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Disease activity of psoriatic arthritis during and after pregnancy: A prospective multicenter study

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ABSTRACT

Objective To study disease activity in women with peripheral psoriatic arthritis (PsA) during and after pregnancy. Previous knowledge on this topic is sparse.

Methods The study included 108 pregnancies in 103 women with PsA from a Norwegian nationwide register. Disease activity was assessed prospectively at seven time points before, throughout and after pregnancy with the disease activity scores DAS28-CRP-3 and BASDAI. Scores assessed at each time point were analyzed in a linear mixed model. We did additional analyses with "tumor necrosis factor inhibitor (TNFi) in pregnancy" as covariate. The same statistical method was used to study self-reported physical function, pain and mental health.

Results About 75% of the women were in remission or had low disease activity during and after pregnancy according to DAS28. Although altogether stable, we found that disease activity decreased in pregnancy and increased within six months postpartum. Disease activity six months postpartum was significantly higher than six weeks postpartum (mean DAS28 2.71 vs. 2.45, p=0.016). Women using TNFi in pregnancy had significantly lower disease activity than women not using TNFi (mean DAS28 six months postpartum 2.22 vs. 2.72, p=0.043). BASDAI-scores were also low and stable, but significantly higher six months postpartum than six weeks postpartum (mean BASDAI 3.69 vs. 2.95, p=0.013).

Conclusion Studying women with PsA, we found that disease activity was highest six months postpartum, but altogether low and stable in the period from planning pregnancy to one year after delivery. Women using TNFi in pregnancy had significantly lower disease activity.

Significance and Innovations

- In the largest prospective study on psoriatic arthritis and pregnancy to date, disease activity was altogether low and stable from preconception to one year postpartum

- However, disease activity decreased in pregnancy and increased significantly by six months postpartum, returning to baseline by twelve months postpartum

- Disease activity was significantly lower in women with psoriatic arthritis using tumor necrosis factor inhibitors in pregnancy

Psoriatic arthritis (PsA) is an inflammatory joint disease associated with the skin disease psoriasis (1). As member of the spondyloarthritis (SpA) family, PsA may present with predominantly peripheral or axial involvement. Reported prevalence of PsA varies between <0.01% and 0.67% (2).

While a study from 2008 confirmed that women with rheumatoid arthritis (RA) achieve remission in pregnancy, though less frequently than previously described (3), little is known about PsA and pregnancy. The only prospective study on the subject demonstrated improvement in pregnancy and deterioration postpartum (4). This study is from 1992, before the widespread use of biological disease-modifying antirheumatic drugs (DMARD). Two small retrospective studies have later shown diverging results concerning disease activity during pregnancy in PsA (5, 6).

In the present study, the main aim was to prospectively study disease activity in women with peripheral PsA from preconception to one year postpartum using validated disease activity measures. Changes in self-reported physical function, pain and mental health were also explored.

PATIENTS AND METHODS

The RevNatus-register

RevNatus is a nationwide Norwegian observational register, run by the National advisory unit on pregnancy and rheumatic diseases since 2006. The register follows women with inflammatory rheumatic diseases from preconception until one year postpartum.

Patient population

This study comprised women included in RevNatus with the diagnosis PsA between January 2006 and October 2017. All women fulfilled the the CASPAR (Classification of Psoriatic Arthritis) criteria (7).

Women with psoriasis and predominantly peripheral arthritis are included in RevNatus as PsA. Patients with mainly axial involvement are included as axial spondyloarthritis (axSpA).

We included women with data from at least one time point in pregnancy, thus excluded women who had not conceived at the time of analyses. Pregnancies not resulting in live birth were also excluded.

Data collection and description of outcome variables

Ideally, women included in RevNatus have seven visits at their local rheumatology unit: Before pregnancy (visit 0), in each trimester (visit 1-3), and six weeks, six months and twelve months after delivery (visit 4-6). Though the aim is to include women when planning pregnancy, the majority were in fact enrolled by their rheumatologist when they were already pregnant.

