Is Disease Activity in Rheumatoid Arthritis during Pregnancy and after Delivery Predictive for Disease Activity in a Subsequent Pregnancy?

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ABSTRACT. ***Objective.*** To determine whether disease activity in women with rheumatoid arthritis (RA) in 1 pregnancy is predictive for disease activity in a subsequent pregnancy.

Methods. In the Pregnancy-induced Amelioration of Rheumatoid Arthritis study, there are prospective data on 27 patients who participated twice. Improvement and deterioration is determined by changes in the Disease Activity Score in 28 joints.

Results. Only 4 patients (14.8%) had comparable disease courses in both pregnancies, whereas treatment remained mostly similar. In contrast, a flare postpartum after the first pregnancy was predictive for a flare after the second pregnancy ($p = 0.003$).

Conclusion. RA disease course in following pregnancies cannot be predicted based upon previous pregnancies. However, a flare postpartum seems to predict subsequent flares. (First Release December 1 2015; J Rheumatol 2016;43:22–5; doi:10.3899/jrheum.150565)

Keyword Indexing Terms:
RHEUMATOID ARTHRITIS DISEASE ACTIVITY PREGNANCY

Pregnancy is the only physiological condition in which rheumatoid arthritis (RA) remits spontaneously in about 50% of cases[1,2,3]. We previously reported in a prospective cohort study on pregnancy and RA that 48% of patients improved during pregnancy, based upon the Disease Activity Score in 28 joints (DAS28) according to the European League Against Rheumatism (EULAR) response criteria[3].

Some studies showed that improvement in the first pregnancy is predictive for improvement in the next pregnancy[1,4]. However, in these studies, assessment of the RA disease activity in the first pregnancies was retrospective and self-reported by the women[1].

Understanding the influence of pregnancy and especially the effect of subsequent pregnancies may provide more insight into the pathophysiological mechanisms underlying RA. Further, increased knowledge on the disease course of RA during subsequent pregnancies might also provide valuable information for daily clinical practice.

To our knowledge, the course of RA disease activity has not been prospectively studied during subsequent pregnancies and after delivery. The aim of our present study was to prospectively determine whether the RA disease activity course is similar in subsequent pregnancies and after delivery, and thereby to determine whether the disease activity course in following pregnancies can be predicted.

MATERIALS AND METHODS

Study population. Our study is embedded in the Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study, a nationwide prospective cohort study from the Netherlands[3]. From May 2002 to August 2008, 475 patients in total who met the 1987 revised criteria of the American College of Rheumatology[5] for RA were recruited by their rheumatologist, and from these, 369 were enrolled in the PARA study. Women were eligible for inclusion if they had a pregnancy wish or were already pregnant (in their first trimester). The PARA study is believed to be a good representation of the general Dutch pregnant RA population between 2002 and 2008. During the study period, 205 women conceived at least once[6]. There were data available on 27 female patients with RA who had 2 successful pregnancies until delivery resulting in a live birth.

Data collection. Data on disease activity and medication use were collected before conception, if possible, at each trimester during pregnancy (8–12, 18–22, and 28–32 weeks), and 3 times postpartum (6, 12, and 26 weeks)[3].

Disease activity. DAS28 was calculated based upon the number of swollen joints, the number of tender joints, and the level of C-reactive protein[7,8].

Improvement and deterioration of the disease activity during pregnancy were calculated as differences in DAS28 between first and second, first and third, or second and third trimesters. Preconception DAS28 was not used in the analysis because this was only available for 6 patients in both pregnancies. Improvement of the disease activity during pregnancy was defined as a decrease in DAS28 > 0.6 and deterioration as an increase in DAS28 > 0.6. Possible disease activity courses were categorized as improvement, deterioration, both improvement and deterioration, and no change. The limit of 0.6 was chosen because it is the lowest meaningful difference according to the EULAR response criteria[3,9]. In contrast to the EULAR response criteria, an initial DAS28 of ≥ 3.2 was not a prerequisite.

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Supported by the Dutch Arthritis Association (Reumafonds).

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Accepted for publication September 30, 2015.

Flares postpartum were calculated as an increase in DAS28 between the third trimester and any of the 3 timepoints postpartum of > 0.6.

Statistical analysis. For all subjects, descriptive statistics were calculated as numbers, percentages, means, and SD. A 2-sample Student t test was used to detect differences in mean disease activity scores. Binomial probability tests were used to analyze whether a flare after the first pregnancy was predictive for a subsequent pregnancy. P values < 0.05 were considered statistically significant. Statistical analyses were performed using STATA software version 13.1 for Windows.

