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The Self-Administered Rheumatoid Arthritis Disease Activity Index (RADAI) is Less Accurate than DAS28-CRP as a Disease Activity Measure in Pregnancy

H. T. W. Smeele, J. Naterop, E. Röder, J. M. W. Hazes, and R. J. E. M. Dolhain

Objective. Disease Activity Score 28 (DAS28)–using the C-reactive protein (CRP) level has been validated to determine disease activity in rheumatoid arthritis (RA) patients during pregnancy. A self-administered questionnaire like Rheumatoid Arthritis Disease Activity Index (RADAI) has practical advantages over DAS28-CRP, and in this study, we aimed to validate the RADAI for use during pregnancy.

Methods. Patients were derived from a prospective cohort on RA and pregnancy (Pregnancy-induced Amelioration of Rheumatoid Arthritis study). To validate the RADAI as a disease activity measure, the disease course over time and the disease activity states were compared with the DAS28-CRP. Furthermore, the RADAI was compared with DAS28-CRP in predicting fertility and pregnancy outcomes. Finally, to test construct validity, correlation of both RADAI and DAS28-CRP with a biomarker (galactosylation of immunoglobulin G [IgG]) were determined and compared.

Results. In total, 269 patients were analyzed in this study. Mean RADAI scores showed a great decline in disease activity in the first trimester compared with DAS28-CRP (mean RADAI, −1.13; mean, DAS28-CRP, −0.04). Correlations between DAS28-CRP and RADAI scores were moderate to good ($0.44 < \rho < 0.71$). Agreement in disease states was low ($0.26 < \kappa < 0.51$). Time to pregnancy was different between disease states according to DAS28-CRP ($P = 0.03$), but not according to RADAI ($P = 0.56$). Only DAS28-CRP could predict birthweight (DAS28-CRP β-0.17, $P = 0.04$; RADAI β-0.09, $P = 0.10$). Both DAS28-CRP and RADAI were associated with galactosylation of IgG at specific time points, but only change in DAS28-CRP was correlated with change in galactosylation of IgG from preconception to pregnancy.

Conclusion. The RADAI could not be validated as a disease activity measure during pregnancy. DAS28-CRP remains the gold standard of measuring disease activity in pregnancy.

INTRODUCTION

Monitoring disease activity in rheumatoid arthritis (RA) and pregnancy should preferably be reliable and straightforward. Currently the Disease Activity Score in 28 joints using the C-reactive protein (DAS28-CRP) level and without a visual analogue scale general health is the only measure for disease activity in RA-patients that has been validated for use during pregnancy (1). The disadvantages of the DAS28-CRP are that it requires a blood sample and a physical examination. Therefore, the DAS28-CRP is time consuming, expensive, and, in some cases, unpractical. The self-administered Rheumatoid Arthritis Disease Activity Index (RADAI) questionnaire, consisting of past and current global disease activity, general pain, morning stiffness, and painful joint count, has been proven feasible and as a valid way to measure disease activity in RA outside pregnancy in clinical, health services, and epidemiologic research (2,3). The influence of pregnancy on the RADAI score has upon today only been studied in a low number of patients (4,5). The RADAI has an advantage over DAS28-CRP because it requires neither blood samples nor physical examinations.

Both fertility and pregnancy outcomes are impaired in RA patients (6–9). A higher DAS28-CRP has been shown to be associated with prolonged time to pregnancy (TTP) (8) and worse pregnancy outcomes, like lower birthweight (7). Impaired fertility and pregnancy outcomes are, among other things, related to disease activity as well as medication use.

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Several research groups have shown that increased galactosylation (glycosylation involving galactose) of immunoglobulin G (IgG) is associated with improvement of RA in pregnancy (10–12). Because of this observation, it has been suggested that galactosylation renders IgG less proinflammatory. Therefore, galactosylation of IgG could be considered an objective representation of the actual disease state and used as a biomarker for improvement of RA during pregnancy.

