Disease activity during and after pregnancy in women with axial spondyloarthritis: a prospective multicentre study

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Abstract

Objective. The aim was 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 DAS BASDAI. Scores assessed at each time point were analysed 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 the highest disease activity and worst self-reported pain in the second trimester, when 45% of the women had active disease. At this time point, disease activity was significantly higher than 6 weeks postpartum (mean BASDAI 3.97 vs 3.46, \( P = 0.005 \)). Self-reported mental health was also stable, but significantly better 6 weeks postpartum than in the 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 the second trimester, but altogether low and stable in the period from planning pregnancy to 1 year after delivery.

Key words: axial spondyloarthritis, disease activity, pregnancy

Introduction

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

The mean prevalence of r-axSpA per 10 000 people has been estimated as 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 of nr-axSpA [3]. Onset most commonly occurs between 20 and 30 years of age, coinciding with women’s fertile age and thus affecting their experience of pregnancy.

Previous studies on disease activity of axSpA in pregnancy have shown divergent 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 attributable to biomechanical changes of pregnancy [5, 6]. A newly published prospective study with a validated disease activity measure demonstrated that 25% of 61 women with axSpA experienced a flare during pregnancy, most often in the second trimester [7]. Increased disease activity in the second trimester was also found in a small prospective study from 2004 [8], whereas 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 study disease activity prospectively during and after pregnancy in a large cohort of women with axSpA using a validated disease activity measure. In contrast 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.

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 12 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 Assessment of SpondyloArthritis International Society criteria for axSpA [10]. RevNatus does not differentiate 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, as follows: before conception (visit 0), in each trimester (visits 1–3) and at 6 weeks, 6 and 12 months after delivery (visits 4–6). Although 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. Enrolment was carried out by rheumatologists and nurses at the participating centres.

At each visit, disease activity was assessed using the BASDAI. The BASDAI is calculated from six patient-reported items: fatigue, back pain, peripheral joint pain and swelling, localized tenderness, duration of morning stiffness, and severity of morning stiffness [10]. Items are scored by numerical response scale (0–10). The scores for questions 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 the numerical response scale) [12].

Concentrations of 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 BASFI. The BASFI contains 10 patient-reported items, each describing the ability to perform a certain practical task, scored by numerical 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 NSAIDs, prednisolone, synthetic 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 the dependent variable and time (seven time points, visit 0-6) as a fixed factor. The reference time point was visit 4 (6 weeks postpartum). We used a three-level model, where visits were nested within pregnancies and pregnancies were nested within women. We carried out additional analyses including the covariates NSAIDs in pregnancy (yes/no), prednisolone in pregnancy (yes/no), SSZ in pregnancy (yes/no) and TNF inhibitor (TNFi) 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 analysed in a linear mixed model. Normality of residuals was checked by inspection of quantile–quantile plots. The CRP values originally had a skewed distribution, but we obtained normality through logarithmic transformation. Analysing both original data and logarithmically transformed data, results
were substantially the same, and for simplicity we present results from the non-transformed CRP data.

We considered a two-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 subjected to any experimental treatment. The study is in compliance with the Declaration of Helsinki.

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 Fig. 1, the study included a total of 179 pregnancies in 166 women with axSpA. One woman had three pregnancies and 12 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.

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 the first trimester, and the proportion of women breastfeeding.

Evaluation of disease activity according to BASDAI and CRP
Analysing 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 Fig. 2). However, there was a significant relationship between disease activity and time point ($P = 0.029$). Disease activity was highest in the second trimester, significantly higher than 6 weeks postpartum (mean BASDAI 3.97 vs 3.46, $P = 0.005$). The lowest disease activity was found 1 year postpartum (mean BASDAI 3.35).

In the second trimester, 45% of the women had active disease (BASDAI $\geq 4$). Among women with data from both the second trimester and 6 weeks postpartum, 42% had a decrease in BASDAI $\geq 1$ and 22% had an equivalent increase in BASDAI, while the rest had smaller changes in either direction.

