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

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ABSTRACT

Objective: We wanted to study disease activity in women with juvenile idiopathic arthritis (JIA) during and after pregnancy. Previous knowledge on this topic is sparse.

Methods: The study included 135 pregnancies in 114 women with JIA. Disease activity was assessed at seven time points before, throughout and after pregnancy with the disease activity score DAS28-CRP-3. Scores assessed at each visit were analyzed in a linear mixed model. The same statistical method was used to study self-reported physical function, pain and mental health.

Results: Almost 80% of the women were in remission or had low disease activity during and after pregnancy. Although disease activity was stable throughout the study period, we found that disease activity six weeks postpartum increased significantly compared to first trimester (DAS28 2.78 vs. 2.51, p=0.005) and third trimester (DAS28 2.78 vs. 2.56, p=0.011). Disease activity decreased significantly between six weeks and twelve month postpartum (DAS28 2.78 vs. 2.54, p=0.014). Self-reported mental health was significantly better six weeks postpartum than before pregnancy (SF-36 Mental health 80.7 vs. 76.5, p=0.039). Self-reported pain was stable. Physical function was significantly worse in third trimester of pregnancy than postpartum (MHAQ 0.57 vs. 0.39, p<0.001).

Conclusion: Studying women with JIA, we found that disease activity was highest six weeks postpartum, but altogether low and stable in the period from planning pregnancy to one year after delivery.

Key indexing terms: juvenile idiopathic arthritis - disease activity - pregnancy

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Running footline: JIA and disease activity in pregnancy

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatic disease in childhood, and affects twice as many girls as boys. A study from 2003 reported an incidence of JIA of 15 per 100 000 per year in Nordic countries (1). More than 40% of women with JIA have active disease or are on medication in fertile age (2, 3).

A well-designed study from 2008 confirmed that women with rheumatoid arthritis achieve remission in pregnancy, but less frequently than previously described (4). The only studies on disease activity in pregnancy in women with JIA date back to the 1990s, before biological disease-modifying antirheumatic drugs were available (5, 6). Both studies were based on questionnaires where women were asked in retrospect about disease activity during and after pregnancy. The majority reported lower disease activity in pregnancy, while about 50% reported higher disease activity postpartum.

The main aim of our study was to prospectively study disease activity in women with JIA during pregnancy and until twelve months postpartum using a validated disease activity measure. In addition, we wanted to explore the women`s self-reported physical function, 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 one year postpartum. The register was established at the Norwegian National advisory unit on Pregnancy and Rheumatic Diseases in 2006.

Patient population. The present study comprises women with JIA included in RevNatus in the period from 1st of January 2006 to 17th of November 2015. All women were diagnosed

by a specialist in rheumatology and according to the ILAR (International League of Associations for Rheumatology) criteria for JIA (7). RevNatus does not contain data on JIA subtypes.

All women with JIA who contributed data from at least one time point in the period from first trimester to one year after delivery were included in the study. We excluded women who did not conceive within one year after inclusion and women who had a miscarriage.

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 three times postpartum; at six weeks, six months and twelve months after delivery (visit 4-6). The objective is that all women in fertile age diagnosed with an inflammatory rheumatic disease are told to contact their rheumatology unit when planning pregnancy, in order to be included in RevNatus. However, only a minority of the women with JIA were in fact enrolled preconception. Thus, not all women attended all visits. Enrollment was carried out by rheumatologists and nurses at each participating center.

At each visit, local rheumatologists evaluated disease activity using Disease Activity Score-28-CRP-3 (DAS28-CRP-3). The score is composed of a 28-joint count for swelling and for tenderness combined with the level of C-reactive protein (CRP) (8). DAS28 is a commonly used disease activity measure in patients with arthritis, and DAS28-CRP-3 is validated for use during pregnancy in women with rheumatoid arthritis (RA) (9). Levels of CRP were measured by local methods. All values < 5 mg/L (the lower detection limit) were defined as 4 mg/L in the calculation.