The primary aim of this study is to validate the RADAI during pregnancy. This will be performed in a cohort in which DAS28-CRP has already been validated as a disease activity measure and as a predictor for both fertility and pregnancy outcomes. To test criterion validity for the RADAI questionnaire in pregnancy, mean scores and disease activity states of the RADAI will be compared to those of the DAS28-CRP. Additionally, the RADAI is compared with DAS28-CRP in predicting fertility and pregnancy outcomes. Furthermore, to test construct validity, correlation of disease activity for both RADAI and DAS28-CRP with galactosylation of IgG will be determined and compared. RADAI scores will be considered valid when the disease course over time is comparable to that of the DAS28-CRP, the percentage of patients in certain disease activity states are comparable with DAS28-CRP, when it is as accurate as DAS28-CRP in predicting fertility and pregnancy outcomes and RADAI scores are associated with galactosylation of IgG. If the RADAI was validated during pregnancy, it could be used both for follow-up of patients who are incapable of traveling to an outpatient clinic and in online longitudinal studies involving RA and pregnancy.

PATIENTS AND METHODS

Patients. This study is embedded in the Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study, a prospective nationwide observational cohort study on pregnancy and RA. The PARA study recruited RA patients, according to the 1987 American College of Rheumatology criteria (13), between 2002 and 2010 (1). Patients who had a wish to conceive or who were already pregnant were recruited. This study was approved by the Erasmus MC ethics review board in compliance with the Helsinki declaration. All patients gave informed consent, were over 18 years of age, and had a good understanding of the Dutch language.

Data collection. In this study, patients were preferably visited before conception, during each trimester, and three times postpartum (at 6, 12, and 26 weeks). Medical history was taken at the first visit by interview. At all timepoints patients were interviewed by a member of the research team, filled in the RADAI questionnaire, blood was drawn, and CRP was determined. At every visit, serum was gathered and galactosylation of IgG was determined as described previously (14). The swollen and tender joints were determined according to the European League against Rheumatism (EULAR) guidelines, and DAS28-CRP was calculated (13). The RADAI questionnaire was not implemented at the start of the study but was introduced in 2004.

Birthweight and gestational age were recorded. Birthweight standard deviation scores (SDS) represent birthweight adjusted for gestational age and sex. Birthweight SDS were calculated using the sex-specific formulas as described by Niklasson et al (15).

Patients were eligible for the analysis on the correlation of the disease score, agreement of disease states, and galactosylation of IgG if they had both a RADAI and DAS28-CRP score on at least one time point, became pregnant, and did not have a miscarriage. For the analysis on birthweight, two extra exclusion criteria were implemented: twins and non-Caucasian. Patients who had both a RADAI and DAS28-CRP score before conception were eligible for the TTP analysis. For patients who participated twice in the cohort, only data of their first participation were included in the TTP analysis.

The TTP was calculated as the time elapsed between the day of the first attempt to conceive a child and the first day of the last menstrual period before pregnancy. In some cases, the couple succeeded within the first month. Therefore, for every participant, a fictitious date for the pregnancy was calculated—to make sure no negative values for the TTP were imputed—by adding 28 days to the start of the last menstrual period.

Disease activity states. Disease activity states for both the RADAI as well as for the DAS28-CRP were determined according to the literature (16,17). RADAI scores are described as low disease activity (less than 2.2), moderate disease activity (a RADAI score between or equal to either 2.2 or 4.9), and high disease activity (more than 4.9). DAS28-CRP was categorized according to the recommendations of the EULAR. Because no state of remission for the RADAI has been defined, the disease states of low disease activity and remission were combined for DAS28-CRP: low disease activity (DAS28-CRP less than or equal to 3.2), moderate disease activity (DAS28-CRP score greater than 3.2 or up to 5.1), and high disease activity (DAS28-CRP greater than 5.1).

