Disease activity during and after pregnancy in women with axial spondyloarthritis: A prospective multicenter study

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ABSTRACT

Objective. To study disease activity in women with axial spondyloarthritis (axSpA) during and after pregnancy.

Methods. The study included 179 pregnancies in 166 women with axSpA from a Norwegian nationwide register. Disease activity was assessed at seven time points before, throughout and after pregnancy with the disease activity score BASDAI. Scores assessed at each time point were analyzed in a linear mixed model. The same statistical method was used to study self-reported physical functioning, pain and mental health.

Results. Altogether, disease activity was stable throughout the study period. We found highest disease activity and worst self-reported pain in second trimester, when 45% of the women had active disease. At this time point disease activity was significantly higher than six weeks postpartum (mean BASDAI 3.97 vs. 3.46, P = 0.005). Self-reported mental health was also stable, but significantly better six weeks postpartum than in first trimester (mean RAND-36 mental health 79.3 vs. 73.2, P < 0.001). Physical functioning was significantly worse in third trimester than postpartum (mean BASFI 3.6 vs. 2.6, P < 0.001).

Conclusion. Studying women with axSpA, we found that disease activity was highest in second trimester, but altogether low and stable in the period from planning pregnancy to one year after delivery.

Key words: axial spondyloarthritis - disease activity – pregnancy

KEY MESSAGES

- Studies on axial spondyloarthritis (axSpA) in pregnancy have shown diverging results, and there are no previous large prospective studies on this topic
- In this large Norwegian longitudinal follow-up of pregnancies in women with axSpA, we found highest disease activity in second trimester, but altogether stable, low disease activity from preconception until one year after delivery
- This study provides reassuring knowledge for women with axSpA considering pregnancy

INTRODUCTION

Spondyloarthritis is the term for a group of diseases characterized by inflammation of the spine, enthesitis, arthritis and dactylitis (1). Axial spondyloarthritis - where the spine is involved - consists of radiographic axial spondyloarthritis (r-axSpA, formerly known as ankylosing spondylitis), with established sacroiliitis on radiography, and non-radiographic axial spondyloarthritis (nr-axSpA) (1).

The mean prevalence of r-axSpA per 10,000 people has been estimated to 23.8 in Europe and 31.9 in North America (2). The prevalence of nr-axSpA is not known. Traditionally seen as a disease affecting men, the male:female ratio is only 2-3:1 after the introduction of the concept nr-axSpA (3). Onset most commonly occurs between twenty and thirty years, coinciding with women`s fertile age and thus affecting their experience of pregnancy.

Previous studies on disease activity of axSpA in pregnancy have shown diverging results. A large retrospective study from 1998, demonstrated no particular pattern of disease activity during pregnancy (4). Other studies have described decreasing functionality and increasing pain in late pregnancy, where one study found the same pattern in healthy women, arguing that this was due to biomechanical changes of pregnancy (5, 6). A newly published prospective study with a validated disease activity measure, demonstrated that 25% out of 61 women with axSpA experienced a flare during pregnancy, most often in second trimester (7). Increased disease activity in second trimester was also found in a small prospective study from 2004 (8), while a small retrospective study found decreased disease activity in pregnancy in 70% of women with r-axSpA (9).

The main aim of our study was to prospectively study disease activity during and after pregnancy in a large cohort of women with axSpA using a validated disease activity measure. Opposed to most previous studies, we included both r-axSpA and nr-axSpA. We also explored the women`s self-reported physical functioning, pain and mental health throughout the study period.

PATIENTS AND METHODS

The RevNatus-register. RevNatus is a Norwegian nationwide register designed for the follow-up of women with inflammatory rheumatic diseases from the planning of pregnancy until twelve months postpartum. The register was established in 2006 by the National advisory unit on pregnancy and rheumatic diseases.

Patient population. This study comprises women with axSpA included in RevNatus between January 2006 and November 2016. All women included in the analyses fulfilled the ASAS (Assessment of SpondyloArthritis International Society) criteria for axSpA (10). RevNatus does not differ between r-axSpA and nr-axSpA.

Women with axSpA and registered with data from at least one time point in pregnancy were included in the study. We excluded women who had not conceived at the time of analyses and women who experienced miscarriage or fetal death.