The European League Against Rheumatism (EULAR) defines four disease categories according to DAS28-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).

Self-reported scores of the medical outcomes study short form 36 items health survey (SF-36) and the Modified Stanford Health Assessment Questionnaire (MHAQ) were also collected at each visit. The SF-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) (11). We studied three of the 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”) (12).

Data on positivity for rheumatoid factor (RF IgM, RF IgG and/or RF IgA), anti-cyclic citrullinated peptide antibodies (ACPA) and anti-nuclear antibodies (ANA) were collected in first trimester.

Information about medication was collected at each visit. We divided medication into oral steroids, synthetic disease modifying antirheumatic drugs (DMARDs) and biological DMARDs.

Data and statistical analysis. We calculated the proportion of women in each EULAR disease activity category at each time point. In order to find out how disease activity changed during and after pregnancy we analyzed DAS28-CRP-3-scores from seven time points (visit 0-6) in a linear mixed model. The reference point was visit 4 (six weeks postpartum), a well-defined non-pregnant time point with few missing DAS28-scores. We used a three level model where visits were nested within pregnancies and pregnancies were

nested within women. We did additional analyses including the variables “oral steroids” (yes/no) and “sulfasalazine” (yes/no) in the mixed model analysis, each at a time.

Scores of MHAQ and the chosen SF-36 dimensions at each time point were also analyzed in a linear mixed model. We considered a 2-sided $P \leq 0.05$ statistically significant. For statistical analysis, we used SPSS for Windows version 22.0.

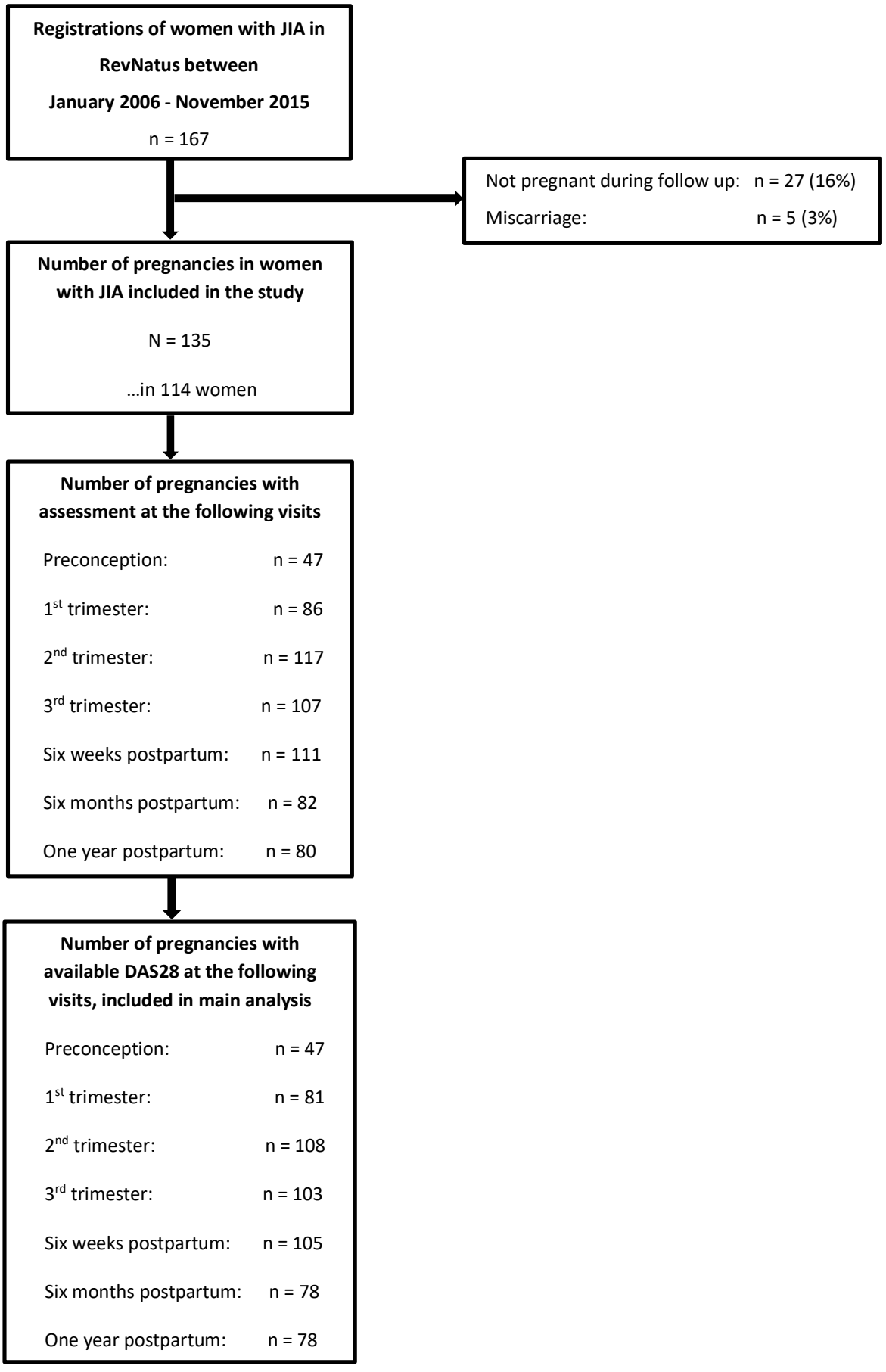
Ethics. The Regional Committee for Medical and Health Research Ethics approved this study in 2013 (REK 2013/649). All women included in RevNatus have given their informed written consent. They were treated according to established standards and were not subject to any experimental treatment. The study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

