

The remission of rheumatoid arthritis during pregnancy

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Abstract Rheumatoid arthritis (RA) is an autoimmune disease that is favorably influenced by pregnancy but relapses after delivery. A variety of circulating factors has been considered as candidates for inducing gestational improvement of RA; however, the factors/pathways responsible remain still elusive. This review discusses recent research on the effect of pregnancy on RA with a focus on immunoregulation, cytokine secretion, HLA antigens, microchimerism, and innate immunity. The complex hormonal and immunological alterations of pregnancy may temporarily correct the disturbed immunoregulation of RA.

Keywords Pregnancy · Rheumatoid arthritis · Hormones · Immune response · Microchimerism

Pathology of RA

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disorder of unknown etiology occurring in 1–2% of the population. RA is associated with certain HLA class II molecules that presumably interact with T cells. The frequency of HLA-DRB1 genes that encode for the so-called shared epitope, an amino acid motif in the third hypervariable chain of the DR β 1 chain, is increased in RA patients [1]. RA is characterized by symmetrical polyarthritis and extra-articular manifestations including subcutaneous nodules, lung disease, pericarditis, neuropathy, and vasculitis. About three times more women are affected from RA than men. The etiology of RA is still unknown. One of the major features of RA is the presence of rheumatoid factor and of anticitrullinated protein antibodies [1]. The synovium, the main target

of the inflammation seen in RA, is infiltrated by T cells, B cells, and macrophages. Autoantigen recognition by specific T cells seems to be a crucial event in RA [2]. The early stages of RA are dominated by activated T cells (30–50% in the synovia), mainly of the CD4⁺ T helper type. Failure of regulatory T cells to control autoimmune effector T cells may contribute to the chronicity of joint inflammation. In addition, recent results about the remission inducing effect of B cell-depleting antibodies argue for a central role of B lymphocytes as well [3]. The chronic stage of arthritis is characterized by the presence of macrophages and their products. Uncontrolled chronic inflammation of joints results in the destruction of cartilage and bone [4]. There is evidence for the dominance of T helper cell type 1 (Th1) cytokines in early stages of RA [5]. Later, T helper cell type 2 (Th2) features emerge, probably as a counter-regulatory effort of the immune system. Regarding clinical signs and typical findings such as synovitis and joint destruction (bony erosions and cartilage thinning), certain cytokines play central roles: tumor necrosis factor α (TNF α), interleukin 1 (IL-1), and IL-6. With the help of blocking strategies it could be proofed that the TNF α and IL-6 pathways are of central importance, while blockage of IL-1 β using the natural receptor antagonist was less effective [6]. It remains to be defined whether other proinflammatory cytokines play essential or contributory roles in the pathogenesis of this autoimmune disease.

The effect of pregnancy on disease activity in women with RA

Pregnancy exerts a beneficial effect on the symptoms and signs of RA [7]. Both retrospective and prospective studies comprising more than 500 pregnancies have shown that about 75% (range 54–86%) of patients experience improvement or even remission of arthritis during gestation [8–10]. Improvement occurs for 50–76% of patients already at the end of the first trimester and is usually sustained

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throughout pregnancy. Symptoms of joint inflammation are either improved or completely suppressed rendering therapy unnecessary. Within 3 months after delivery, a relapse is observed in 90% of patients [10].

The risk of early or late miscarriage is not increased in RA. Except for a slight increase in prematurity and intrauterine growth restriction in patients with active disease, the course of pregnancy and outcome is favorable in RA [11, 12]. Thus, there is no indication for the disease process of RA to disturb fertilization, implantation, or placental function except in severely ill patients.

The pregnancy-induced amelioration and postpartum relapse of RA

A variety of biochemical and immunological changes take place in pregnancy. The mechanisms by which tolerance to the semiallogeneic fetus is established are truly involved in the suppression of autoimmunity during pregnancy. A number of circulating factors has been considered in the pregnancy-induced amelioration of RA [13]. As a rule, these were proteins that had shown immunosuppressive properties in-vitro like suppression of T cell activation and proliferation or inhibition of the mixed lymphocyte culture [14]. Among the candidate factors studied, neither increased serum cortisol concentrations, elevated levels of sex hormones, pregnancy-associated α -2 globulin, nor reversal of abnormalities in the percentage of IgG immunoglobulins lacking the terminal galactose emerged as a convincing explanation for improvement of RA during pregnancy [13, 15–18] (Table 1). Given the fact that the survival of the fetus is secured by a redundancy of protective mechanisms, the factor(s) responsible for the gestational remission of RA still remain(s) elusive. A main difficulty is to separate primary events crucial for an effect on RA from secondary phenomena that occur further downstream. Clues emerge as more pathogenetic mechanisms of RA are revealed.

