

Does Rheumatoid Arthritis Really Improve During Pregnancy? A Systematic Review and Metaanalysis

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ABSTRACT. Objective. We performed a systematic review and metaanalysis to assess rheumatoid arthritis (RA) disease activity during pregnancy using objective disease activity scoring systems.

Methods. A systematic review of PubMed, EMBASE/Medline, Cochrane, and LactMed databases was performed. Our inclusion criteria for analysis were prospective studies, more than 5 patients per study, and data on RA using an objective scoring system conducted by a clinician/health professional.

Results. Ten studies were eligible for final analysis, which included 237 patients, of which prepartum data were available for 204 patients. Postpartum disease activity was recorded in 135 pregnancies.

Conclusion. Disease activity improved in 60% of patients with RA in pregnancy and flared in 46.7% postpartum. (J Rheumatol First Release November 1 2018; doi:10.3899/jrheum.180226)

Key Indexing Terms:

INFLAMMATORY ARTHRITIS
DISEASE ACTIVITY

RHEUMATOID ARTHRITIS

PREGNANCY
PROSPECTIVE

The effects of pregnancy on inflammatory arthritis have been debated for many years, with early observations indicating a beneficial response in rheumatoid arthritis (RA) dating back to the 19th century¹. In particular, many studies have reported that disease activity improves in up to 90% of patients with RA during pregnancy with a risk of subsequent postpartum flare².

Historical data, however, are based mostly on retrospective studies, which lack standardized and objective measures of disease activity. More recent prospective studies of patients with RA using objective disease activity scores demonstrate more modest improvements in disease activity during pregnancy.

RA often affects women of childbearing age, who frequently have concerns about the potential effect of disease-

modifying antirheumatic drugs (DMARD) upon their pregnancy. Accurate knowledge of the effect of pregnancy upon RA disease activity is therefore important to enable more-informed decision making during prepregnancy counseling to maintain DMARD that are compatible with pregnancy, to avoid disease relapse.

Therefore, we carried out this systematic review of prospective studies using serial, objective evaluations of joint disease to examine whether RA truly does improve during pregnancy and to what extent. Specifically, we aimed to answer the following questions: (1) does RA disease activity improve during pregnancy; and (2) how common is a postpartum flare in patients with RA?

MATERIALS AND METHODS

Publication search and selection of studies. This review was conducted according to guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). A systematic review of PubMed, EMBASE/Medline, Cochrane, and LactMed databases was performed (Supplementary Figure 1, available from the authors on request). Additional studies were identified through checking the reference lists and other author publications of articles selected for full-text analysis. Two independent reviewers (HJ and SL) screened the retrieved articles by reading the title and abstract to identify studies that met these inclusion criteria: human observational prospective studies, more than 5 patients per study, and containing data on RA disease activity gathered using an objective scoring system conducted by a clinician/health professional, with serial assessments of disease activity during pregnancy. Postpartum data were recorded when listed. Efforts were made to ensure duplicate data were not included, notably multiple studies derived from the Pregnancy-Induced Amelioration of Rheumatoid Arthritis (PARA) cohort study, for which only the first study was included to avoid replication of data (de Man, *et al*, 2008³). Reviews containing no original data, conference abstracts, and non-English-language studies were excluded. Where necessary, original authors were contacted for further information.