RESULTS

Patient inclusion data. In the period between January 2006 and November 2015 RevNatus included 140 pregnancies in women with JIA. In addition, the registry included 27 women with JIA who did not conceive within one year after inclusion. Of the 140 pregnancies registered, five pregnancies ended in miscarriage. As shown in Figure 1, the study included a total of 135 pregnancies in 114 women with JIA. One woman had three pregnancies and 19 women had two pregnancies. One woman was pregnant with twins. One women had no registered DAS28-scores, and was excluded from the main analysis.

Not all women had data from all time points. The mean number of visits per pregnancy was 4.3. Only 47 women (35%) had data from the preconception-visit and five women had no visits until after pregnancy.

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 JIA with a median age of 29 years (range 18 - 38 years*)* and median disease duration of 20 years (range 4 - 36 years*).* Almost half of the pregnancies were in previous nulliparous women. Table 1 shows demographics and disease characteristics reported in first trimester, and the proportion of women breastfeeding.

Table 1. Characteristics of study population

Basic characteristics (N =86)	**Mean (SD) or n/N (%)**
Age in years	28.7 (4.9)
Disease duration in years	20.0 (6.9)
Body mass index	24.4 (4.0)
Smoking	5 (5.9)
Nulliparous*	41 (47.7)
Clinical characteristics (N = 86)	**n/N (%)**
Rheumatoid factor present	11 (12.8)
ACPA** present	15 (17.4)
ANA*** present	11 (12.8)
History of enthesitis	1 (1.2)
History of sacroilitis	2 (2.3)
History of psoriatic skin disease	1 (1.2)
History of organ affection	1 (1.2)
Breastfeeding	**n/N (%)**
Breastfeeding six weeks after delivery	86/111 (77.5)

Breastfeeding six months after delivery	38/82 (46.3)
Breastfeeding one year after delivery	10/80 (12.5)

*Never given birth to live child **Anti-cyclic citrullinated peptide antibodies ***Anti-nuclear antibodies

Evaluation of disease activity according to DAS28-CRP-3. Figure 2 shows the percentage of women in each EULAR disease category at each time point. We found that almost 80% were in remission or had low disease activity from planning pregnancy to one year after delivery.