Analysis of CRP values in a linear mixed model demonstrated low, stable CRP concentrations throughout the study period and no significant relationship between CRP level and time point in the study period. The estimated mean CRP was lowest before pregnancy (mean CRP 7.3 mg/l), highest 1 year postpartum (mean CRP 9.5 mg/l), and showed no peak in the second trimester (mean CRP 7.9 mg/l). Figure 2A and B shows changes in BASDAI and CRP throughout the study period.

Evaluation of physical functioning and aspects of quality of life
BASFI values were highest in the third trimester, corresponding to the lowest functionality. Analysing BASFI values from all time points in a linear mixed model, we found that functionality in the second and third trimesters was significantly worse than 6 weeks postpartum (mean BASFI 3.2 vs 2.6, $P = 0.001$ and mean BASFI 3.6 vs 2.6, $P < 0.001$, respectively). In line with this result, the physical functioning score of RAND-36 was significantly lower in the second and third trimesters compared with 6 weeks postpartum (mean physical functioning 63.1 vs 71.0, $P < 0.001$ and 54.5 vs 71.0, $P < 0.001$, respectively). Functionality 1 year after delivery was similar to functionality before pregnancy.

The women reported considerable pain throughout the study period, with the worst reported pain in the second trimester. At this time point, bodily pain scores were significantly lower than 6 weeks after delivery (mean RAND-36 bodily pain 44.3 vs 49.6, $P = 0.014$).

Reported mental health was significantly better 6 weeks postpartum than in all time points in pregnancy. We found the largest difference in RAND-36 mental health between the first trimester and 6 weeks postpartum (mean mental health 73.2 vs 79.3, $P < 0.001$). Mental health score decreased within 1 year postpartum, but remained higher than before pregnancy. Figure 2C and D shows changes in reported functionality and mental health.

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. Table 2 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 the second trimester, the time point when 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 the second trimester was 4.76 in women using NSAIDs compared with 3.97 in women not using NSAIDs.

Women using prednisolone also had higher disease activity ($P = 0.154$). In women using prednisolone, the mean
BASDAI in the second trimester was 4.95, compared with 3.94 in women not using prednisolone. The proportion of women using prednisolone was stable, but with the highest proportion (8%) in the third trimester, coinciding with the lowest use of NSAIDs. Doses were mostly kept <10 mg.

Although 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 the first trimester, but from the third trimester onwards the proportion was the same as before pregnancy. Nine women used SSZ in pregnancy, three women with IBD used AZA, and seven women used MTX before and after pregnancy. Women using SSZ had slightly lower disease activity than women not using SSZ ($P = 0.633$), with the mean BASDAI in the second trimester 3.74 in women using SSZ compared with 4.00 in women not using SSZ.

Of the women using biological DMARDs, all used TNFi. Although 78 women (44%) used TNFi before pregnancy,
only eight women (5%) used TNFi in pregnancy. Among women using TNFi in pregnancy, four had IBD 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 the second trimester was 3.59 in women using TNFi compared with 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 the third trimester, almost 70% did not take any medication for their rheumatic disease. This proportion was <20% before pregnancy and only 13% 1 year postpartum.

### Discussion

Studying women with axSpA from before pregnancy to 1 year postpartum, we found stable, low disease activity. This was despite the fact that the proportion of women without anti-inflammatory drugs in late pregnancy was 70%, compared with ~20% preconception. However, disease activity in the second trimester was significantly higher than at 6 weeks postpartum. At this time point, 45% of the women had active disease (BASDAI ≥ 4).

This is the largest prospective study so far 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 den Brandt et al. [7] also found the highest disease activity in the second trimester. Using ASDAS-CRP, they were able to demonstrate a flare in pregnancy in 25% of the women. In contrast to 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]. Assessing disease activity only in the third trimester, that study could have missed an increase in disease activity in the 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 attributable to the fact that the majority of women restarted NSAIDs, and ~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 the restarting of medication in this period.