Data collection process. A data extraction sheet was developed and its relia-

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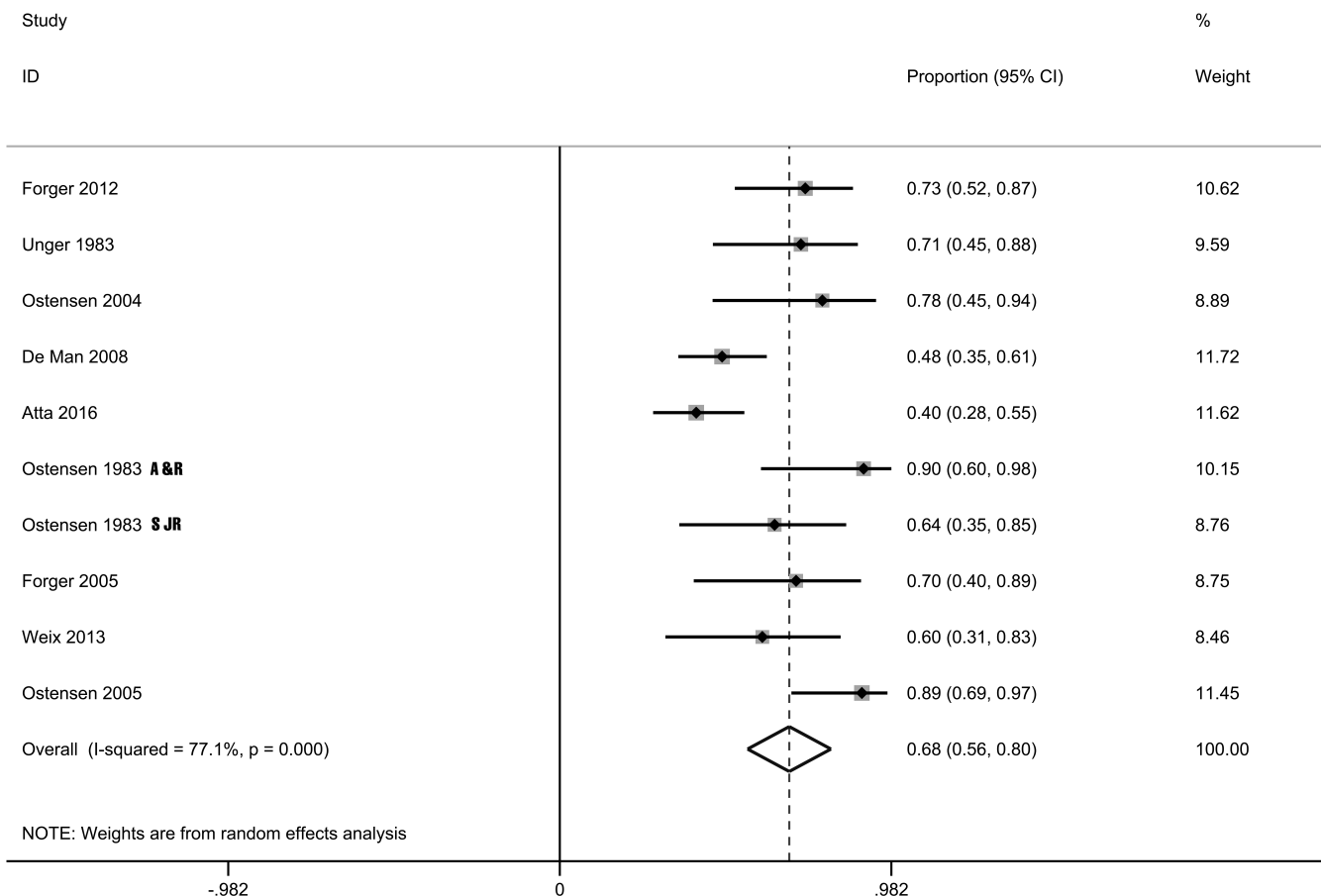


Figure 1. Forest plot of studies reporting the percentage of women experiencing improvement in rheumatoid arthritis disease activity during pregnancy. Heterogeneity between studies ($I^2 = 77.1\%$; $p < 0.001$) was noted. A&R: *Arthritis and Rheumatology*; SJR: *Scandinavian Journal of Rheumatology*.

bility examined on 10 randomly selected studies. It was then refined accordingly to ensure that all relevant data were recorded. Two authors (HJ and SL) extracted and independently checked the data. Disagreements were resolved by discussion with author (IG). Each selected article was systematically examined to note study characteristics pertaining to the population, intervention, comparison, outcome, and time frame.

Statistics. A chi-square test for heterogeneity was performed to determine whether findings were consistent between studies. In all studies, the principal summary measure extracted from each study was the percentage of patients who showed disease improvement or deterioration noted by an improvement or decline in their disease activity scores from baseline in pregnancy or postpartum. This measure was used because exact quantification of the extent of improvement or deterioration was not possible owing to the different measures of disease activity used.