Statistics. Firstly, to validate the RADAI as a disease activity score for RA patients in pregnancy, the course of time from prepregnancy until 6 months after delivery using RADAI was compared with DAS28-CRP. In line with previous literature (2,3), correlation was determined by Spearman's rank correlation. Also, because scales for DAS28-CRP and RADAI are different, a point increase or decrease in disease activity for DAS28-CRP does not indicate a similar change in disease activity for the RADAI. Therefore, SDS were calculated for every time point so as to compare scores directly. This was done by subtracting the mean score at preconception from the individual scores and then dividing these scores by the total SD. Secondly, both RADAI and DAS28-CRP were stratified into disease activity states as previously described.

Agreement in disease activity states was determined by κ statistic measurements. We accepted the following categories for κ values: 0-0.20 = no agreement, 0.21-0.39 = minimal agreement, 0.40-0.59 = weak agreement, 0.60-0.79 = moderate agreement, 0.80-0.90 = strong agreement, and above 0.90 = almost perfect agreement (18). Thirdly, to validate RADAI as a predictor for fertility and pregnancy outcomes, it was tested in explaining prolonged TTP and predicting birthweight (as expressed by birthweight SDS). These results were compared with those of DAS28-CRP. A multivariable Cox regression was performed including variables age, nulliparity, smoking, disease duration, rheumatoid factor (RF) status, anticitrullinated protein antibody (ACPA) status, non-steroidal anti-inflammatory drug (NSAID) use, prednisone use, sulfasalazine use, previous methotrexate (MTX) use, and disease activity. These variables were chosen in line with the literature (8). For disease activity, either the DAS28-CRP or RADAI scores were imputed in the analysis. Furthermore, a Kaplan-Meier survival analysis was executed for the explanation of prolonged TTP according to different disease states. Significance between the curves was tested using a log-rank test. The predictive value of the RADAI in the third trimester for birthweight was determined by a linear regression model, with birthweight SDS as dependent variables, and the results were compared with those of DAS28-CRP. Because parity and maternal age are important determinants of birthweight, these factors were corrected for (7). Fourthly, correlation between DAS28-CRP or RADAI and the percentage of galactosylation of IgG at specific time points were determined by using Spearman's rank correlations. Moreover change over time in galactosylation of IgG and change in disease activity were calculated, which was done by subtracting the scores from preconception and pregnancy (preconception to first trimester), during pregnancy (first trimester to third trimester), and between pregnancy and postpartum (third trimester to 12 weeks postpartum). Spearman's rank correlations between change in galactosylation of IgG and change in disease activity were determined. All statistical analyses were performed using Stata 15 (StataCorp LP).

RESULTS

Patients. The PARA study recruited 475 patients; initially, 373 patients were included in the study, but a total of 269 patients were eligible for analysis (Figure 1). The number of available patients for analysis are as follows: at preconception, n= 97; first trimester, n = 149; second trimester, n = 156; third trimester, n = 157; 6 weeks postpartum, n = 166; 12 weeks postpartum, n = 163; and 26 weeks postpartum, n = 165. The mean age (SD) of the patients was 32.2 (3.9) years, the duration of RA prior to conceive was 6.6 (6.1) years, and the mean birthweight was 3.287 (0.563) kg. A detailed description of this cohort is given in Table 1.

DAS28-CRP and RADAI mean and SDS. Before conception the RADAI shows a mean score of 3.54 (2.04) and the DAS28-CRP shows a mean score of 3.59 (1.19). Mean RADAI scores show a rapid decline in disease activity in the first trimester compared with DAS28-CRP scores (mean RADAI: –1.13, mean