Data collection and description of outcome variables. Women included in RevNatus ideally have seven visits at their local rheumatology unit: Before conception (visit 0), in each trimester (visit 1-3), and at six weeks, six months and twelve months after delivery (visit 4-6). Though the objective is to include all women with an inflammatory rheumatic disease in RevNatus at the planning stage of pregnancy, only a minority of the women with axSpA

were in fact enrolled preconception. Thus, not all women attended all visits. Enrollment was carried out by rheumatologists and nurses at the participating centers.

At each visit, disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The BASDAI is calculated from six patient-reported items: 1) fatigue, 2) back pain, 3) peripheral joint pain and swelling, 4) localized tenderness, 5) duration of morning stiffness, and 6) severity of morning stiffness (10). Items are scored by numeric response scale (0-10). The scores for question 5 and 6 are averaged, then the result is averaged with the remaining four question scores to give a final score of minimum 0 ("no disease activity") and maximum 10 ("maximal disease activity"). A cut off of 4 is commonly used to define active disease (11). The minimum clinically important difference in BASDAI-score from the patient`s perspective has been reported as 10 mm (equivalent to 1 using numeric response scale) (12).

Levels of C-reactive protein (CRP), measured by local methods, were also registered at each visit. We defined all values <5 mg/L (the lower detection limit) as 3 mg/L.

The women`s physical function was assessed at each visit, using the Bath Ankylosing Spondylitis Functional Index (BASFI). The BASFI contains ten patient-reported items, each describing the ability to perform a certain practical task, scored by numeric response scale (from 0 = "easy" to 10 = "impossible") (10). The average gives the overall index score, between 0 ("no functional impairment") and 10 ("maximal functional impairment").

In addition, self-reported scores of the RAND 36-Item Health Survey (RAND-36) were collected at each visit. The RAND-36 is composed of 36 questions in eight health related dimensions, which results in one score in each dimension with a value 0-100 (where 100 =

"best possible health") (13). We studied three of the dimensions: Physical functioning, bodily pain and mental health.

Information about medication was collected at each visit. We divided medication into non-steroidal anti-inflammatory drugs (NSAIDs), prednisolone, synthetic disease modifying antirheumatic drugs (DMARDs) and biological DMARDs.

Data and statistical analysis. In order to study how disease activity changed during and after pregnancy, we used a linear mixed model with BASDAI-scores as dependent variable and time (seven time points, visit 0-6) as fixed factor. The reference time point was visit 4 (six weeks postpartum). We used a three level model where visits were nested within pregnancies and pregnancies were nested within women. We did additional analyses including the covariates "NSAIDs in pregnancy" (yes/no), "prednisolone in pregnancy" (yes/no), "sulfasalazine in pregnancy" (yes/no) and "tumor necrosis factor inhibitor in pregnancy" (yes/no) in the mixed model analyses, each at a time.

CRP-values, scores of BASFI and the chosen RAND-36 dimensions at each time point were also analyzed in a linear mixed model. Normality of residuals was checked by inspection of quantile-quantile plots. CRP-values originally had a skewed distribution, but we obtained normality through log transformation. Analyzing both original data and log transformed data, results were substantially the same, and for simplicity we present results from the not transformed CRP-data.

We considered a 2-sided $P \leq 0.05$ statistically significant. For statistical analysis, we used SPSS for Windows version 22.0.

Ethics. This study was approved by the Regional committee for medical and health research ethics in 2013 (REK 2013/649). Women included in RevNatus have given their