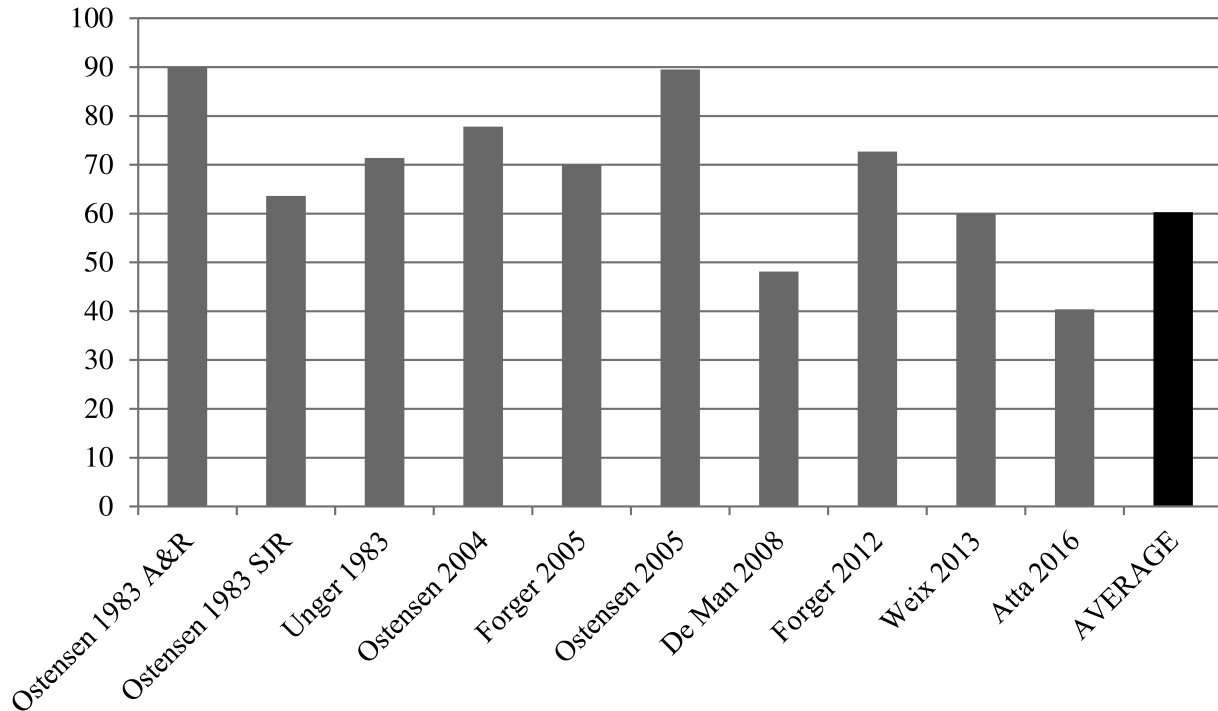
RESULTS

A total of 4673 articles were identified. Duplicate papers and those unsuitable by title alone were excluded, leaving 193 articles. Abstracts of these articles were analyzed further and from 63 articles selected for full-length review, a total of 10 studies were eligible for final analysis. Details of the number and reasons for article exclusion are listed in Supplementary Figure 2 (available from the authors on request). A total of 237 patients/pregnancies were identified from these 10 studies; prepartum data were available for 204 patients, and

postpartum data were available for 135 patients. Six studies included preconception disease activity data (Ostensen 1983 A & R⁴, Unger 1983⁵, Ostensen 2004⁶, de Man 2008³, Forger 2012⁷, and Atta 2016⁸). Five studies documented serial measurements of disease activity in each trimester and up to 3 timepoints up to 24 or 26 weeks postpartum (Ostensen 2004⁶, Forger 2005⁹, de Man 2008³, Forger 2012⁷, and Weix 2013¹⁰); 1 study compared disease activity only in trimesters 1 and 3 (Atta 2016⁸).