At each visit, local rheumatologists evaluated disease activity using Disease Activity Score-28-CRP-3 (DAS28-CRP-3). DAS28-CRP-3 consists of a 28-joint count for swelling and tenderness combined with the level of C-reactive protein (CRP) (8). CRP was measured by local methods. Values <5 mg/L (the lower detection limit) were defined as 3 mg/L in the calculation. DAS28-CRP-3 is considered the best clinimetric index to evaluate disease activity in pregnant women with RA (9).

According to the European League Against Rheumatism (EULAR), we defined four disease categories of the DAS28-CRP-3-score: Remission (DAS28 ≤ 2.6), low disease activity (2.6 < DAS28 ≤ 3.2), moderate disease activity (3.2 < DAS28 ≤ 5.1) and high disease activity (DAS28 > 5.1) (10).

We used Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) to assess axial disease activity. 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, and gives a final score of minimum 0 ("no disease activity") and maximum 10 ("maximal disease activity") (11).

Activity of psoriasis was measured using Psoriasis Area and Severity Index (PASI). PASI combines the assessment of severity of the psoriasis lesions and area affected into a single score in the range 0 ("no disease") to 72 ("maximal disease") (12).

Self-reported scores of the RAND 36-Item Health Survey (RAND-36) and the Modified Stanford Health Assessment Questionnaire (MHAQ) were collected at each visit. 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 dimensions: Physical functioning, bodily pain and mental health. MHAQ is composed of one question from each of the original eight HAQ categories, all describing the ability to perform a certain practical task on a 4-point Likert scale (from 0 = "without difficulty" to 3 = "unable to do") (14).

Finally, information about medication was collected at each visit. We divided medication into non-steroidal anti-inflammatory drugs (NSAIDs), prednisolone, synthetic and biological DMARD.

Data and statistical analysis

We estimated the distribution of EULAR disease activity categories at the different time points. To analyze the longitudinal course of the disease from preconception until one year postpartum, , we used a linear mixed model with DAS28-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 "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.

Likewise, we analyzed scores of BASDAI, MHAQ and the chosen RAND-36 dimensions in a linear mixed model. MHAQ-values originally had a skewed distribution, but we obtained normality through logarithmic transformation. For simplicity we present results from the not transformed MHAQ-data, since results were substantially the same when analyzing both original data and logarithmically transformed data. We checked normality of residuals by inspection of quantile-quantile plots. We considered a 2-sided $P \leq 0.05$ statistically significant. For statistical analysis, we used SPSS version 24.