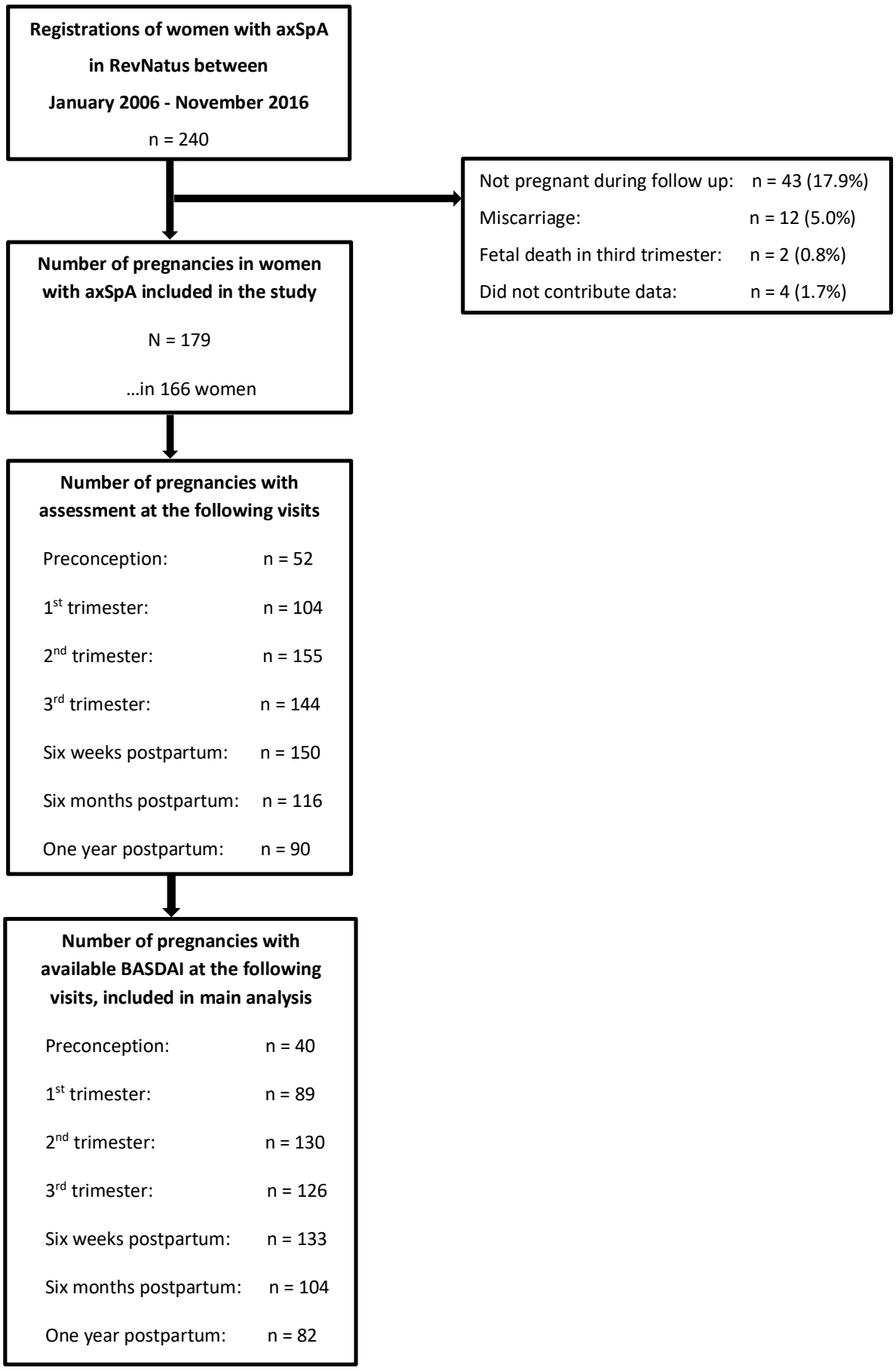
informed written consent and were treated according to established standards and not subject to any experimental treatment. The study is in compliance with the Helsinki Declaration.

RESULTS

Patient inclusion data. RevNatus included 197 pregnancies in women with axSpA between January 2006 and November 2016. In addition, the registry included 43 women with axSpA who did not conceive. Twelve pregnancies ended in miscarriage and two in fetal death. In four pregnancies, data relevant for analyses was missing. As shown in Figure 1, the study included a total of 179 pregnancies in 166 women with axSpA. One woman had three pregnancies and eleven women had two pregnancies. Two women pregnant with twins were included, after confirming that results of analyses were substantially the same when excluding twin pregnancies.

Not all women had data from all time points. The mean number of visits per pregnancy was 4.5. Only 40 women (22%) had data from the preconception-visit.

Figure 1. Flow chart showing inclusion data and data available for main analysis



Demographics, disease characteristics and breastfeeding. The study population consisted of women with axSpA with a median age of 31 years (range 21-41 years) and median disease duration of 5 years (range 0-21 years).

Swollen joints were found in pregnancy in 35 women. Most of these women had one or two swollen joints. Table 1 shows demographics and disease characteristics reported in first trimester, and the proportion of women breastfeeding.