These 10 studies used the following disease activity scoring systems: 28-joint count Disease Activity Score (DAS28) using C-reactive protein (4 studies)^{3,7,8,10}, RA Disease Activity Index (3 studies)^{6,9,11}, Camp index (1 study)⁵, and other scoring systems that included objective measurements, such as joint counts and grip strength (2 studies)^{4,12}. Heterogeneity between studies was noted ($I^2 = 77.1\%$; $p < 0.001$), so a random effects metaanalysis was used to obtain a pooled estimate and 95% CI of the percentage with an improvement in activity score, accounting for this observed heterogeneity (Figure 1). Of the 204 pregnancies, disease activity improved in 123 (60.3% overall); across studies, this varied widely from 40.4% (Atta 2016)⁸ to 90% (Ostensen 1983 A & R⁴; Figure 2A).

% Improved during pregnancy



% Flared postpartum

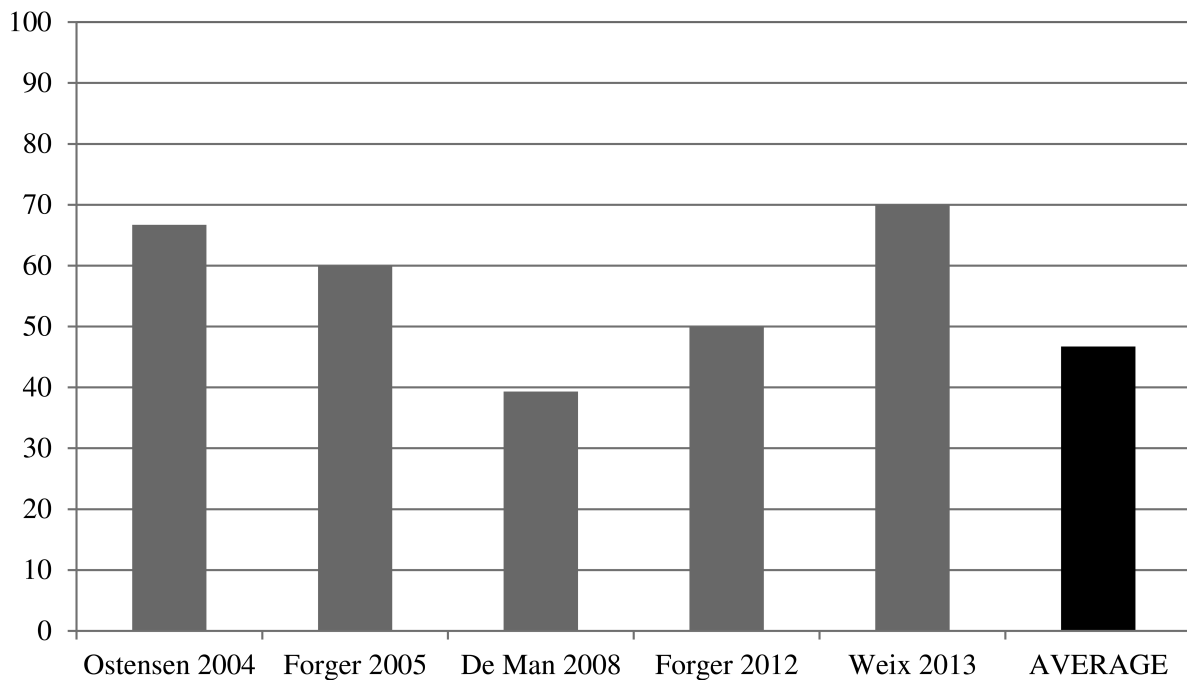


Figure 2. Percentage of patients whose disease activity improved during pregnancy (A) and relapsed postpartum (B) in each of the papers included in the metaanalysis, including overall average percentages. A. Of the 204 pregnancies for which data were available during pregnancy, percentage of improvement in disease activity scores during pregnancy varied widely, from 40.4% to 90%. B. Of the 135 pregnancies for which postpartum data were available, a flare in disease activity was noted in an average of 63 patients (46.7%). A&R: *Arthritis and Rheumatology*; SJR: *Scandinavian Journal of Rheumatology*.