After delivery, the maternal system adjusts again to the nonpregnant state. The postpartum flare of RA could be

viewed as a kind of withdrawal symptom related to the decrease in steroid hormones [19], the re-establishment of a Th1-dominated immune response, and the unopposed action of proinflammatory cytokines [20].

Alteration of the immune response in pregnancy

Pregnancy induces changes in the maternal immune system to protect the fetus from immunologic attack by the mother. There are several excellent reviews on this topic [21, 22]. In the context of RA characterized by a Th1-type immune response, the shift to a type-Th2 response during pregnancy is of interest [23]. Interferon γ (IFN- γ), IL-12, TNF α , and IL-1 are proinflammatory cytokines that contribute to synovitis and joint destruction in RA [4]. During pregnancy, cytokines of the Th2-type immune response like IL-4 and IL-10 have been shown to prevail and, as a consequence, suppress inflammation [20].

Studies of maternal serum levels of cytokines and their receptors have shown that an increase in IL-1 and IL-6 is observed parallel with an increase in their receptors [24]. Soluble TNF receptors (sTNFRs) increase throughout pregnancy [25]. In one study, the inhibitors of the proinflammatory cytokines IL-1 and TNF α , the IL-1 receptor antagonist, as well as the sTNFR-75 were elevated in late stages of pregnancy both in pregnant patients with rheumatic disease and in healthy pregnant women [26]. However, the cytokines measured in the maternal circulation showed no pattern typical for a Th2 response. Collectively, these results argue for a pregnancy-induced up-regulation of anti-inflammatory mechanisms, which in turn counteract the inflammatory process of RA.

A shift to a TH2 cytokine profile is observed in peripheral lymphocytes in pregnancy. Activation of peripheral T cells has been shown by demonstrating an increase both in IFN- γ - and IL-4-secreting cells [27]. The ratio of IFN γ /IL-4 decreases as a reflection of the shift to a Th2 response [27]. This still promotes a Th2 response because high levels of IL-4 dominate over IFN- γ effects. Elevated levels of

Table 1 Overview over various proteins investigated as candidates of disease remission in RA

Factor studied	Effect on disease activity	References
Cortisol	Anti-inflammatory. Induces a Th2 cytokine pattern and production of TGF β . No clear association to disease activity in pregnancy	[15, 19, 20]
Estrogen	Estradiol reduces cytotoxicity of T cells, induces Treg, and potentiates their suppressive activity. Beneficial effect of pregnancy on disease activity	[34, 36, 37]
Pregnancy-associated α -2 globulin	Suppression of lymphocyte activation, phagocytosis and chemotaxis. Inverse relationship between RA disease activity and PAG levels in two studies	[16, 17]
a-Galactosyl immunoglobulin G	Normalization of galactosylation of IgG during pregnancy renders IgG less antigenic. An increase in galactosylated IgG was correlated to low disease activity of RA during pregnancy	[18]

mRNA expression for IL-10 and an increase in IL-10 secretion were found in peripheral blood mononuclear cells of four pregnant RA patients studied prospectively during and after pregnancy [28]. A study of monocytes isolated from third-trimester pregnant women showed significantly reduced production of TNF α and IL-12 compared to postpartum [29]. Thus, on the cellular level, there is indeed a predominance of a Th2 cytokine pattern with an increase in IL-4 and IL-10 that antagonize the proinflammatory cytokines involved in the pathology of RA. The beneficial effect of pregnancy on RA may be a down-regulation of a Th1 response rather than an up-regulation of the Th2 response.

Hormones in pregnancy

Pregnancy induces changes in the whole neuroendocrine system, and interactions occur in a very complex manner. Cells involved in immunoinflammatory events express receptors for cortisol and sex steroid hormones, and thus, hormones modulate immune responses. There is a progressive rise in total plasma cortisol levels with advancing gestation [30]. Both the bound and unbound fractions of cortisol increase as well as the cortisol-binding globulin. The free, active form of cortisol reaches about twice its plasma concentration compared to the nonpregnant state. One of the reasons for the increase is high levels of estrogen, which decrease the metabolic clearance of cortisol. The increase in cortisol is most marked in the first half of pregnancy but remains elevated throughout pregnancy. Together with sex steroids, glucocorticoids promote a Th2 response and are the most potent inhibitors of proinflammatory cytokines like IL-1, IL-6, IL-2, IFN- γ , and TNF α [20, 31]. Furthermore, glucocorticoids induce the production of transforming growth factor β , which in turn is an antagonist of proinflammatory cytokines.