Table 1. Characteristics of study population in first trimester

Basic characteristics	**Mean (S.D.) or n/N (%)**
Age in years	30.6 (4.1)
Disease duration in years	5.9 (4.7)
Body mass index	25.0 (4.6)
Smoking	9/179 (5.0)
Nulliparous[1]	90/179 (50.3)
Clinical characteristics	**n/N (%)**
HLA-B27 positive	89/115 (77.4)
History of peripheral joint affection	51/166 (30.7)
History of psoriatic skin disease	9/166 (5.4)
History of inflammatory bowel disease[2]	14/166 (8.4)
History of uveitis	23/166 (13.9)
Breastfeeding	**n/N (%)**
Breastfeeding six weeks after delivery	122/150 (81.3)
Breastfeeding six months after delivery	72/116 (62.1)
Breastfeeding one year after delivery	24/90 (26.7)

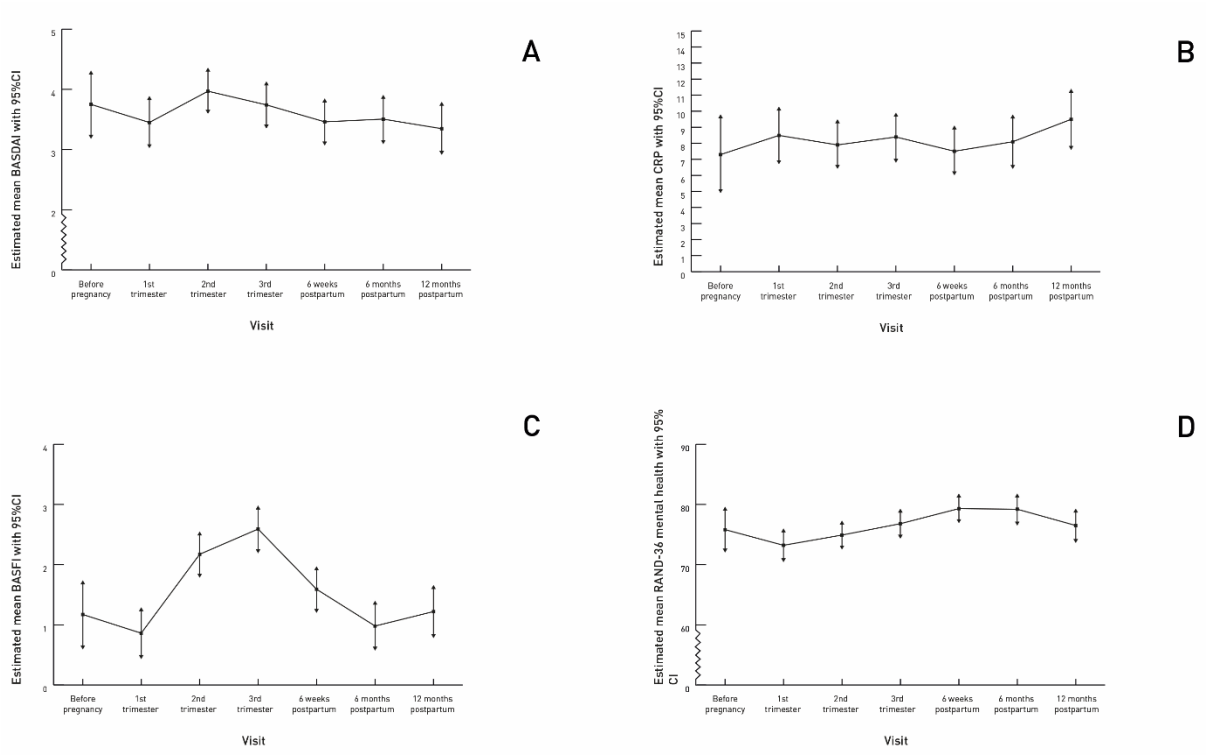
[1]Never given birth to live child [2]Crohn`s disease (n=8), ulcerative colitis (n=4) and unspecified inflammatory bowel disease (n=2)

Evaluation of disease activity according to BASDAI and CRP. Analyzing BASDAI-values from seven time points (visit 0-6) before, during and after pregnancy in a linear mixed model, we found low and relatively stable disease activity throughout the study period, see Figure 2. However, there was a significant relationship between disease activity and time point (P = 0.029). Disease activity was highest in second trimester, significantly higher than six weeks postpartum (mean BASDAI 3.97 vs. 3.46, P = 0.005). The lowest disease activity was found one year postpartum (mean BASDAI 3.35).

