Impact of pregnancy on rheumatoid arthritis activity

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Assistant Professor of Medicine, Division of Rheumatology & Immunology, Duke University Medical Center, Box 3535, Trent Drive, Durham, NC 27710, USA ■ Tel.: +1 919 681 2045 ■ Fax: +1 919 681 8298 ■ megan.clowse@duke.edu

Evaluation of: de Man YA, Dolhain RJ, van de Geijn FE, Willemsen SP, Hazes JM: Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum.* 59(9), 1241–1248 (2008). For many women with rheumatoid arthritis (RA), pregnancy is remembered as a time of relative comfort and well-being, with arthritis frequently entering remission. Since the 1930s, it has been recognized that RA abates during pregnancy and flares after delivery. In this study, almost half of women with RA had a moderate improvement of symptoms during pregnancy, and 40% worsened following delivery, a more modest change in disease activity than that observed in prior studies. Medication changes surrounding pregnancy were dramatic, with two-thirds of women discontinuing DMARD therapy during pregnancy, and 90% returning to it following delivery. Pregnancy creates in the mother an immunologically unique environment in which tolerance to a semi-allogeneic transplant (the fetus) develops. This altered immunological state in turn may promote maternal tolerance to self and amelioration of RA activity. Improved understanding of these immune changes during pregnancy may lead to the discovery of novel therapies for RA in the future.

Summary of methods & results

This study enrolled women with rheumatoid arthritis (RA) throughout The Netherlands either prior to or soon after conception [1]. Data was collected during home visits prior to conception, once per trimester, and three times postpartum. At each visit, the research clinician performed a 28-joint count, and disease activity was scored using the DAS28-CRP-3. This version of the Disease Activity Score includes a 28-joint count for swollen and tender joints and the C-reactive protein (CRP) level, but not a patient's assessment of disease activity. The same group previously demonstrated that CRP was a more reliable marker of inflammation during pregnancy, as the sedimentation rate may increase simply due to pregnancy [2].

Of 346 patients referred to the study, complete data from the first trimester through 26 weeks postpartum were available for 84 pregnancies; preconception data were available for 41 of these mothers. The average age at delivery was 32 years. The disease duration averaged 4.8 years prior to conception. All but three of the patients were Caucasian. Serum rheumatoid factor was positive in 71%; anti-CCP was positive in 72%; and erosions were present in 72%.

Medication use changed dramatically with pregnancy (Figure 1). Prior to pregnancy, 28% of women took methotrexate, and 49% took sulfasalazine. During pregnancy, however, none were taking methotrexate, and only 33% were treated with sulfasalazine. Overall, 65% of women taking DMARD medications prior to pregnancy discontinued them around the time of conception. Use of prednisone increased modestly, from 28% prior to pregnancy to 35% in the third trimester, but the median daily dose remained at 7.5 mg/day throughout, except for a rise to 10 mg/day 6 weeks postpartum. NSAID use decreased from 32% prior to pregnancy to just 4% during pregnancy. Only 7% of women were taking biologics prior to conception, and all discontinued these for pregnancy. Within 6 weeks of delivery, the percentage of woman taking DMARD therapy increased by 75% over the third trimester.

Despite the large number of women who stopped DMARD therapy before conception, RA activity rarely flared and generally improved during pregnancy. By the third trimester, twice the number of women had either mild or inactive RA compared with the period prior to conception. The percentage of women with moderate RA declined from 70% prior to pregnancy to approximately 40% during pregnancy (Figure 2). The greatest DAS28-CRP-3 improvement was seen in women with the most active disease. Those with moderate-to-severe RA saw their average DAS28-CRP-3 fall from 4.5 pre-pregnancy to 3.8 during the third trimester, and almost half had a 'moderate response' according

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Keywords
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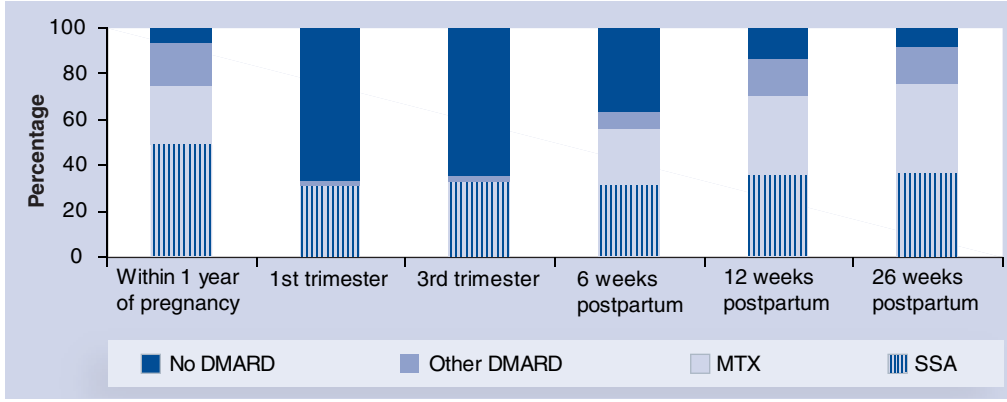

Figure 1. Medication use prior to, during and following pregnancy. Note the dramatic decrease in DMARD use during pregnancy and the prompt re-initiation following delivery. Despite these changes in medication use, RA activity improved during pregnancy and increased postpartum in many women.
MTX: Methotrexate; RA: Rheumatoid arthritis; SSA: Sulfasalazine.

to EULAR response criteria. Following delivery, RA activity increased in approximately 40% of patients, with only 4% suffering a severe flare.