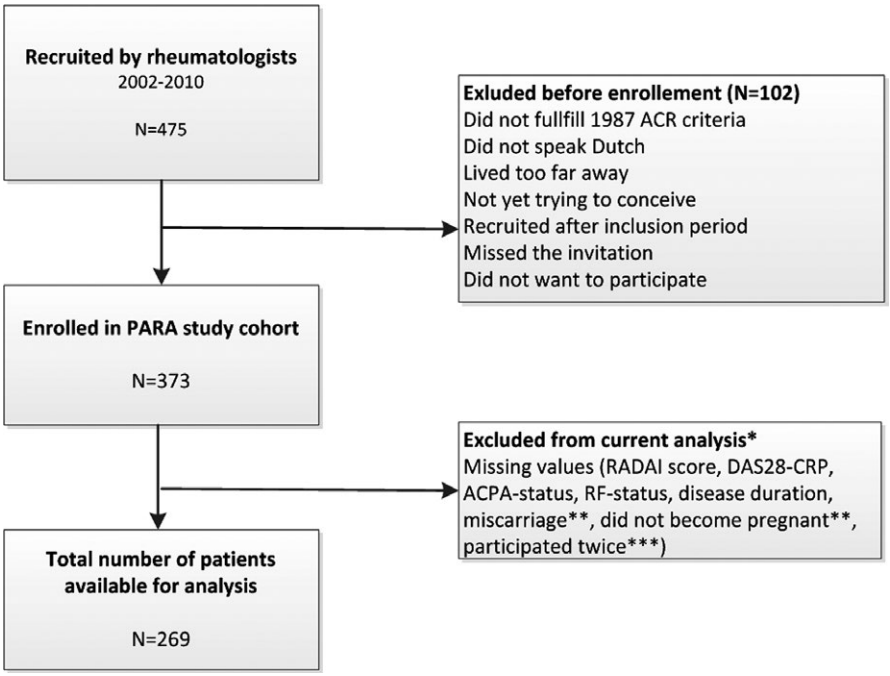

Figure 1. Flow chart showing the number of patient in the PARA study who were eligible for current analysis. * Number of missing variables differs between time-points. ** Included in time to pregnancy analysis. *** Included in all analysis except for the time to pregnancy analysis.

Table 1. Clinical and demographic features from 269 patients with rheumatoid arthritis and a wish to conceive and their successful pregnancies (n = 194)

Variable	Value
Mean age at delivery, years (SD)	32.2 (3.9)
Mean disease duration at first visit, years (SD)	6.6 (6.1)
RF positive, n (%)	199 (74)
ACPA positive, n (%)	177 (66)
Nulliparity, n (%)	141 (52)
Erosions (self-reported), n (%)	161 (60)
Gender of newborn	
• Male, n (%)	104 (54)
• Female, n (%)	90 (46)
Mean gestational age, weeks (SD)	38.6 (4.3)
Mean birth weight, kg (SD)	3.287 (563)
Birthweight SDS (SD)	−0.05 (1.05)
Medication during pregnancy (any use), n (%):	
Sulfasalazine only	27 (15)
Prednisone only	52 (27)
Hydroxychloroqine only	1 (1)
Prednisone + sulfasalazine	27 (15)
Hydroxychloroqine + sulfasalazine	3 (2)
No medication	78 (41)

Abbreviation: ACPA, anticitrullinated protein antibody; RF, rheumatoid factor; SDS, SD score.

DAS28-CRP: –0.04) (Figure 2A). For both RADAI and DAS28-CRP, the lowest mean values were observed during the third trimester (DAS28-CRP 3.29 (1.08); RADAI 2.12 (1.64). After delivery, a flare in disease activity was observed, with highest scores occurring 12 weeks postpartum (DAS28-CRP 3.68 [1.29]; RADAI 2.90 [1.69]).

SDS for RADAI and DAS28-CRP show the same trend as the mean scores. In the first trimester, the mean RADAI SDS dropped by –0.55 (0.82), whereas the mean DAS28-CRP SDS in pregnancy remained similar to the scores before conception (–0.03 [0.96]) (Figure 2B). RADAI SDS throughout pregnancy and postpartum sustained lower scores when compared with DAS28-CRP SDS.

Correlation of DAS28-CRP and RADAI. The correlations between DAS28-CRP and RADAI ranged between $0.44 < \rho < 0.71$, with correlation at preconception being $\rho = 0.44$, correlations during pregnancy $0.61 < \rho < 0.67$, and correlations postpartum $0.61 < \rho < 0.71$.

Agreement in disease activity states. Patients were stratified according to disease states. During pregnancy, more patients registered low disease activity levels according to the RADAI, especially in the first trimester (DAS28-CRP, 42%; RADAI, 55%; Figure 2C and 2D). The agreement on the disease activity states between RADAI and DAS28-CRP at all time points was low ($0.26 < \kappa < 0.51$).