In second trimester 45% of the women had active disease (BASDAI ≥4). Among women with data from both second trimester and six weeks postpartum, 42% had a decrease in BASDAI ≥1 and 22% had an equivalent increase in BASDAI, while the rest had smaller changes in either direction.

Analyzing CRP-values in a linear mixed model, demonstrated low, stable CRP-levels throughout the study period and no significant relationship between CRP-level and time point in study period. Estimated mean CRP was lowest before pregnancy (mean CRP 7.3), highest one year postpartum (mean CRP 9.5), and showed no peak in second trimester (mean CRP 7.9). Figure 2 shows changes in BASDAI and CRP throughout the study period (panel A and B).

Figure 2. Estimated mean BASDAI (A), CRP (B), BASFI (C) and RAND-36 mental health (D) with 95%CIs before, during and after pregnancy



Evaluation of physical functioning and aspects of quality of life. BASFI-values were highest in third trimester, corresponding to lowest functionality. Analyzing BASFI-values from all time points in a linear mixed model, we found that functionality in second and third trimester was significantly worse than six weeks postpartum (mean BASFI 3.2 vs. 2.6, P = 0.001 and mean BASFI 3.6 vs. 2.6, P < 0.001). In line with this result, the physical functioning-score of RAND-36 was significantly lower in second and third trimester compared to six weeks postpartum (mean physical functioning 63.1 vs. 71.0, P < 0.001 and mean physical functioning 54.5 vs. 71.0, P < 0.001). Functionality one year after delivery was similar with functionality before pregnancy.

The women reported considerable pain throughout the study period, with worst reported pain in second trimester. At this time point, bodily pain-scores were significantly lower than six weeks after delivery (mean RAND-36 bodily pain 44.3 vs. 49.6, P = 0.014).

Reported mental health was significantly better six weeks postpartum than in all time points in pregnancy. We found the largest difference in RAND-36 mental health between first trimester and six weeks postpartum (mean mental health 73.2 vs. 79.3, P < 0.001). Mental health-score decreased within one year postpartum, but remained higher than before pregnancy. Figure 2 shows changes in reported functionality and mental health (panel C and D).

Medication use before, during and after pregnancy. Table 2 shows the percentage of women using NSAIDs, prednisolone, synthetic and biological DMARDs, before, during and after pregnancy. The table also shows the percentage of women who discontinued one of these drugs before pregnancy.

About one fifth of the women used NSAIDs during pregnancy. The highest proportion was found in second trimester, the time point where disease activity was highest. When including "NSAIDs in pregnancy" as a covariate in the mixed model analysis, we found that women using NSAIDs had higher disease activity than women not using NSAIDs (P = 0.052). Mean BASDAI in second trimester was 4.76 in women using NSAIDs compared to 3.97 in women not using NSAIDs.

Women using prednisolone also had higher disease activity (P = 0.154). In women using prednisolone mean BASDAI in second trimester was 4.95 compared to 3.94 in women not using prednisolone. The proportion of women using prednisolone was stable, but with

the highest proportion (8%) in third trimester, coinciding with the lowest use of NSAIDs. Doses were mostly kept below 10 mg.

Though one third of the women had peripheral arthritis, only 19 (11%) used synthetic DMARDs before pregnancy. The proportion of women using synthetic DMARDs increased in first trimester, but from third trimester onwards the proportion was the same as before pregnancy. Nine women used sulfasalazine in pregnancy, three women with inflammatory bowel disease used azathioprine, while seven women used methotrexate before and after pregnancy. Women using sulfasalazine had slightly lower disease activity than women not using sulfasalazine (P = 0.633), with mean BASDAI in second trimester 3.74 in women using sulfasalazine compared to 4.00 in women not using sulfasalazine.

Of the women using biological DMARDs, all used tumor necrosis factor inhibitors (TNFi). While 78 women (44%) used TNFi before pregnancy, only eight women (5%) used TNFi in pregnancy. Among women using TNFi in pregnancy, four had inflammatory bowel disease and one had active peripheral arthritis. When including “TNFi in pregnancy” as a covariate in the mixed model analysis, we found that women using TNFi tended to have lower disease activity, but no statistically significant difference (P = 0.692). Mean BASDAI in second trimester was 3.59 in women using TNFi compared to 3.89 in women not using TNFi. One year postpartum 36 (40%) of the women used TNFi, mostly the same women who used TNFi before pregnancy.