Ethics. Our study is in compliance with the Helsinki Declaration. The Medical Ethics Committee at the Erasmus Medical Center Rotterdam, the Netherlands, approved the PARA study.

RESULTS

Participants. Descriptive statistics of the study population are shown in Table 1. In the first and second pregnancies, the mean maternal age was 31.2 years and 33.6 years, respectively (p < 0.007). Mean duration of RA was 6.5 years in the first pregnancy and 8.7 years in the second pregnancy group. In total, 70.4% of the patients were RF-positive, 55.6% were anti-CPP–positive, and 74.1% had erosive RA. General characteristics of the selected patients were comparable with the other patients in the PARA study (data not shown)[3].

Disease activity during pregnancy. Mean DAS28 changed during first pregnancy from 3.84 (first trimester) to 3.52 (third trimester) to 3.75 (12 weeks postpartum) and finally to 3.82 (26 weeks postpartum). The mean DAS28 during second pregnancy at those timepoints was 3.81, 3.55, 3.74, and 3.41, respectively. In the first pregnancy, in total 37.0% of the patients improved, 22.2% deteriorated, 22.2% both improved and deteriorated, and 18.5% had no change in disease activity. In the second pregnancy, these numbers were 37.0%, 22.2%, 14.8%, and 25.9%, respectively (Table 2). Only 4 patients (14.8%) had a comparable disease activity course during their first and second pregnancies, represented by asterisks in Table 2.

Disease courses in the first and second pregnancies are shown in Appendix 1.

Medication use during pregnancy. None of the pregnant women received methotrexate (MTX), biologicals, or hydroxychloroquine in the 3 months before conception or during pregnancy. Patients received prednisone, sulfasalazine (SSZ), both prednisone and SSZ, or no medication. In the first and second pregnancies, respectively, 14 (51.9%) and 12 patients (44.4%) did not receive any medication. Treatment and also the medication doses were overall similar in 22 patients (81.5%) in both pregnancies.

Flare postpartum. Twenty patients (74.1%) had a flare postpartum after their first pregnancy. In total, 17 patients (63.0%) had a flare after both pregnancies. The occurrence of a flare postpartum after the first pregnancy was predictive for a flare after the second pregnancy (p = 0.003). Three patients (11.1%) had no flare after both pregnancies. Three patients (11.1%) had a flare after their first pregnancy and no flare after their second pregnancy. In 4 patients (14.8%), the RA flared postpartum after their second pregnancy while it did not flare after their first pregnancy. The mean time span between 2 subsequent pregnancies in patients with and without a flare after the first pregnancy was 924 and 727 days, respectively (p = 0.07).

Medication use postpartum. Eleven patients (40.7%) restarted medication after both pregnancies, which they did not use during pregnancy, within 6 weeks after delivery. At 26 weeks, 18 (66.7%) and 22 patients (81.5%) had started additional medication after their first and second pregnancies, respectively. From these, 10 (37.0%) started with MTX or a

Table 1. Descriptive statistics of study population. Values are n (%) unless otherwise specified.

Characteristics	First Pregnancy, n = 27	Second Pregnancy, n = 27
Age, yrs, mean (SD)	31.2 (3.6)	33.6 (3.4)
Smoking	3 (11.1)	2 (7.4)
RA duration, yrs, mean (SD)	6.5 (5.6)	8.7 (6.0)
DAS28-CRP first trimester, mean (SD)	3.84 (1.11)	3.81 (1.22)
Patients with moderate and high disease activity, DAS28-CRP ≥ 3.2, at first trimester	19 (70.4)	17 (63.0)
Prednisone use during pregnancy	7 (25.9)	11 (40.7)
SSZ use during pregnancy	5 (18.5)	3 (11.1)
Both prednisone and SSZ use during pregnancy	1 (3.7)	2 (7.4)
No medication during pregnancy	14 (51.9)	11 (40.7)
	In Total	
RF-positive	19 (70.4)	
Anti-CCP–positive	15 (55.6)	
Erosion	20 (74.1)	
MTX use ever	17 (63.0)	

RA: rheumatoid arthritis; DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; SSZ: sulfasalazine; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide; MTX: methotrexate.

Table 2. No. patients in the disease course categories improvement, deterioration, both improvement and deterioration, and no change during first and second pregnancies. Values are n (%).