Data on postpartum disease activity were available in 5 papers that used a variety of disease activity scoring systems on 135 pregnancies (Table 1). All these studies included disease activity measures at 6 weeks postpartum; some also included data at 12 and 24 or 26 weeks. A postpartum increase in disease activity was noted in 63 (46.7%) of these pregnancies (Figure 2B). Pregnancy outcomes were reported in only 3 studies with no increase in adverse events, although of the 135 pregnancies, 17 babies (23%) were born prematurely and 16 babies (22%) were small for their gestational age^{4,6,8}.

DISCUSSION

Disease management during pregnancy is complicated by several factors including an increased burden of pregnancy morbidity and adverse pregnancy outcomes that has been linked with increased disease activity^{13,14}. Accurate knowledge of the effects of pregnancy upon RA is therefore required for pre-pregnancy counseling.

Historical reports of up to 90% of patients with RA improving in pregnancy were mostly from retrospective studies, which lacked objective measures of disease activity. Findings from our systematic review of prospective studies using serial, objective measures of disease activity have revealed more modest ameliorative effects of pregnancy on RA disease activity, with only 60% of patients demonstrating improvement in disease activity. Our data also demonstrated a postpartum increase in disease activity in about half of all pregnancies.

It is important to note that the most accurate record of changes of disease activity around pregnancy are obtained when a prepregnancy assessment within a defined time frame before conception has been made and serial measurements performed in each trimester of pregnancy. Further, postpartum disease flares are best collected by at least 2 assessments within 3–6 months after delivery, when relapses of disease activity occur most frequently. This gold standard

Table 1. Summary of disease activity scoring systems used in the 10 papers evaluated for final analysis, and an indication of the different objective disease activity scoring systems and criteria for disease activity alterations used during pregnancy and postpartum.

First Author, Year	Disease Scoring Systems Used	Criteria for Improvement of Disease Activity during Pregnancy	Criteria for Postpartum Relapse
Ostensen, 1983 ⁴ (A&R)	Score derived from duration of morning stiffness, Ritchie articular index, swollen joint count, grip strength, functional class, performance of activities of daily living	Not specified	
Ostensen, 1983 ¹² (SJR)	Score derived from duration of morning stiffness, Ritchie articular index, swollen joint count, grip	Not specified	
Unger, 1983 ⁵	Camp index	If the clinician defined the patient as having low disease activity prepregnancy (1–3 active joints), remission defined as mean Camp index < 6 in third trimester (T3); if moderate disease activity prepregnancy (≥ 4 active joints), remission defined as mean Camp index < 16 in T3	
Ostensen, 2004 ⁶	RADAI, 44 joint count, HAQ	Remission defined as morning stiffness duration < 15 min, no soft tissue swelling, no joint tenderness/pain on movement, no drug treatment required	Not specified; 6 and 12 weeks postpartum
Forger, 2005 ⁹	RADAI, SF-36	Not specified	Not specified; 6, 12, and 24 weeks postpartum
Ostensen, 2005 ¹¹	RADAI, tender joint count, swollen joint count, physician's global assessment	Not specified	
De Man, 2008 ³	DAS28-CRP3	EULAR response criteria; patients all had DAS28-CRP3 ≥ 3.2 in T1; moderate/good response during pregnancy defined as reduction of DAS28-CRP3 > 0.6 in T3, compared to T1	Reversed EULAR response criteria. Moderate/severe flare defined as > 0.6 increase in DAS28-CRP3 at 12 or 26 weeks postpartum, compared to 6 weeks postpartum
Forger, 2012 ⁷	DAS28-CRP	DAS28-CRP < 3.2 in T3: either low disease activity throughout or decreasing disease activity during pregnancy	DAS28-CRP > 3.2 at 6 weeks postpartum
Weix, 2013 ¹⁰ Atta, 2016 ⁸	DAS28-CRP DAS28-CRP3	DAS28 < 2.6 in T2/T3 Not specified	DAS28-CRP > 3.2 at 6 weeks postpartum

RADAI: Rheumatoid Arthritis Disease Activity Index; SF-36: Medical Outcomes Study Short Form-36; HAQ: Health Assessment Questionnaire; DAS28-CRP3: 28-joint count Disease Activity Score using C-reactive protein 3; EULAR: European League Against Rheumatism; A&R: *Arthritis and Rheumatology*; SJR: *Scandinavian Journal of Rheumatology*.

was not achieved in all of our selected studies, which recorded disease activity in 6 studies pre-pregnancy, 9 studies in all trimesters, 1 study in the first and third trimesters, 4 studies at 3 timepoints up to 24 or 26 weeks postpartum, and 1 study at only 6 weeks postpartum. Therefore, although it is conceivable that some alterations in disease activity may have been missed, we do not believe that has adversely affected our findings.