In third trimester, almost 70% did not take any medication for their rheumatic disease. This proportion was less than 20% before pregnancy and only 13% one year

postpartum.

Table 2. Medication use before, during and after pregnancy

Medication	Discontinued 3-12 months before	Discontinued <3 months before	Discontinued at confirmed pregnancy	Used before pregnancy	Used in 1st trimester	Used in 2nd trimester	Used in 3rd trimester	Used 6 weeks after	Used 6 months after	Used 12 months after
	(N=179)	(N=179)	(N=179)	(N=179)	(N=104)	(N=155)	(N=144)	(N=150)	(N=116)	(N=90)
Synthetic DMARD	6 (3%)	0 (0%)	1 (1%)	19 (11%)	17 (16%)	20 (13%)	15 (10%)	17 (11%)	13 (11%)	8 (9%)
Biological DMARD	10 (6%)	28 (16%)	34 (19%)	78 (44%)	6 (6%)	6 (4%)	2 (1%)	28 (19%)	44 (38%)	36 (40%)
Prednisolone	NA	NA	NA	NA	6 (6%)	8 (5%)	12 (8%)	6 (4%)	8 (7%)	2 (2%)
NSAIDs	NA	NA	NA	NA	19 (18%)	36 (23%)	12 (8%)	38 (25%)	51 (44%)	49 (54%)
No steroids, NSAID or DMARD	NA	NA	NA	NA	60 (58%)	86 (55%)	100 (69%)	68 (45%)	24 (21%)	12 (13%)

[1]NA=not available.

DISCUSSION

Studying women with axSpA from before pregnancy to one year postpartum, we found stable, low disease activity. This despite the fact that the proportion of women without anti-inflammatory drugs in late pregnancy was 70%, compared to about 20% preconception. However, disease activity in second trimester was significantly higher than six weeks postpartum. At this time point 45% of the women had active disease (BASDAI ≥4).

This is so far the largest prospective study of disease activity during and after pregnancy in women with axSpA, and the first to use a linear mixed model.

The results of a prospective study of nine pregnant women with r-axSpA, were similar to ours (8). Studying 61 pregnant women with axSpA prospectively, van der Brandt et al also found highest disease activity in second trimester (7). Using ASDAS (Ankylosing

Spondylitis Disease Activity Score)-CRP, they were able to demonstrate a flare in pregnancy in 25% of the women. Opposite this, a small study retrospectively assessing ASDAS-CRP in women with r-axSpA before pregnancy and in late pregnancy, showed that the majority experienced decreased disease activity in pregnancy (9). Only assessing disease activity in third trimester, this study could have missed an increase in disease activity in second trimester. The retrospective design also makes the results less reliable, as is the case for the large study from 1998, which demonstrated no particular pattern of disease activity in pregnancy in women with r-axSpA (4).

According to the above mentioned study from 1998, 60% of the women with r-axSpA experienced a postpartum flare (4). Later, two small studies have also demonstrated deterioration postpartum (8, 9). Contrary to this, we found lower disease activity postpartum. This may be due to the fact that the majority of women restarted NSAIDs and about 40% of the women restarted TNFi. Overall, we cannot tell much about the natural course of the disease in the year after delivery, because of restart of medication in this period.

The question of whether the deterioration demonstrated in second trimester represents a “true” increase in disease activity midpregnancy, remains unanswered. The deterioration in second trimester could be related to the discontinuation of TNFi before/at confirmed pregnancy. NSAIDs on the other hand, were mostly discontinued after second trimester. Considering that the changes in BASDAI during pregnancy were so small, despite 40% of the women discontinuing TNFi, we cannot exclude a potential beneficial effect of pregnancy.

It has been argued that the increasing disease burden of women with axSpA in late pregnancy is due to the biomechanical changes of pregnancy (6). However, both BASDAI-scores and scores of RAND-36 bodily pain peaked in second trimester, not in third trimester, when the burden of biomechanical changes is worst. Functionality, on the other hand, was worst in third trimester. Förger et al demonstrated the same in a small prospective study from 2005 (5).