Analyzing DAS28-CRP-3-values from seven time points (visit 0-6) before, during and after pregnancy in a linear mixed model, we also found that disease activity was low and relatively stable throughout the study period. However, there was a significant relationship between disease activity and time point in the follow-up period ($p<0.001$). Disease activity six weeks after delivery was significantly higher than in first trimester (mean DAS28 2.78 vs. 2.51, $p=0.005$), third trimester (mean DAS28 2.78 vs. 2.56, $p=0.011$) and one year after delivery (mean DAS28 2.78 vs. 2.54, $p=0.014$). We found a non-significant decrease in disease activity between the preconception-visit and first trimester (mean DAS28 2.65 vs. 2.51). Figure 3 shows changes in disease activity throughout the study period (panel A).

A change in DAS28 of ≥ 1.2 is often regarded clinically significant (13). Of the women with data from both third trimester and six weeks postpartum, 22% had a postpartum increase in DAS28 ≥ 1.2 and 4% had a postpartum decrease in DAS28 ≥ 1.2, while the majority of the remaining had a smaller increase in disease activity.

Including "oral steroids" as a variable in the mixed model analysis, we found that women using oral steroids had significantly higher disease activity than women not using oral steroids (for example mean DAS28 six weeks postpartum 3.09 vs. 2.66, $p<0.001$).

Women using sulfasalazine also tended to have higher disease activity throughout the study period, but this was not a significant finding (results not shown).