Ethics

The Regional Committee for Medical and Health Research Ethics approved this study (REK 2013/649). Women included in RevNatus have given their informed written consent. They were treated according to established standards and were not subject to any experimental treatment. The study is in compliance with the Helsinki Declaration.
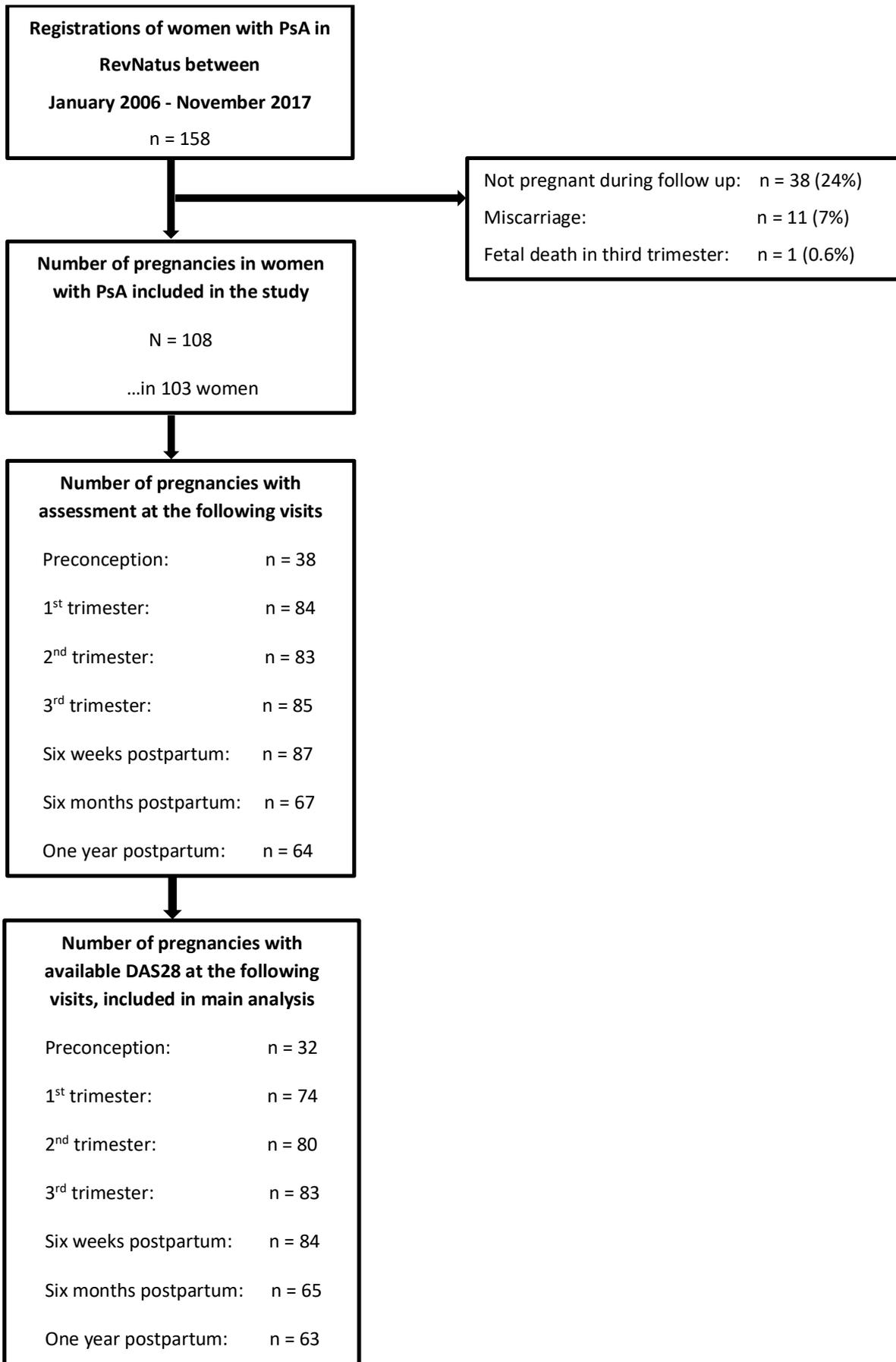
RESULTS

Patient inclusion data

Between January 2006 and October 2017 RevNatus included 120 pregnancies in women

with PsA. In the same period, 38 included women with PsA did not conceive. We excluded

twelve pregnancies that did not result in live birth. As shown in Figure 1, the present study

comprised a total of 108 pregnancies in 103 women with PsA. Five women contributed with

two pregnancies, and one woman had twins.

As shown in Figure 1, not all women attended all visits. Mean number of visits per

pregnancy was 4.4. The preconception-visit had lowest attendance (35%).

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

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┌─────────────────────────────────┐
│ Registrations of women with PsA in│
│        RevNatus between          │
│  January 2006 - November 2017    │
│            n = 158               │
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┌──┐
│ Not pregnant during follow up: n = 38 (24%)   │
│ Miscarriage: n = 11 (7%)   │
│ Fetal death in third trimester: n = 1 (0.6%)   │
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┌─────────────────────────────────┐
│ Number of pregnancies in women  │
│  with PsA included in the study  │
│                                  │
│            N = 108               │
│                                  │
│        ...in 103 women           │
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┌─────────────────────────────────┐
│  Number of pregnancies with      │
│ assessment at the following visits│
│                                  │
│ Preconception:          n = 38   │
│ 1st trimester:          n = 84   │
│ 2nd trimester:          n = 83   │
│ 3rd trimester:          n = 85   │
│ Six weeks postpartum:   n = 87   │
│ Six months postpartum:  n = 67   │
│ One year postpartum:    n = 64   │
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┌─────────────────────────────────┐
│  Number of pregnancies with      │
│ available DAS28 at the following │
│  visits, included in main analysis│
│                                  │
│ Preconception:          n = 32   │
│ 1st trimester:          n = 74   │
│ 2nd trimester:          n = 80   │
│ 3rd trimester:          n = 83   │
│ Six weeks postpartum:   n = 84   │
│ Six months postpartum:  n = 65   │
│ One year postpartum:    n = 63   │
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Demographics, disease characteristics and breastfeeding