TTP. Cox regression analysis (n = 109) with the following variables: disease activity (DAS28-CRP or RADAI score), age, nulliparity, smoking, disease duration, RF status. ACPA status, NSAID use, prednisone use, sulfasalazine use, and previous MTX use, showed that both high DAS28-CRP and high RADAI scores were associated with a reduced probability of a pregnancy. Hazard ratios per one-point increase of DAS28-CRP were 0.78 (95% confidence interval [CI]: 0.64-0.93, $P = 0.001$) and 0.86 for RADAI (95% CI: 0.76-0.98, $P = 0.02$). Hazard ratios for the SDS were DAS28-CRP (SDS) 0.74 (95% CI: 0.59-0.92, $P = 0.001$) and RADAI (SDS) 0.75 (95% CI: 0.59-0.95, $P = 0.02$).

Survival analysis curves (n = 109) show that disease activity states, according to DAS28-CRP, had a statistically significant different TTP ($P = 0.03$) (Figure 3B). Stratification into disease activity states of RADAI did not show the same pattern, and TTP was not statistically significant different between disease activity states according to RADAI ($P = 0.56$) (Figure 3A).

Birthweight. A linear regression with birthweight SDS as the dependent variable, corrected for maternal age and parity, and disease activity in the third trimester (n = 148) showed that DAS28-CRP was associated with birthweight SDS: β –0.17 (95% CI: –0.33 to –0.01, $P = 0.04$). For the RADAI, only a trend could be observed: β –0.09 (95% CI: –0.20 to 0.18, $P = 0.10$).

Galactosylation of IgG. Spearman's rank correlations between DAS28-CRP or RADAI and percentage of galactosylation of IgG show that at the visit before conception, only DAS28-CRP could significantly explain the percentage of galactosylation of IgG (DAS28-CRP: $\rho = -0.31$, $P = 0.006$, RADAI: ρ –0.083, $P = 0.47$). During pregnancy and postpartum, both disease activity scores were significantly correlated with the percentage of galactosylation of IgG (DAS28-CRP $-0.36 < \rho < -0.26$ and RADAI $-0.41 < \rho < -0.18$). Only change in DAS28-CRP was significantly associated with change in the percentage of galactosylation of IgG from preconception to pregnancy (ΔDAS28-CRP $\rho = -0.22$, $P = 0.05$; ΔRADAI $\rho = -0.04$, $P = 0.76$). During pregnancy and from pregnancy to postpartum, change both in RADAI and DAS28-CRP disease activity were associated with change in galactosylation of IgG (first to third trimester: ΔDAS28-CRP $\rho = -0.28$, $P > 0.001$; ΔRADAI $\rho = -0.22$, $P = 0.01$; and third trimester until 12 weeks postpartum ΔDAS28-CRP $\rho = -0.20$, $P = 0.02$; ΔRADAI $\rho = -0.19$, $P = 0.03$).

DISCUSSION

In this prospective cohort on female RA patients and pregnancy, we showed that DAS28-CRP and RADAI scores have a moderate to good correlation. RADAI scores showed a pro-

