020. The pregnancies in women with axSpA were followed prospectively in the four participating registries. Despite using different data sources, a homogeneous group of patients was achieved by applying stringent inclusion criteria and selecting only women who fulfilled the ASAS classification criteria for axSpA. As a limitation, it can be considered that these different data sources also introduce a certain level of heterogeneity even though all four registries are comparable in their study design.[11] Different social and healthcare structures, varying prescription and reimbursement patterns in the different countries can be the causes. Only the variables defined in the protocol were available for this analysis. Due to heterogeneity of the registries and differences in data collection, some results could not be investigated in more detail, for example, indications for C-section, treatments besides TNFi, reasons for stopping TNFi treatment or comorbidities such as hypertension and diabetes. Although a relatively large cohort of pregnancies in patients with axSpA was available, we were not able to investigate risk factors for adverse outcomes by regression models. In particular, the interplay of treatment, disease activity and APOs should be deciphered by adjusted analyses. Several reasons hindered such an approach, for example, low number of outcomes and uneven distribution within registries, missing information or unavailability of covariates. Finally, a selection bias of rather planned and well-controlled pregnancies followed mainly in centres with a wide experience and particular interest on the management of pregnancies in patients with rheumatic diseases cannot be ruled out and the positive outcomes observed here may not be generalisable to all women with axSpA.

CONCLUSION

This is the first collaborative analysis of four European pregnancy registries in rheumatology with reassuring results for women with axSpA who want to become pregnant. We found favourable outcomes of pregnancies in women with underlying axSpA who were observed in rheumatologic centres with an expertise on pregnancies in women with rheumatic diseases. The pooled rates of pre-eclampsia, PTB and SGA in these patients were within expected rates in the general population. Our findings underline the importance of pre-conception counselling, pregnancy planning and tight monitoring aiming at low disease activity or remission and assume that they contribute to achieve good pregnancy outcomes in women with axSpA.

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Patient consent for publication Not applicable.

Ethics approval The study is based on the secondary use of anonymised data. The single registries contributing to the study were approved by the respective national data protection agencies and research ethical committees according to legal regulatory requirements in the participating countries. Participants gave informed consent to participate in the study before taking part.

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