All included women had peripheral arthritis. Mean age was 31 years and mean disease duration 8 years. Table 1 shows characteristics of the study population and the proportion of women breastfeeding. HLA-B27 status was unknown in the majority of the women, since HLA-B27 was not collected in RevNatus before 2016.

**Table 1. Characteristics of study population in first trimester and proportion breastfeeding. Mean (SD) and n/N (%).**

Basic characteristics	
Age in years	30.9 (4.7)
Disease duration in years	7.6 (6.1)
Body mass index	24.0 (5.4)
Smoking	11/84 (13.1%)
Nulliparous[1]	55/108 (50.9%)
Clinical characteristics	
Axial involvement[2]	13/108 (12%)
Uveitis	3/108 (3%)
Breastfeeding	
Breastfeeding six weeks after delivery	63/87 (72.4%)
Breastfeeding six months after delivery	32/67 (47.8%)
Breastfeeding one year after delivery	13/64 (20.3%)

[1]Never given birth to live child [2]Registered with sacroilitis without information about diagnostic imaging

Evaluation of disease activity

Figure 2 demonstrates the distribution of the EULAR disease activity categories at each time

point. About 75% of the women were in remission or had low disease activity from planning

pregnancy to twelve months postpartum.

**Figure 2. Percentage of women in each European League Against Rheumatism category
before, during and after pregnancy**

*pp=postpartum
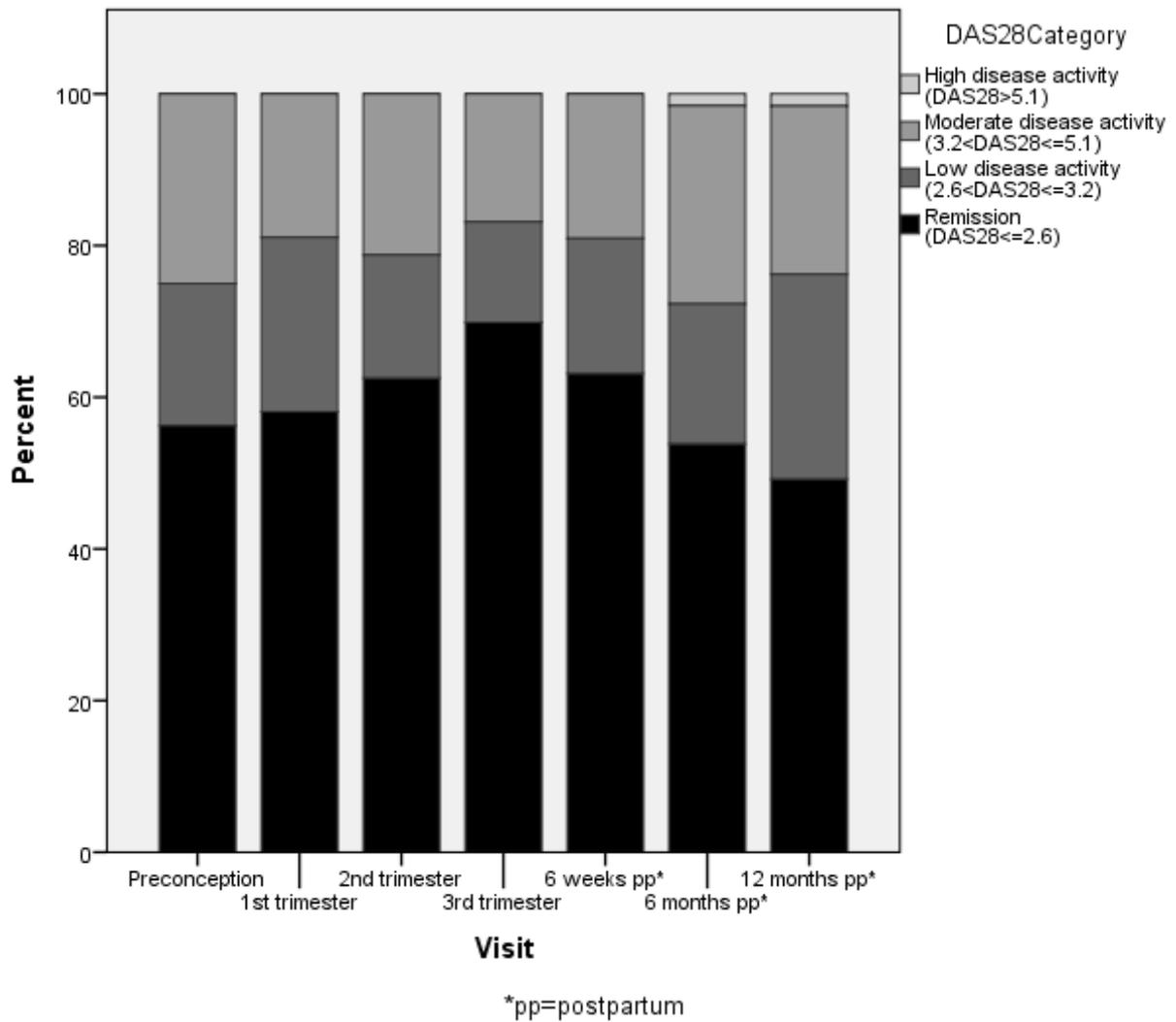
Mean DAS28-CRP-3-values were low and relatively stable, see Figure 3 (panel A). However, the variation in disease activity between time points was statistically significant (p=0.018). After amelioration in pregnancy, disease activity increased after delivery, with a peak six months postpartum. At this time point, disease activity was significantly higher than the reference time point six weeks postpartum (mean DAS28-CRP-3 2.71 vs. 2.45, p=0.016).