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

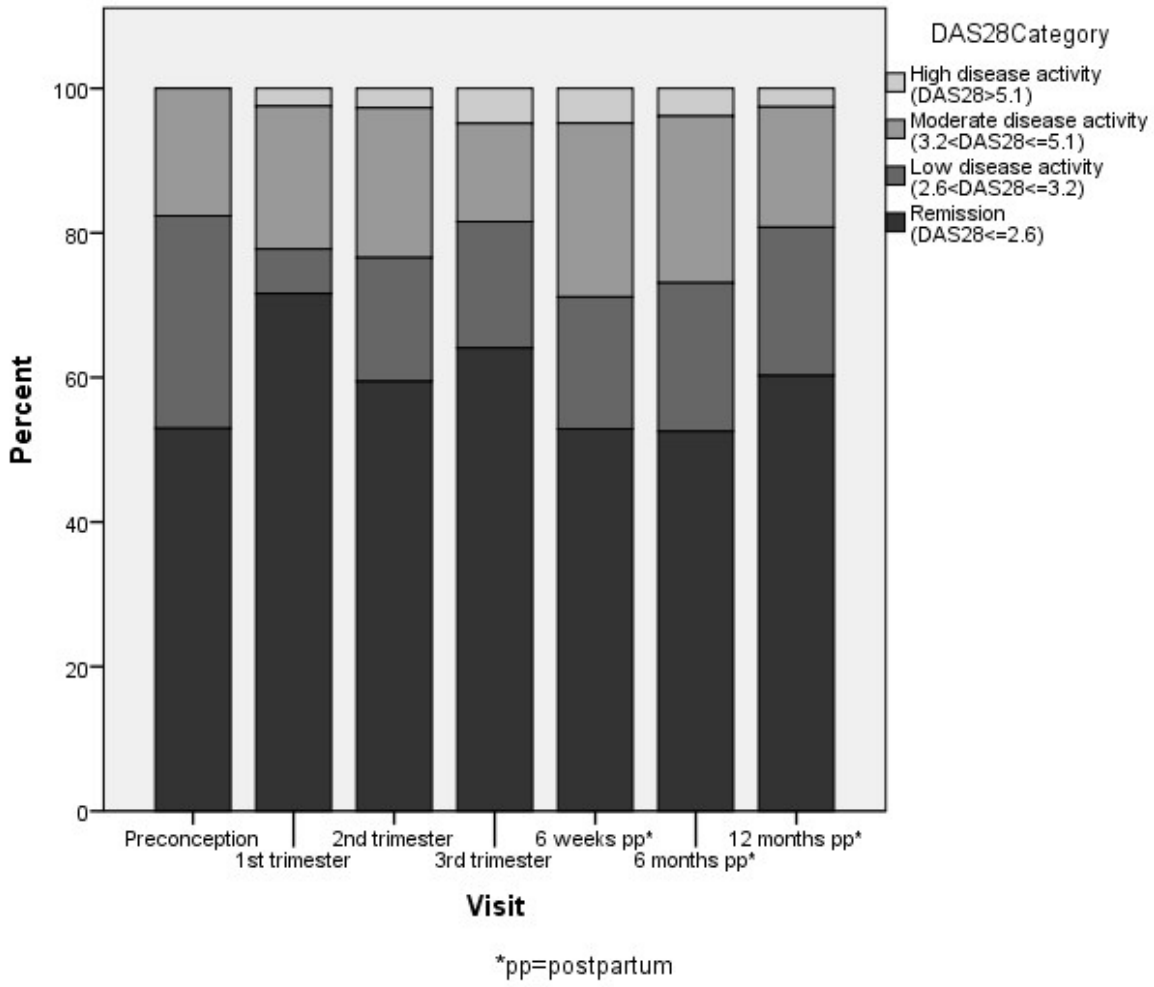
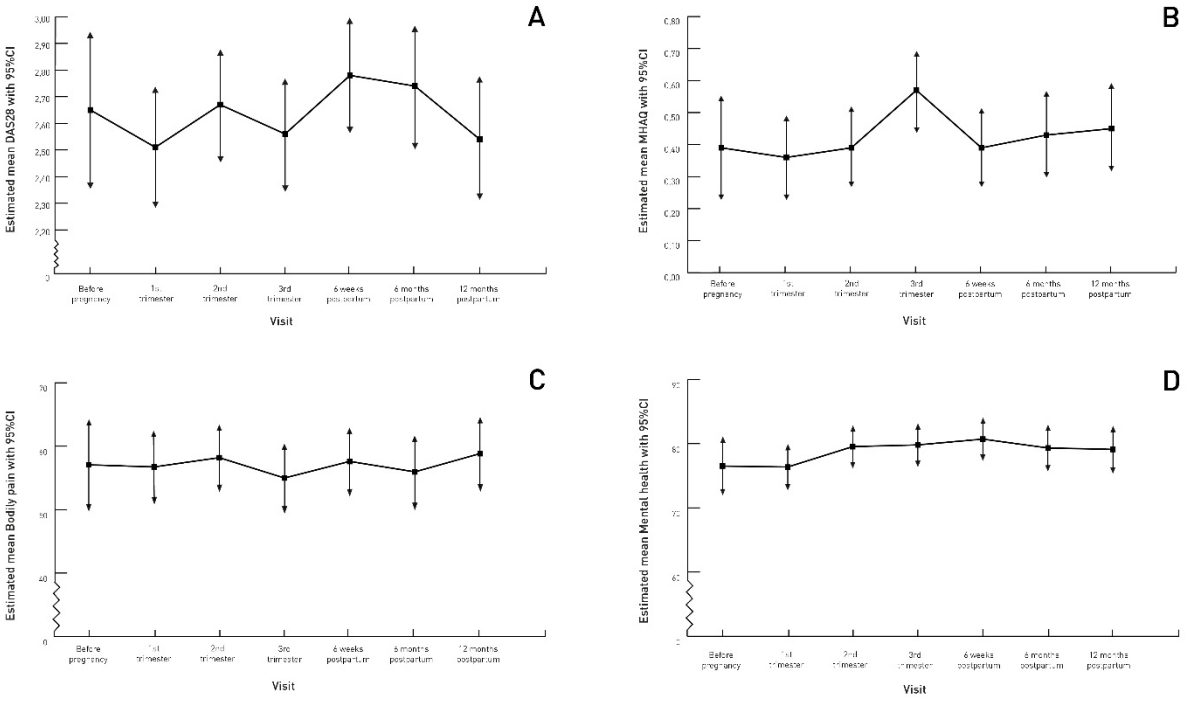