Discussion

The observation that RA activity decreases during pregnancy and increases postpartum is not new. However, the impact of more aggressive therapy for RA may diminish the expected degree of disease fluctuation with pregnancy. Advances in our understanding of the pathogenesis of RA and immune changes of pregnancy are providing new insights into the possible mechanistic basis for this clinical phenomenon.

The degree of fluctuation in RA activity during and following pregnancy in this study was less dramatic than in prior studies. Over 500 pregnancies in women with RA have been studied over the last 70 years. On average, these studies show that 75% of women improve with pregnancy (range 54–86%), and 90% relapse in the 3 months following delivery [3]. Compared with these rates of improvement and relapse, the results of the current study appear more modest. This is likely caused by several factors:

- RA disease assessment was based on physician joint count, not patient assessment. Patient assessment of disease activity might include factors such as general well-being, degree of pain and medication cessation that are not included in a more objective joint count. Most of the prior studies were based on patient report, often retrospective, of the condition of RA prior to and during pregnancy. This study relied on the DAS28-CRP-3, which did not include a patient-reported outcome, nor include an assessment of current medication usage.
- RA activity was better controlled prior to pregnancy due to treatment with DMARD therapy. The high percentage of women treated with DMARD therapy prior to

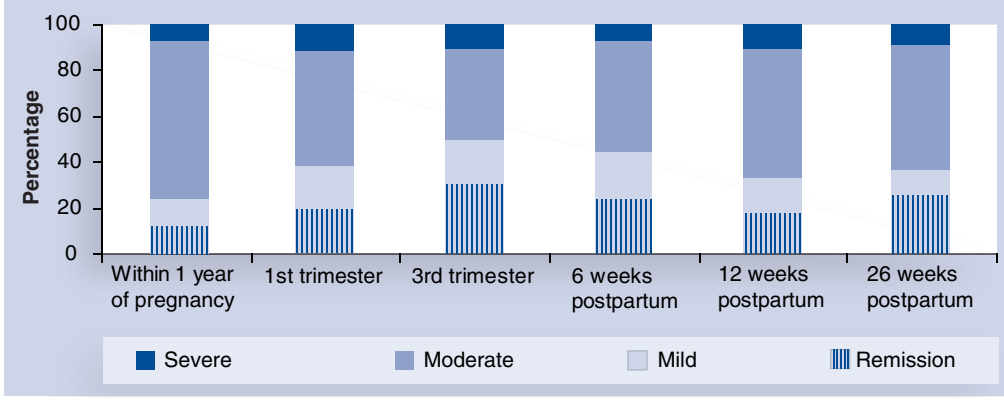

Figure 2. Distribution of RA activity prior to, during and following pregnancy. Severity based on DAS28-CRP-3. Severe: DAS28 ≥ 5.1; moderate: DAS28 3.2–5.0; mild: DAS28 2.6–3.1; remission: DAS28 < 2.6.
DAS28: Disease Activity Score 28; RA: Rheumatoid arthritis. Adapted from [1].

conception may have decreased the baseline DAS28-CRP-3 below that seen in earlier studies, allowing less room for improvement during pregnancy. The maintenance of mild-to-moderate disease activity during pregnancy, despite the withdrawal of DMARD therapy, is consistent with the hypothesis that pregnancy partially suppresses the chronic inflammatory process.

- Aggressive medical treatment of RA may dampen postpartum flares. Within 6 weeks of delivery, 63% of women were taking DMARD medications, up from 36% in the third trimester. It appears that rheumatologists were reinstituting DMARD therapy with the expectation of a post-pregnancy flare. This treatment plan may be effective in decreasing the severity and frequency of postpartum flare.

Why does pregnancy affect rheumatoid arthritis activity?

This study begs the question: how does pregnancy suppress RA activity? The answer remains a mystery, but answers may be found in the burgeoning field of reproductive immunology.

Maintenance of pregnancy demands a uniquely tolerant environment, as the maternal immune system must modulate in order to avoid rejection of the semi-allogeneic fetus. A functional maternal immune system, however, is essential to protect both mother and fetus from pathogens. Therefore, the immune modulation required to allow fetal tolerance must be finely tuned to protect the fetus, yet enable an adequate host defense. In women with RA, it seems likely that fetal tolerance leads to maternal self-tolerance, resulting in a temporary decline in disease manifestations. After delivery, the maternal immune system reverts to its former state (or perhaps overshoots), with recrudescence of disease activity.