Of the 53 women with data from both late pregnancy and six months postpartum, 21% had a postpartum increase in DAS28-CRP-3 ≥1.2 and 2% had an equivalent decrease. Most of the remaining women experienced a smaller increase in disease activity.

Figure 3. Mean (A) DAS28-CRP-3; (B) RAND-36 Bodily Pain scale; (C) RAND-36 Physical Functioning scale; (D) RAND-36 Mental Health scale, with 95% CI before, during and after pregnancy
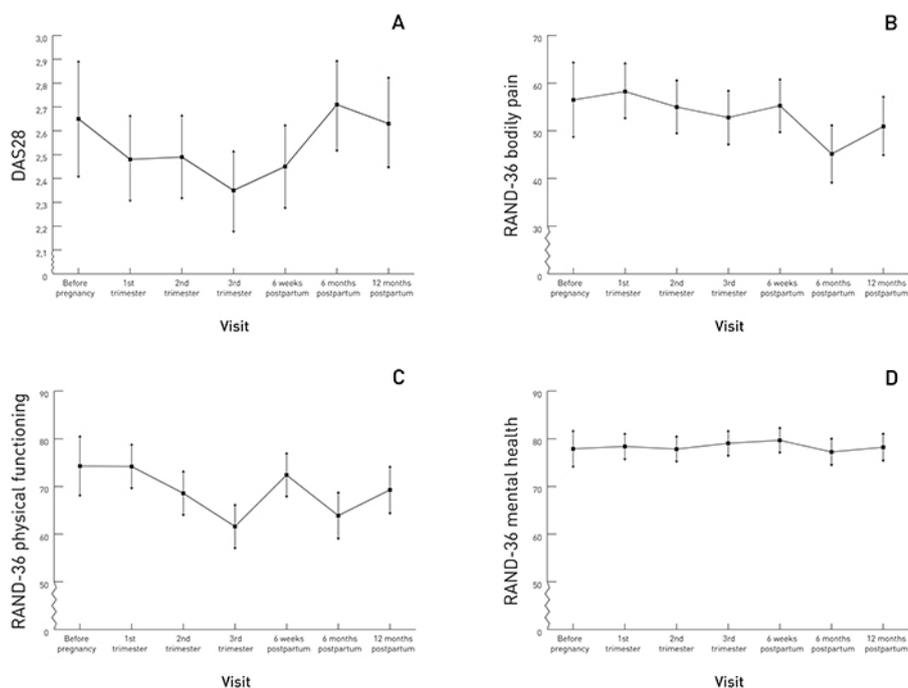
As for peripheral disease, axial disease activity was low and stable, yet with a statistically significant relationship between disease activity and time point (p=0.033). Again, the scores were highest six months postpartum, significantly higher than six weeks postpartum (mean BASDAI 3.69 vs. 2.95, p=0.013).