The first study by de Man, *et al* (2008)³ to use the DAS28 as a validated disease activity score to measure disease activity before and at multiple timepoints during and after pregnancy in the PARA cohort identified that the ameliorative effects of pregnancy on disease activity in the third trimester were more marked in those who had moderate to high disease activity in the first trimester compared to those with baseline low disease activity. Further, 39% of these patients had at least a moderate flare postpartum. The PARA cohort has subsequently expanded and been intensely studied in further publications that include serial measures of disease activity throughout pregnancy but have focused on other aspects of RA pregnancy, such as the effect of ACPA positivity¹⁵ and influence of maternal cytokines on fetal growth¹⁶. Therefore, we included only the original PARA study in our analysis to avoid duplication of the original cohort data and thus dilution of other study findings.

Although many of the studies included data on antibody status, data were not expressed in a format by which we could interpret whether antibody status affects disease activity during pregnancy or postpartum. Forger, *et al* (2012), however, identified that the group of patients who entered pregnancy and continued to have high disease activity had higher levels of anticyclic citrullinated peptide antibody (anti-CCP) compared to those with low disease activity⁷. Subanalyses by de Man, *et al* (2008), however, found that presence of anti-CCP or rheumatoid factor did not alter the course of disease activity during pregnancy or postpartum³. Further, although many of the papers include some limited data on medication use, we were unable to meaningfully interpret whether this affected disease activity.

It is difficult to obtain conclusions from the papers regarding whether the patients who improved during pregnancy were more likely to flare postpartum; however, Forger, *et al* (2012) report that at 6 weeks postpartum, a DAS28 > 3.2 was seen in all patients who demonstrated persistent active disease during pregnancy, but in only 31.3% in those with low or inactive disease during pregnancy⁷.

There are several limitations to this metaanalysis, which is highlighted by the high degree of heterogeneity between studies that is likely due to differences in study design or variations in the patient population (for example, disease duration, disease severity, demographic differences). The most notable difference between study designs is in disease activity measurements and definitions of disease improvement or relapse. The papers included used different disease activity scoring systems, and even papers that used the same

scoring system had different definitions of active disease to compare whether activity improved or worsened. Further, the studies were inconsistent in their methodologies, and assessed disease activity at different points during pregnancy and postpartum; therefore it is difficult to accurately compare these results. For example, the time span of assessment postpartum varied from 6 weeks to 6 months. Although treatment data were not included in our study, we note the wide time span from the earliest studies to the most current (> 30 yrs), during which period there have been many alterations in treatment with the introduction of combination therapies, new drugs (particularly biologics), and treat-to-target regimens. Interestingly, studies dating from 1983 to 2005 noted a greater improvement in disease activity scores during pregnancy compared to those from 2008 to 2016 (77% and 55.3%, respectively). This reduction may be a consequence of these more effective treatment regimens inducing remission or low disease activity in more patients with RA, who thus plan pregnancy and experience less impressive gestational improvement.

Additionally, although all studies included either a validated disease activity score or an objective score based on clinical assessment as a primary inclusion criterion, some of them also used subjective measures. In these cases, measures of disease improvement or deterioration used for final analysis may have included subjective measures for reasons beyond our control. But upon review of the final results of papers that included some subjective measurements, we concluded that those results did not have a significant effect on our final analysis.

Our systematic analysis of prospective studies using objective markers of disease activity and related scoring systems found that 60% of patients with RA improve during pregnancy and 47% relapse postpartum. This information is important when counseling patients with RA prepartum.

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