In 1993, Nelson and colleagues published the initial report linking disparity in maternal and fetal HLA class II allo-antigens and relief from arthritis symptoms during pregnancy [4]. In the report, 76% of pregnancies associated with disease remission had maternal–fetal disparity in alleles of *HLA-DRB1*, *DQA* and *DQB*, while only 25% of pregnancies with persistent disease activity had these disparities ($p = 0.003$).

Nelson and colleagues recently speculated how the HLA class II disparity could induce maternal tolerance [5]. It begins with maternal exposure to the fetal antigens through regular apoptosis of placental syncytiotrophoblasts with extrusion of blebs into the maternal circulation. As these cells break apart, fetal DNA is released into the maternal circulation and fetal HLA class II antigens in blebs are consumed by maternal dendritic cells. The maternal dendritic cells process these cell pieces and present the fetal HLA class II antigens on their own maternal HLA antigens, resulting in tolerance through mechanisms of deletion, anergy and the induction of regulatory T cells (T_{reg}). The HLA disparity comes into play if the induction of T_{reg} cells is dependent on differences between the fetal and maternal HLA antigens. Consistent with this notion is the fact that decreased RA activity has been associated with higher amounts of fetal free DNA in the maternal circulation; fetal free DNA is a possible marker for maternal exposure to fetal HLA class II antigens [6].

T_{reg} cells have been strongly implicated in the mechanisms of self-tolerance, and may be the link between maternal tolerance during pregnancy and diminished RA activity. T_{reg} cells promote tolerance by diminishing the number and activity of effector T cells and dendritic cells, and producing the anti-inflammatory cytokines IL-10 and TGF-β. They also modulate dendritic cell maturation and promote the production of indoleamine 2,3-dioxygenase, which starves effector T cells of tryptophan [7].

T_{reg} cells may play an important role in the pathogenesis of RA. In the peripheral blood of patients with RA, the percentage of T_{reg} cells may be similar to healthy patients, but the ability of these T_{reg} cells to inhibit T-cell production of TNF-α and IFN-γ is impaired [8]. Treatment with anti-TNF-α therapy appears to restore the suppressive activity of T_{reg} cells in patients with active RA that responded to the drug.

In pregnancy, T_{reg} cells appear to play an important role in promoting maternal tolerance to the fetus. The overall number of circulating T_{reg} cells peaks in the second trimester and declines postpartum, with increased numbers found at the maternal–fetal interface [9]. During pregnancy, up to a third of T cells in the uterus are T_{reg} cells, compared with less than 5% in other tissues, and T_{reg} cell percentages increase in the maternal spleen, lymph nodes and peripheral blood. In a mouse model, removal of all T_{reg} cells leads to pregnancy loss, demonstrating that these cells are necessary to protect the fetus from destruction [10].

Forger and colleagues have recently studied the association between maternal T_{reg} cells during pregnancy and RA activity [11]. They found that not only do T_{reg} cells increase in number as

pregnancy progresses, but they also increase in their suppressive activity. T_{reg} cells isolated from women during the third trimester showed more FOXP3 expression and produced more IL-10 than T_{reg} cells isolated postpartum. On the contrary, effector T cells had diminished proliferation and production of IFN-γ and TNF-α during the third trimester, compared with postpartum. Taken together, these findings, which were similar for women with RA and healthy controls, point to an anti-inflammatory cytokine mileu during pregnancy, where the maternal cytokine pattern shifts from Th1 to Th2 [3]. The clinical improvement during pregnancy and postpartum worsening correlated with the degree of TNF-α suppression [11].

Future perspective

For decades, studies have demonstrated what many woman will report – that RA improves during pregnancy. The current study reinforces this association by showing that remission occurs in a significant number of women during pregnancy despite frequent withdrawal of DMARD therapy. Further research will be necessary to elucidate more precisely the tolerance-inducing mechanisms of pregnancy and the role of T_{reg} cells in the development of fetal tolerance. *Ex vivo* expanded populations of T_{reg} cells may have therapeutic applicability, as studies are now underway to investigate their potential efficacy and safety in graft versus host disease. The intersection of fetal tolerance and maternal self-tolerance during pregnancy may be a model for illuminating the potential role of this and other novel approaches to the treatment of immune-mediated diseases such as RA.

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Executive summary

- Rheumatoid arthritis (RA) activity diminishes during pregnancy and frequently flares postpartum.
- Two-thirds of the women taking DMARD therapy prior to conception discontinued it during pregnancy. Despite this, few women had a flare of RA during pregnancy.
- Over 60% of women took DMARD therapy within 6 weeks of delivery, perhaps accounting for the lower than expected postpartum flare rate (40%) in this study.
- RA probably improves during pregnancy because of changes in the maternal immune system that promote tolerance of the fetus.
- The induction of regulatory T cells (T_{reg}) during pregnancy may help ameliorate RA activity.
- Future studies of the immunologic changes during pregnancy may lead to new approaches to RA treatment.

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- ▪ of interest
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