The question of whether the deterioration demonstrated in the second trimester represents a true increase in disease activity midpregnancy remains unanswered. The deterioration in the second trimester could be related to the discontinuation of TNFi before/at confirmed pregnancy. NSAIDs, in contrast, were mostly discontinued after the 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 attributable to the biomechanical changes of pregnancy [6]. However, both BASDAI scores and scores of RAND-36 bodily pain peaked in the second trimester, not in the third trimester, when the burden of biomechanical changes is worst. Functionality, in contrast, was worst in the third trimester. Förger et al. [5] demonstrated the same in a small prospective study in 2005.

If the increased BASDAI scores in the 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 den Brandt et al. [7] in 2017. We did not find a peak in CRP in the second trimester. One reason might 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 the highest estimated mean CRP 1 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 SSZ or TNFi tended to have lower disease activity, but the differences were small, and our study is not suitable for evaluating the effect of medication. We did

### Table 1 Characteristics of study population in first trimester

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>30.6 (4.1)</td>
</tr>
<tr>
<td>Disease duration, mean (s.d.), years</td>
<td>5.9 (4.7)</td>
</tr>
<tr>
<td>BMI, mean (s.d.)</td>
<td>25.0 (4.6)</td>
</tr>
<tr>
<td>Smoking, n/N (%)</td>
<td>9/179 (5.0)</td>
</tr>
<tr>
<td>Nulliparous, n/N (%)</td>
<td>90/179 (50.3)</td>
</tr>
<tr>
<td>Clinical characteristics, n/N (%)</td>
<td></td>
</tr>
<tr>
<td>HLA-B27 positive</td>
<td>89/115 (77.4)</td>
</tr>
<tr>
<td>History of peripheral joint affection</td>
<td>51/166 (30.7)</td>
</tr>
<tr>
<td>History of psoriatic skin disease</td>
<td>9/166 (5.4)</td>
</tr>
<tr>
<td>History of IBD b</td>
<td>14/166 (8.4)</td>
</tr>
<tr>
<td>History of uveitis</td>
<td>23/166 (13.9)</td>
</tr>
<tr>
<td>Breastfeeding, n/N (%)</td>
<td></td>
</tr>
<tr>
<td>Breastfeeding 6 weeks after delivery</td>
<td>122/150 (81.3)</td>
</tr>
<tr>
<td>Breastfeeding 6 months after delivery</td>
<td>72/116 (62.1)</td>
</tr>
<tr>
<td>Breastfeeding 1 year after delivery</td>
<td>24/90 (26.7)</td>
</tr>
</tbody>
</table>

*Never given birth to live child. bCrohn’s disease (n = 8), ulcerative colitis (n = 4) and unspecified IBD (n = 2).*
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 et 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 socio-economically homogeneous. 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 the second trimester. In addition, the preconception visit was the visit least clearly defined, theoretically occurring any time between 1 year and 1 week before conception. We chose 6 weeks postpartum as a reference point because this was a well-defined non-pregnant time point with few missing BASDAI scores.

When the analysis was performed, ~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 contrary, as miscarriage and fetal death might 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 12 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 favourable properties compared with BASDAI and is now the recommended disease activity measure in axSpA. Although 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 the possibility that women with nr-axSpA react in a different way to pregnancy compared with women who have r-axSpA, or that women with psoriasis or IBD react in a different way from women without such co-morbidities. However, the subpopulations with relevant co-morbidities 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 the 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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**Table 2. Medication use before, during and after pregnancy.**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Used before pregnancy</th>
<th>Used in first trimester</th>
<th>Used in second trimester</th>
<th>Used in third trimester</th>
<th>Used 6 weeks after pregnancy</th>
<th>Used 6 months after pregnancy</th>
<th>Used 12 months after pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic DMARD</td>
<td>6 (3)</td>
<td>10 (6)</td>
<td>19 (11)</td>
<td>34 (19)</td>
<td>60 (35)</td>
<td>86 (53)</td>
<td>100 (68)</td>
</tr>
<tr>
<td>Biological DMARD</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>NA</td>
<td>28 (16)</td>
<td>78 (44)</td>
<td>19 (10)</td>
<td>60 (35)</td>
<td>86 (53)</td>
<td>100 (68)</td>
</tr>
<tr>
<td>No CS, NSAID or DMARD</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values are given as n (%), NA: not available.
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