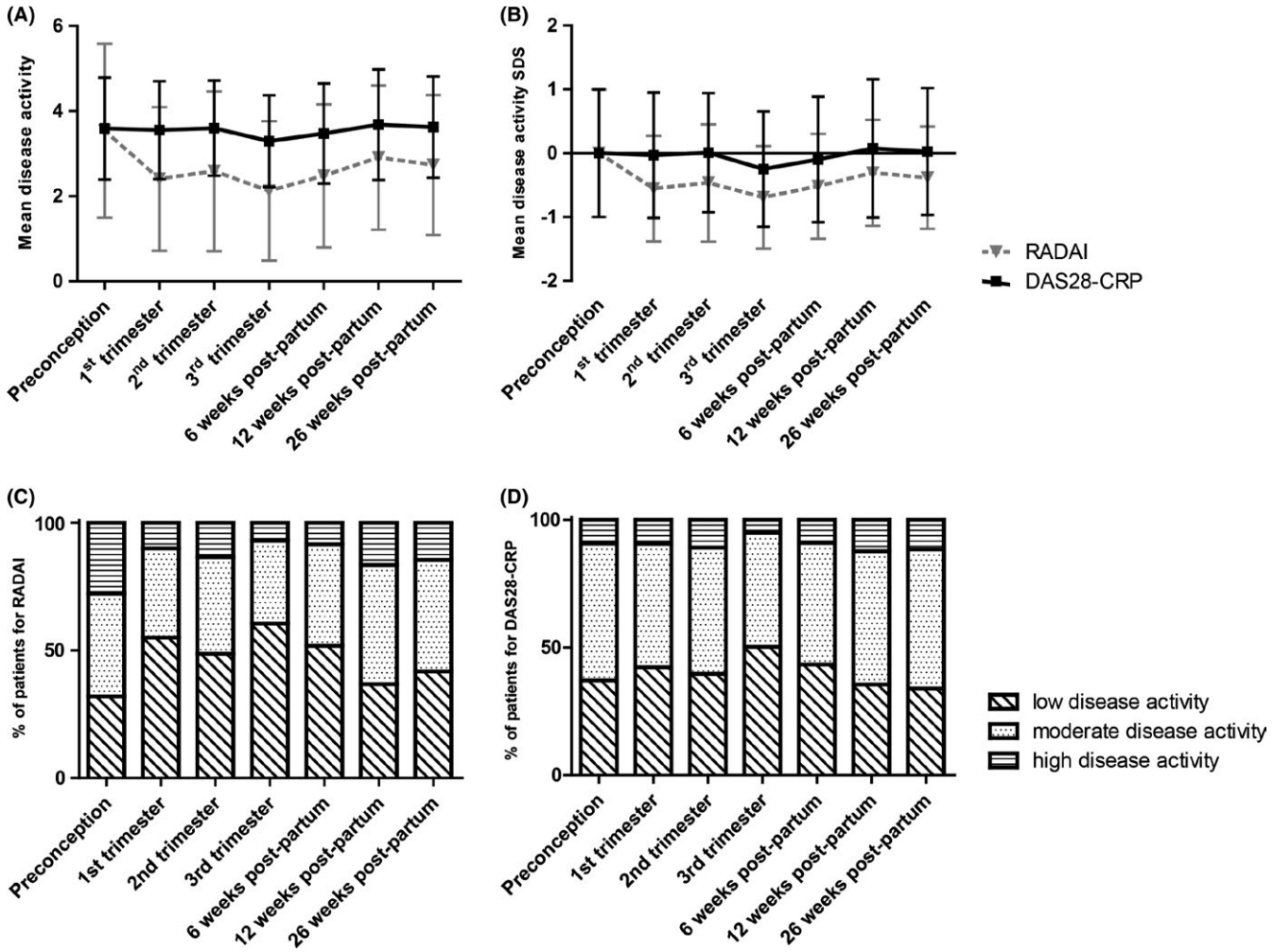

Figure 2. Graph showing RADAI and DAS28-CRP (mean, SD) scores over time (**A**) and showing RADAI SDS and DAS28-CRP SDS (mean, SD) scores over time (**B**). The x-axis displays specific time-points before, during and after pregnancy and the y-axis represents mean (SD) disease activity. Figure 2C and 2D: Bar charts showing disease activity states for RADAI (**C**) and DAS28-CRP (**D**). The x-axis displays the specific time-points before, during and after pregnancy, the y-axis shows the percentage of patients in low, moderate or high disease activity. The correlation in disease activity states is 0.26 〈 kappa 〈0.51.

nounced decline in disease activity during pregnancy compared with DAS28-CRP scores, especially in the first trimester. The agreement in disease activity states between RADAI and DAS28-CRP was low, and DAS28-CRP had better correlations with TTP as a fertility outcome and birthweight as a pregnancy outcome. Both RADAI and DAS28-CRP were correlated with galactosylation of IgG at every time point. However, changes only in DAS28-CRP could explain the changes in galactosylation of IgG from preconception to pregnancy, probably due to the rapid drop of RADAI scores in the first trimester.