Figure 3. Estimated mean (A) DAS28-CRP3; (B) MHAQ; (C) SF-36 Bodily Pain scale; and (D) SF-36 Mental Health scale, with 95% CI before, during, and after pregnancy



Evaluation of physical function and aspects of quality of life. MHAQ-values were highest in third trimester, corresponding to lowest functionality. Analyzing MHAQ-values from all seven time points in a linear mixed model, we found that functionality in third trimester was significantly worse than six weeks postpartum (mean MHAQ 0.57 vs. 0.39, $p<0.001$). In line with this result, the Physical functioning-score of SF-36 was significantly lower in third trimester compared to six weeks postpartum (mean Physical functioning 60.8 vs. 72.8, $p<0.001$).

Bodily pain-scores were lowest in the third trimester of pregnancy (mean Bodily pain=55.0), corresponding to highest reported pain, but altogether reported pain was stable. The women reported significantly better mental health six weeks postpartum than before pregnancy (mean Mental health=80.7 vs. 76.5, $p=0.039$) and in first trimester (mean Mental

health 80.7 vs. 76.4, p=0.006). Figure 3 shows changes in reported functionality, pain and mental health throughout the study period (panel B, C and D).

Medication use before, during and after pregnancy. Table 2 shows the percentage of women using oral corticosteroids, synthetic DMARDs and biological DMARDs respectively, in the year before pregnancy, during pregnancy and in the year after delivery. The table also shows the percentage of women who discontinued one of these drugs before pregnancy.

The proportion of women using a DMARD (synthetic, biological or both) decreased from 55% preconception to about 22% in pregnancy.

In the year before pregnancy, 24 women discontinued a synthetic DMARD, of whom 20 had used methotrexate. Two of the women who discontinued methotrexate changed to hydroxychloroquine, the others stayed without a synthetic DMARD. Of the women discontinuing a synthetic DMARD before pregnancy, 21 women did so more than three months prior to conception.

Altogether 18% of all included women used a synthetic DMARD throughout pregnancy. Of these 80% used sulfasalazine, while the rest used hydroxychloroquine. One year postpartum 40% used a synthetic DMARD and more than half of these women used methotrexate, mostly the same women who used this drug prior to pregnancy. For about one third of the women who did not breastfeed six months postpartum, this was related to the restart of methotrexate.

Altogether 48 women discontinued a biological DMARD in the year prior to pregnancy. Of these women, 23 discontinued the drug more than three months prior to conception, 17 did so less than three months prior to conception, while 8 did so at confirmed pregnancy. Less than 5% of the women used a biological DMARD during pregnancy, of whom all used a TNFα-inhibitor (three out of five of these cases were women with uveitis). Most women

using a biological DMARD in the year before and/or during pregnancy used the same biological DMARD six and twelve months postpartum.

While 10 women (out of 47) used oral steroids at the preconception-visit, this number was 24 (out of 85) in first trimester and 30 (out of 81) six months postpartum. Prednisolone-doses before and during pregnancy were mostly kept below 10 mg daily. Postpartum doses were up to 30 mg daily.