If the increased BASDAI-scores in second trimester represent increased inflammation, we would expect CRP-values to peak at the same time point. This was the case for women discontinuing TNFi at conception in the study of van der Brandt et al from 2017 (7). We did not find a peak in CRP in second trimester. One reason may be that our study population had generally lower CRP-values, which could make it more difficult to demonstrate changes throughout the study period. Surprisingly, we found highest estimated mean CRP one year postpartum. We found no indications of infections explaining this, but we do not have reliable data on infections. The changes in CRP throughout the study period were small and not statistically significant, and it is not possible to say whether they were clinically relevant.

We found that women using NSAIDs or prednisolone had higher disease activity. These women were probably prescribed these drugs because of active disease. Women using sulfasalazine or TNFi tended to have lower disease activity, but the differences were small and our study is not suited for evaluating effect of medication. We did not include basic characteristics, such as maternal age and parity, in the analyses. These factors were constant throughout the period and thus should not influence disease activity during follow-up.

As demonstrated by Förger at al (5), we found stable self-reported mental health throughout the study period, with better mental health postpartum than before pregnancy. This is important to communicate to women with axSpa considering motherhood.

The most important strengths of our study are the prospective design, the size of the study and the statistical method. The mixed model-approach made it possible to study how disease activity developed throughout a time period in the same subjects. The method allows missing data as long as they are missing at random, and thus contributed to our large study population. A model where visits are nested within pregnancies and pregnancies are nested within women, takes into account that measurements within the same woman are correlated. Thus, we could include women with more than one pregnancy.

Another strength of our study is that all women were diagnosed and treated by a rheumatologist in the Norwegian public health care system, securing proper diagnosis and equal health services. The study population was socioeconomically homogenous. The majority of the participants had stable incomes, were in relationships, and were Caucasian.

The main limitation of our study was that not all women had data from all time points. Only 22% of the women were included preconception. Women with low disease activity are probably less likely to be in contact with a rheumatologist before pregnancy. Consequently, missing values at the preconception-visit were not missing entirely at random, and disease activity at this time point might be overestimated. If this were the case, we cannot exclude a more evident deterioration between the preconception-visit and second trimester. In addition, the preconception-visit was the visit least clearly defined, theoretically occurring any time between one year and one week before conception. We chose six weeks postpartum as reference point, since this was a well-defined non-pregnant time point with few missing BASDAI-scores.

When the analysis was performed, about 10% of the women had not yet completed follow-up postpartum. These registrations were missing at random.

Most Norwegian women with axSpA are included in RevNatus. There are possibly some women with low disease activity in general practice, less likely to be included in the register, resulting in a selection of women with higher disease activity in our study. On the other hand, since miscarriage and fetal death may be associated with high disease activity, excluding women who experienced miscarriage or fetal death could have resulted in a selection of women with lower disease activity. However, looking further at these women, we found that the twelve women who experienced miscarriage had a mean BASDAI of 2.1 at the last registration before the miscarriage, lower than the women included in the study.

ASDAS-CRP has several favorable properties compared to BASDAI, and is now the recommended disease activity measure in axSpA. While ASDAS-CRP, like BASDAI, contains subjective patient-reported items, these are weighted, and combined with the objective inflammatory marker CRP. We would have preferred to use ASDAS-CRP, but until 2015 the total BASDAI-score was the only disease activity measure registered in RevNatus in women with axSpA. To date no disease activity measure for axSpA has been validated in pregnant women. This is a limitation of all studies on the subject of axSpA in pregnancy.

We cannot exclude that women with nr-axSpA react differently to pregnancy than women with r-axSpAAS, or that women with psoriasis or inflammatory bowel disease react differently than women without such comorbidities. However, the subpopulations with relevant comorbidities were too small for analyses with sufficient statistical power, and we did not have access to information about the women`s radiographs.

CONCLUSION

In the largest prospective study to date exploring disease activity during pregnancy in women with axSpA, we found that the majority experienced stable, low disease activity. In accordance with two previous studies, we found a small increase in disease activity in second trimester. Future research on pregnancy in women with axSpA should differentiate between subgroups of the disease, and aim to include objective assessment of inflammation.

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DISCLOSURE STATEMENT

The authors declare no conflicts of interest.

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Trondheim; Sørlandet Hospital Kristiansand, Kristiansand; University Hospital of North Norway, Tromsø; Vestre Viken Hospital, Drammen; Østfold hospital, Moss.

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