In clinical practice, it is important to monitor disease activity during pregnancy because disease activity is associated with pregnancy outcomes (7). Monitoring disease activity in pregnancy via a self-administered questionnaire has practical advantages: it has low costs, takes only minutes to complete, and could be performed online. Bermas et al (4) showed that the correlations between individual DAS28-CRP and RADAI scores during pregnancy are high and suggested that the RADAI might be an useful tool for follow-up of RA disease activity in individual patients during pregnancy outside of a rheumatology clinic. In our current study, we observed good correlations between individual RADAI and DAS28-CRP scores; however, the agreement between disease activity states was low. Treatment and disease control are, in clinical practice, based upon disease activity states; reaching low disease activity or remission is considered tight control of disease. During pregnancy, a greater percentage of patients was in low disease activity according to RADAI. Treatment based upon disease activity scores for RADAI might be inaccurate; therefore, the need for intensification of treatment might be underestimated.

Anderson et al (19) suggested different disease activity states for the RADAI: a RADAI score of 2.0 or less was considered as low or inactive disease; however, they did not establish other additional disease categories. We repeated our analysis using these thresholds for disease activity and found similar results (data not shown).

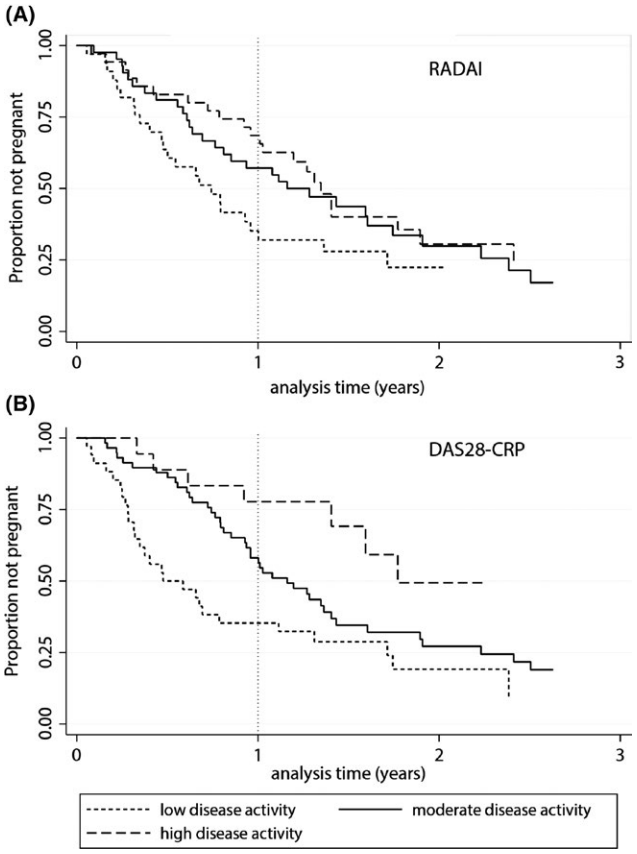

Figure 3. Kaplan Meier survival analysis explaining time to pregnancy for different disease stages for RADAI (**A**) and DAS28-CRP (**B**). The x-axis shows the analysis time in years, the y-axis represents the proportion of patients who are not yet pregnant. The survival analysis curves show that disease activity states according to RADAI did not reported a statistically significant different TTP ($P = 0.56$) whereas TTP was statistically significant according to the disease activity states for DAS28-CRP ($P = 0.03$).

One can argue that the established disease activity states for RADAI in literature are not suitable for use during pregnancy. A solution would be to investigate adjusted cut-off points for disease activity states of RADAI in pregnancy. However, by changing the cut-off points for disease activity states, the results found at preconception, in pregnancy, and postpartum will not be comparable, and clinical follow-up of patients will be complicated.