Altogether activity of psoriasis was low, with PASI=0 in 54% of the assessments and PASI >10 in only three women.

Evaluation of physical function and aspects of quality of life

Functionality was worst in third trimester and six month after delivery, both estimated by RAND-36 physical functioning and MHAQ. Changes in RAND-36 physical functioning was statistically significant, with mean physical functioning 73.3 at the reference time point six weeks postpartum compared with 62.4 in third trimester (p<0.001) and compared with 64.7 six months postpartum (p=0.001). MHAQ was never higher than 0.50, and there were no significant changes.

Self-reported pain was worse six months after delivery compared with six weeks after delivery, with significantly lower RAND-36 bodily pain-scores (mean bodily pain 46.0 vs. 56.1, p=0.003).

Self-reported mental health was good and stable, with highest RAND-36 mental health-scores six weeks after delivery (mean mental health=79.8). Figure 3 shows changes in reported pain, functionality and mental health throughout the study period (panel B, C and D).

Medication use before, during and after pregnancy

Table 2 shows the proportion of women using NSAIDs, prednisolone, synthetic and

biological DMARD, before, during and after pregnancy, and the proportion of women who

discontinued one of these drugs prior to pregnancy.

The proportion of women using DMARD (synthetic, biological or both) decreased

from 58% preconception to about 17% in late pregnancy.

In the year before pregnancy, 37 out of 108 women discontinued a synthetic

DMARD, of whom 30 had used methotrexate. In pregnancy, only 17 out of 85 women used

synthetic DMARD. All women except one used sulfasalazine. Including "sulfasalazine in

pregnancy" as covariate in the mixed model analysis, we found that women using

sulfasalazine had higher disease activity (p=0.057): Mean DAS28-CRP-3 six months

postpartum was 2.97 in women using sulfasalazine compared with 2.65 in women not using

sulfasalazine. Of the 22 out of 64 women using synthetic DMARD one year postpartum, the

majority had restarted methotrexate. One fourth of the women who did not breastfeed six

months postpartum, had restarted methotrexate.

Among women using biological DMARD, one used an interleukin inhibitor, the rest

used tumor necrosis factor inhibitors (TNFi). While 39 women (36%) used TNFi before

pregnancy, only seven women (8%) used TNFi in pregnancy. When including "TNFi in

pregnancy" as covariate, we found that women using TNFi had significantly lower disease

activity (p=0.043): Six months postpartum, mean DAS28-CRP-3 was 2.22 in women using

TNFi opposed to 2.72 in women not using TNFi. By six months postpartum, 27 women (40%)

used TNFi, mostly the same women using TNFi before pregnancy.

Six months postpartum, mean DAS28-CRP-3 was 2.78 in women using prednisolone

in pregnancy compared with 2.68 in women not using prednisolone (p=0.529). Both the

proportion of women on prednisolone and the proportion on NSAIDs were highest when disease activity peaked six months postpartum. Prednisolone-doses were usually kept between 5-10 mg, both in and after pregnancy.