Table 2. Medication use before, during and after pregnancy

Medication	Discontinued 3-12 months before (N=135)	Discontinued <3 months before (N=135)	Discontinued at confirmed pregnancy (N=135)	Used before pregnancy (N=135)	Used in 1st trimester (N=85)	Used in 2nd trimester (N=116)	Used in 3rd trimester (N=106)	Used 6 weeks after (N=110)	Used 6 months after (N=81)	Used 12 months after (N=79)
Synthetic DMARD	21 (16%)	2 (1%)	1 (1%)	34 (25%)	15 (18%)	21 (18%)	19 (18%)	19 (17%)	20 (25%)	32 (41%)
Biological DMARD	23 (17%)	17 (13%)	8 (6%)	52 (39%)	4 (5%)	5 (4%)	2 (2%)	27 (25%)	40 (49%)	39 (49%)
Oral steroids	NA	NA	NA	NA	24 (28%)	27 (23%)	28 (26%)	34 (31%)	30 (37%)	23 (29%)
No steroids or DMARD	NA	NA	NA	NA	50 (59%)	81 (70%)	64 (60%)	47 (43%)	24 (30%)	22 (28%)

*NA=not available

DISCUSSION

Studying women with JIA from before pregnancy to one year postpartum, we found that almost 80% were in remission or had low disease activity throughout the study period. This despite the fact that the proportion of women using DMARDs (synthetic, biological or both) decreased from 55% in the year prior to pregnancy to 22% during pregnancy. Altogether disease activity was stable, but we found that disease activity six weeks after delivery was significantly higher than in first trimester, third trimester and twelve months postpartum.

This is the first to prospective study of disease activity during and after pregnancy in women with JIA, and the first to use a validated disease activity score instead of questionnaires and hospital records.

Two previous, retrospective studies and one case series demonstrated that women in remission before pregnancy remained in remission during pregnancy and that more than half of the women with active disease at baseline experienced amelioration (5, 6, 14).

Our study population differed from those of previous studies: The majority had stable low disease activity, and many had planned pregnancies with treatment optimized at baseline and continued throughout pregnancy (22% used a DMARD). In the previous studies, more women had active disease at baseline and only one woman used a DMARD (5, 6). In a population with larger proportion of participants with active disease at baseline, it could be easier to detect a relative amelioration. However, we cannot exclude a potential beneficial effect of pregnancy in our population: With a large decrease in women on DMARDs, we would expect an increase in disease activity. Opposite, we found stable low disease activity, and even a small decrease in disease activity in first trimester compared to preconception.

The previous studies demonstrated a flare after delivery, occurring between three and twelve months postpartum (5, 6). A reason why they did not find the early flare demonstrated in our study, could be that the women were not examined as early as six weeks postpartum. In our study, the early flare may be underestimated, considering that the percentage of women using a biological DMARD increased from 2% to 25%. After six weeks postpartum, the percentage of women using a biological DMARD doubled, probably contributing to the decrease in disease activity between six weeks and one year postpartum. Overall, we cannot tell much about the natural course of the disease in the year after delivery, because of restart of DMARDs in this period.

A change in DAS28 of ≥ 1.2 is often regarded clinically significant (13). In our study, the difference in DAS28 between first trimester and six weeks postpartum, though statistically significant, was only 0.27. With the percentage of women in remission decreasing from 72%

to 53% in the same period, and the percentage with high disease activity doubling, we argue that this finding is clinically relevant despite the small change in estimated mean DAS28. The fact that 22% of the women with data from both third trimester and six weeks postpartum experienced clinically significant worsening according to the above definition, opposed to only 4% experiencing clinically significant amelioration, also supports that the increase in DAS28 postpartum was clinically relevant.

We found that women using oral steroids had significantly higher disease activity. These women were most probably prescribed steroids because of their high disease activity. Women using sulfasalazine also tended to have higher disease activity. One reason might be that women with the more serious disease were continuing DMARDs in pregnancy. We did not include basic characteristics, such as maternal age, disease duration and parity. These factors were constant throughout the period and thus should not influence disease activity during follow-up.

As expected, we found that functionality was worst in late pregnancy. Previous studies using HAQ have demonstrated the same in healthy pregnant women and pregnant women with RA (9, 15). As noted in these studies, it is not possible to distinguish the effect on functionality of pregnancy itself from the effect of the disease.