If the RADAI was validated during pregnancy, longitudinal research on RA and pregnancy could be performed via RADAI scores. The RADAI questionnaire has been proven to be a useful tool in research on RA outside pregnancy (3). Unfortunately, our study demonstrates that RADAI scores during pregnancy are not as reliable as DAS28-CRP scores. DAS28-CRP scores show stronger correlations with fertility and pregnancy outcomes. Nevertheless, continuous RADAI scores show a trend with fertility and pregnancy outcomes, so they may be a useful additional tool in databases with a large number of patients. However, the results from RADAI questionnaires in these databases should be interpreted with caution.

RA improves during pregnancy, a phenomenon that has been observed in studies since 1938 (20). In these historic studies, using self-reported measures, the favorable effect of pregnancy on RA could already be detected as early as the first trimester. In more recent studies, when using objective ways to determine disease activity, a less pronounced effect of pregnancy on disease activity was observed. In our study, the self-reported RADAI scores show a similar pattern as the historic studies; a clear improvement of RA was observed in the first trimester. DAS28-CRP scores did not improve in the first trimester. The challenge is to find out whether RADAI or DAS28-CRP represents the actual disease state. One can argue that because RADAI scores showed a prominent decrease in disease activity during the first trimester the RADAI is thus more sensitive and therefore more capable of detecting early changes. However this phenomenon was not observed when studying postpartum flares. Correlation with an objective biomarker could provide more clarification: change in galactosylation of IgG is thought to be one of the potential explanations for the improvement of RA during pregnancy. The most pronounced change in galactosylation of IgG takes place during the first trimester of pregnancy and only change in DAS28-CRP was associated with the change in galactosylation of IgG, which suggests that DAS28-CRP scores display the actual disease state in pregnancy more accurately than RADAI scores.

A possible explanation for the difference in disease course between RADAI and DAS28-CRP during pregnancy is because the RADAI is self-reported. It is tempting to speculate that RADAI scores could be more prone to psychological factors. Patients who have just found out that they are pregnant will experience a positive effect on their psychosocial wellbeing, which could have a greater impact on RADAI scores than on DAS28-CRP scores. This could also explain the difference in disease course in pregnancy between old, self-reported studies and new studies in which disease activity is objectively measured.

In literature, a change in RADAI scores of more than 1.4 for an individual patient is considered clinically meaningful (19). Our study shows a mean decline in RADAI scores in the first trimester of 1.13 for the total group. This raises the question of whether the observed decline in disease activity in the first trimester is clinically meaningful. Therefore, we calculated the percentage of patients with a clinically meaningful change in disease activity in the first trimester. Over half of the patients (51%) had a change in RADAI score of more than 1.4.

A limitation of this study is that the RADAI questionnaire was not integrated at the start of the study. This results in a smaller group of patients with a RADAI score available at all time points. To overcome this problem, only patients who had both scores available were included in the analysis.

In conclusion, this study demonstrates that the RADAI could not be validated as a disease activity measure during pregnancy.

RADAI scores showed another course over time in pregnancy, stratified a greater number of patients in low disease activity, and showed weaker correlations with fertility and pregnancy outcomes compared with DAS28-CRP. A tool to asses disease activity should be as accurate as possible because a tightly controlled disease will contribute to a healthier mother and child. Treatment and achieving low disease activity in pregnant RA patients is not only for the health of the mother but also aimed at improving pregnancy outcomes. Therefore the RADAI cannot replace DAS28-CRP in clinical follow-up of RA patients during pregnancy and in studies where mechanisms of RA and pregnancy are investigated. DAS28-CRP remains the gold standard of measure for disease activity in pregnancy. Because correlations between RADAI scores and DAS28-CRP were moderate to good, and, with the limitations in mind, the RADAI could be useful in pregnancy for determining maternal disease activity, especially when no DAS28-CRP is available.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. H.T.W. Smeele and R.J.E.M Dolhain had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Hazes, Dolhain, Naterop, Röder, Smeele.

Acquisition of data. Hazes, Dolhain.

Analysis and interpretation of data. Hazes, Dolhain, Röder, Smeele.

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