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=108)	(N=108)	(N=108)	(N=108)	(N=84)	(N=83)	(N=85)	(N=87)	(N=67)	(N=64)
Synthetic DMARD	26 (24%)	4 (4%)	7 (6%)	54 (50%)	17 (20%)	13 (16%)	13 (15%)	16 (18%)	18 (27%)	22 (34%)
Biological DMARD	9 (8%)	15 (14%)	8 (7%)	39 (36%)	7 (8%)	4 (5%)	1 (1%)	20 (23%)	27 (40%)	26 (41%)
Prednisolone	NA	NA	NA	NA	11 (13%)	14 (17%)	13 (15%)	14 (16%)	15 (22%)	13 (20%)
NSAIDs	NA	NA	NA	NA	6 (7%)	7 (8%)	7 (8%)	18 (21%)	20 (30%)	16 (25%)
No prednisolones, NSAID or DMARD	NA	NA	NA	NA	47 (56%)	52 (63%)	55 (65%)	31 (36%)	8 (12%)	12 (19%)

[1]NA=not available.

DISCUSSION

We found that about 75% of women with PsA were in remission or had low disease activity from planning pregnancy to one year after delivery. This despite DMARD-use decreasing from 58% prior to pregnancy to only 17% in late pregnancy. Although altogether stable, disease activity decreased in pregnancy and increased significantly six months postpartum, then returning to preconception state by one year postpartum.

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

Our results are in accordance with the only previous prospective study on PsA in pregnancy (4), and with a retrospective study of 42 women with PsA from 2017 (5). Both studies demonstrated improvement in pregnancy followed by deterioration postpartum. A case series from 2017 also found a tendency for flare postpartum, but a less clear pattern in pregnancy (6). None of these studies used validated disease activity scores, and direct comparison with our study is difficult.

A change in DAS28 of ≥1.2 is considered clinically meaningful (15). In our study, the largest difference in mean DAS28 was 0.36, found between third trimester (mean DAS28 2.35) and six months postpartum (mean DAS28 2.71). However, looking only at the women with data from both third trimester and six months postpartum, 21% experienced a clinically meaningful worsening according to the above definition, opposed to only 2% experiencing a clinically meaningful amelioration. The distribution of women into EULAR categories also showed deterioration between third trimester and six months postpartum, with the proportion of women in remission decreasing from 68% to 52%, while the proportion with moderate disease activity increased.

We note that the increase in disease activity six months postpartum was found despite 40% of the women using TNFi at this time point. Generally, we cannot tell much about the natural course of the disease in the year following pregnancy, because of restart of medication.

Our study is the first to demonstrate lower disease activity in women with PsA using TNFi in pregnancy. Van der Brandt et al. has previously demonstrated that among women with RA and axSpA respectively, those who discontinued TNFi at the time of positive pregnancy test had a relative risk for flare of more than 3 (16). However, no study has been designed for evaluating the disease modifying effect of TNFi in pregnancy. Women using

prednisolone or sulfasalazine tended to have higher disease activity. This is likely due to confounding by indication, since women receiving prednisolone and sulfasalazine respectively, probably were prescribed these drugs because of their high disease activity.

We did not include as covariates, basic characteristics, such as age and parity. These factors were constant and thus should not influence disease activity during follow-up.

While finding low activity of psoriasis during pregnancy is in accordance with previous studies, we did not find the previously demonstrated deterioration postpartum (17-19). However, PASI-scores were missing in half the visits and we did not perform a mixed model analysis. Assessment of PASI can be time-consuming, and we cannot exclude that more women with active skin disease lacked PASI-score.

Decreased functionality in third trimester has been demonstrated in both juvenile idiopathic arthritis (JIA), axSpA, RA and healthy pregnant women (9, 20-22). However, deMan et al. have demonstrated that the effect of pregnancy makes HAQ unsuitable for assessment of functionality in pregnant women (9). Studying women with PsA, we found an additional decrease in functionality when disease activity peaked six months postpartum. At the same time point, self-reported pain peaked. Opposed to this, previous studies have shown stable self-reported pain during and after pregnancy in women with axSpA and JIA (20-22). In accordance with previous studies on RA, axSpA and JIA (20-22), we found good self-reported mental health despite pain and decreased functionality.