SF-36 has been used in a previous study of pregnant women with RA and ankylosing spondylitis (AS), demonstrating that women with RA experienced less pain during pregnancy while women with AS, like our study population, had unchanged Bodily pain-scores (16). Further, both women with RA and women with AS, like our population, reported stable mental health. Noteworthy, in our population we found a significant improvement in reported mental health six weeks after delivery, at the same time point where disease

activity was highest. Demonstrating a stable mental health is of importance when communicating with women considering motherhood.

The most important strengths of our study are the prospective design, the use of a validated disease activity score and the statistical method. The choice of DAS28-CRP-3 as disease activity score was based on the widespread use of DAS28 in chronic arthritis in adults and the validation of DAS28-CRP-3 in pregnant women with RA (9). In pediatrics, there is increasing use of the Juvenile Arthritis Disease Activity Score (JADAS) (1). JADAS has not been validated in adults, and not in pregnancy.

The mixed model-approach made it possible to study how disease activity developed throughout a time period in the same subjects. The choice of method contributed to our relatively large study population, since it allows missing data as long as they are missing at random. Choosing a model were visits were nested within pregnancies and pregnancies were nested within women, we took into account that measurements within the same woman were correlated. Thus, we could include women with more than one pregnancy. We included five women who only contributed with DAS28-scores post pregnancy, after confirming that results of analysis were substantially the same when excluding them (results not shown). One woman with twin pregnancy was included, also after confirming that results were substantially the same when excluding the twin pregnancy (results not shown). MHAQ-values originally had a skewed distribution, but we obtained normality through log transformation. Analyzing both original data and log transformed data in a linear mixed model, results were substantially the same (data not shown), and for simplicity we present results from the not transformed MHAQ-data. Normality of residuals was checked by inspection of quantile-quantile plots.

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.

Our study population was socioeconomically homogenous, as the majority of the women were in relationships, had stable incomes, and were Caucasian.

The main limitation of our study was that not all women had data from all time points. Only 35% of the women were included before conception. It is possible that women with less severe disease were 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. Also, there could be a tendency towards milder disease in women missing the early visits of pregnancy, contributing to an overestimation of disease activity in pregnancy. However, this would strengthen our finding that there was a significant increase in disease activity between pregnancy and six weeks postpartum. When the analysis was performed, 17% of the women had not yet completed the follow-up postpartum. These registrations were missing at random.

Selection-bias may potentially influence our results in several ways. Even though inclusion in RevNatus is the norm in Norwegian rheumatology units, some women in long term remission may be in care of their general practitioner and therefore not included in the register. This could result in a selection of women with higher disease activity in our study. On the other hand, our study might not have included the women with poorest health, since high disease activity, organ affection or comorbidities may exclude motherhood.

Our results cannot be directly transferred to countries with other health care systems. In countries with less focus on planning pregnancies in women with rheumatic diseases, disease activity would probably have been higher.

By narrowing the definition of visits (for example defining 1st trimester as between 8-12 weeks of pregnancy), data would be more precise. The multicenter design and the practicalities of planning consultations made this difficult. The preconception-visit was the visit least clearly defined and could theoretically be 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 DAS28-scores.

Another limitation of our study is that we did not have information about the women`s subtype of JIA. JIA subtypes have different pathophysiology (17), and may represent different patterns of disease activity during pregnancy. As shown in table 1, less than 4% in our population had spondyloarthritis (psoriatic arthritis and enthesitis-related arthritis combined) and only one woman had organ affection, while 13% were positive for RF. According to a Norwegian study on disease progression of JIA into adulthood (3), our study overestimated the proportion of patients positive for RF (3% in the study) and underestimated the proportion with spondyloarthritis and systemic JIA.

CONCLUSION

In this first study prospectively exploring disease activity during and after pregnancy in women with JIA, using a validated disease activity score, we found that the majority experienced low and relatively stable disease activity. A small, but significant increase in disease activity six weeks postpartum calls for tight follow-up of women with JIA in the first weeks after delivery. Future research on pregnancy in subgroups of JIA would be of interest.

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