Disease Activity during Pregnancy	Improvement Second Pregnancy	Deterioration Second Pregnancy	Improvement and Deterioration Second Pregnancy	No Change Second Pregnancy	Total First Pregnancy
Improvement first pregnancy	2 (7.4)*	3 (11.1)	2 (7.4)	3 (11.1)	10 (37.0)
Deterioration first pregnancy	4 (14.8)	0 (0)*	0 (0)	2 (7.4)	6 (22.2)
Improvement and deterioration first pregnancy	2 (7.4)	2 (7.4)	1 (3.7)*	1 (3.7)	6 (22.2)
No change first pregnancy	2 (7.4)	1 (3.7)	1 (3.7)	1 (3.7)*	5 (18.5)
Total second pregnancy	10 (37.0)	6 (22.2)	4 (14.8)	7 (25.9)	27 (100)

* Similar disease courses in both pregnancies.

combination after their first pregnancy and 14 (51.9%) after their second pregnancy. Overall, treatment postpartum was different in 20 patients (74.1%).

DISCUSSION

To our knowledge, ours is the first prospective study that shows that the disease course in female patients with RA is different in subsequent pregnancies. In our present study, only 14.8% of the patients had a comparable disease activity course while treatment in both pregnancies remained mostly similar. These findings are in contrast to previous studies that claimed that if the disease activity improves during a pregnancy, improvement is likely to occur in subsequent pregnancies as well[1,4]. The most likely explanation for this discrepancy is the fact that in those studies, disease activity was retrospectively determined by self-report.

That the improvement rate in our study is lower (37%) than the 48% reported earlier in the PARA study[3] is probably the result of using different definitions. In our current study, we chose not to define improvement according to the EULAR response criteria because this would lead to a loss of a considerable number of subjects, since the prerequisite of an initial DAS28 ≥ 3.2. With the EULAR response criteria, 15 out of 35 pregnancies (43%) were classified as improvement. This does not differ from the 48% reported earlier ($p = 0.67$). Seventeen patients (63.0%) had a flare postpartum after both pregnancies. The occurrence of a flare postpartum after the first pregnancy was predictive for a flare after the second pregnancy ($p = 0.003$), despite the differences in treatment between both pregnancies.

Because we have shown that RA disease activity has a different course during subsequent pregnancies, it is tempting to speculate that fetal-related factors might be more important in the improvement of RA during pregnancy than pure maternal factors. The sex of the children was not associated in our current study with a certain disease activity course (data not shown). Previous studies have shown that incompatibility of HLA class II between mother and child seems to positively influence RA disease activity during pregnancy[10,11,12]. The HLA-related mechanisms were not analyzed because that was beyond the purpose of our article.

Finally, our study has some limitations. First, although in its kind it is a large (predominantly) descriptive study, a study with 27 subjects is still relatively small compared with others in this field. Nevertheless, the analysis on postpartum flare reached statistical significance. Second, in the majority, no data on preconception DAS28 were available because some patients were included in their first trimester. However, we have previously reported no significant difference between preconception and first trimester DAS28[6].

Our study shows that we cannot predict the RA disease course in subsequent pregnancies based on the disease course in the first pregnancy. Each pregnant patient with RA should be treated to achieve low disease activity without taking into account the disease course of a possible previous pregnancy. However, because the occurrence of flares after delivery in subsequent pregnancies seems to be related to previous flares, this phenomenon can be anticipated both by patients as well as their treating physicians.

ACKNOWLEDGMENT

We are grateful to all patients participating in the Pregnancy-induced Amelioration of Rheumatoid Arthritis study, as well as to the Dutch rheumatologists for their contributions. We thank Yaël de Man, Fleur van de Geijn, and all research assistants and laboratory workers for their help with data collection.

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APPENDIX 1. Different disease courses in the first and second pregnancies during the 3 trimesters of pregnancy. On the X-axis, the 3 measurement points during pregnancy are shown. The mean disease activity is depicted on the Y-axis as a mean DAS28-CRP (with standard errors). The black line represents the first pregnancy and the gray line the second pregnancy. Please bear in mind that because of the differences in disease course between first and second pregnancies in individual patients, the first and second pregnancies of the same patients are not always allocated to the same subfigure. (A) Improvement in 10 patients in the first and 10 in the second pregnancies. (B) Deterioration in 6 patients in the first and 6 in the second pregnancies. (C) Both improvement and deterioration in 6 patients in the first pregnancy and 4 patients in the second pregnancy. (D) No change during pregnancy in 5 patients in the first and 7 patients in the second pregnancies. DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein levels; 1st trim: first trimester of pregnancy; 2nd trim: second trimester of pregnancy; 3rd trim: third trimester of pregnancy.