The most important strengths of our study are the size of the study, the prospective design, and the statistical method. The mixed model-approach made it possible to study changes in disease activity over time. This analysis included subjects with missing data at one or more time point, thus including all available data. Furthermore, a complete case

analysis would have given unbiased results only if data were missing completely at random, while a mixed model analysis is unbiased under the less restrictive missing at random assumption. A model where visits are nested within pregnancies and pregnancies are nested within women, takes into account the correlation structure of the data.

Another advantage of our study was that all women were diagnosed and attended by rheumatologists in the public health care system, ensuring correct diagnosis and equal health services. Most of women were in relationships, with financial security, and were Caucasian, making up a socioeconomically homogenous study group.

The main limitation of our study was assessing disease activity in PsA using DAS28. PsA often affects distal interphalangeal joints and ankles (1), joints not counted in DAS28. Thus, DAS28 potentially underestimates disease activity in PsA. Many now prefer assessing joint affection in PsA with the DAPSA (Disease Activity Index for Psoriatic Arthritis) (23, 24). DAPSA is calculated from a 66-joint count for swelling and a 68-joint count for tenderness, patient global assessment, patient pain assessment and CRP. However, before the introduction of DAPSA in 2010, DAS28 was validated and commonly used in PsA (25-27). DAS28 is considered the best clinimetric index in pregnant women with RA (9), and has also been used to assess disease activity in PsA in pregnancy (5). Neither DAS28 nor DAPSA assess skin, entheses, dactylitis or axial involvement.

Using DAS28, our study might have underestimated the absolute disease activity at each time point. We still argue that our results regarding changes throughout the study period, with a flare six months postpartum, are valid. This is supported by the fact that BASDAI, MHAQ and self-reported pain peaked simultaneously with DAS28.

As for peripheral involvement, there is no instrument assessing the axial involvement of PsA validated in pregnancy. Both back pain and fatigue are common in pregnancy, and

could influence the validity of BASDAI in pregnant women. We would have preferred to use ASDAS (Ankylosing Spondylitis Disease Activity Score)-CRP. Including the inflammation marker CRP and weighing the subjective components, ASDAS-CRP is a more objective instrument for measuring axial disease than BASDAI (28). However, until 2015 BASDAI was the only assessment of axial disease in RevNatus.

Another weakness of our study was that not all women were assessed at all time points. Only one third 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 probably to some degree missing not at random, and disease activity at this time point might be overestimated. In addition, the preconception visit had a much wider time span than the other visits, as the time of registration might be a few weeks up to one year before conception. As reference point, we chose six weeks postpartum, a well-defined non-pregnant time point with few missing DAS28-scores.

About one fifth of the women had not yet completed follow-up postpartum at the time of analyses. These registrations were plausibly missing completely at random.

Most Norwegian women with PsA are included in RevNatus. There are possibly some women with low disease activity in general practice, less likely to be included in RevNatus, and our results may not be generalizable to these women.

Since miscarriage may be associated with high disease activity, only including pregnancies that resulted in live birth could have led to a selection of women with lower disease activity. However, looking further at the eleven women who miscarried, we found that they had a mean DAS28 of 1.8 at the last assessment before the miscarriage, lower than the women included in the study.

PsA is a heterogeneous disease, and this study did not include women with predominantly axial involvement and did not differ between subtypes of peripheral PsA (29). We cannot exclude that women with different subtypes of PsA react differently to pregnancy. RevNatus does not provide information about subtypes of PsA and our population was too small for subgroup analyses. However, subtypes of PsA often overlap, making subgroup analyses difficult even in larger populations.

CONCLUSION

In this large prospective study on disease activity of PsA in pregnancy, we found that the majority of women experienced stable, low disease activity. However, disease activity tended to decrease in pregnancy, increased significantly by six months postpartum, before returning to baseline by one year postpartum. Women using TNFi in pregnancy had significantly lower disease activity throughout the study period. Future research on pregnancy in women with PsA should include extended joint count (66/68 joints), and assessment of dactylitis, entheses, axial skeleton and psoriasis.

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