RA patients show a relative corticosteroid deficiency and an impaired response to corticosteroids [32, 33]. It was, therefore, originally believed that the gestational rise of plasma cortisol alone could explain the gestational improvement of RA. Studies in the 1960s, however, showed no convincing correlation between corticosteroid levels measured in pregnancy and disease activity [15]. In addition, improvement of RA is observed in the first trimester in about 75% of the patients, at a time when free cortisol levels are still low [8].

Pregnancy-associated concentrations of estrogens, progesterone, and glucocorticoids may collectively promote an anti-inflammatory environment. Sex hormones can block some important mechanisms involved in the development of RA, including immunoregulation, inflammatory response, cytokine secretion, and cartilage damage [34]. Estradiol has shown a protective effect on cartilage preventing proteoglycan degradation in arthritic mice [35]. Estrogens show a biphasic effect with low concentrations activating and high

concentrations suppressing T cell functions. Low, nonpregnant levels of estradiol stimulate IFN- γ production in T cells [36]. High levels of steroid hormones during pregnancy have discrete regulatory effects on the Th1/Th2 balance. Pregnancy levels of estrogens induce secretion of IL-10 and suppress TNF α production in T cells [31] as well as suppressing cytotoxicity of T cells [37]. Progesterone enhances IL-4 and IL-10 production in human T cells, thereby promoting the expansion and differentiation of T helper cells with a TH2-type cytokine response [31]. Lymphocytes develop progesterone receptors during pregnancy and release a protein named progesterone-induced blocking factor (PIBF) [38]. PIBF has a strong anti-natural killer (NK) cell activity, and PIBF-positive lymphocytes secrete IL-10 [39].

It has been hypothesized that autoimmune phenomena in the postpartum period could be associated with low hypothalamic secretion of the corticosteroid-releasing hormone, which remains suppressed for about 3 months [40]. The question if the resulting, relative hypocortisolism is involved in postpartum aggravation of RA remains unanswered. The timing of the postpartum flare does not coincide with the return of cortisol plasma levels to normal 2–5 days after delivery. Furthermore, treatment with glucocorticoids postpartum does not prevent a flare [41]. Prolactin has been proposed to play a role in the postpartum relapse of RA [42]. Some studies have found an association between breast-feeding, a state with elevated prolactin levels, and disease relapse of RA [42]. Hypophysectomized mice did not develop adjuvant arthritis unless they were treated with prolactin [43].

Regulatory T cells

Several subsets of regulatory T cells (Treg) have been identified [44]. Treg have a key role in the maintenance of immune tolerance to both self and foreign antigens. Treg suppress activation and proliferation of conventional T cells and are able to suppress autoimmunity. In the following, we discuss data published on CD4+CD25+forkhead family transcription factor 3 (Foxp3)+ Treg because they are the most studied in RA.

CD4+CD25+ Treg

Depletion and reconstitution experiments in mice have shown that CD4+CD25+ T cells can prevent or ameliorate autoimmune disease like diabetes or collagen-induced arthritis [45]. CD4+CD25+ Treg inhibit both the activation and proliferation of autoreactive CD4+ T cells in an Ag-nonspecific fashion that is contact dependent but cytokine independent [46]. The expression of Foxp3 is regarded a characteristic of CD4+CD25+ Treg and differentiates them from activated CD4+ T cells [47]. Numbers of CD4+CD25+ Treg are

reduced in peripheral blood [48] but elevated in the inflamed synovium of RA patients and of juvenile idiopathic arthritis (JIA) [49, 50]. However, synovial responder T cells show decreased susceptibility to the regulatory effect of Treg cells and fail to respond with a Th2-type cytokine secretion in coculture [51]. The presence of TNF α in arthritis inflammation may be responsible for the down-regulation of the CD4+CD25+ Treg suppressive function [52]. Interestingly, a correlation between high numbers of Treg locally and sustained remission of arthritis was observed in JIA [50]. An increase in CD4+CD25+ Treg in peripheral blood has been found after successful therapy in RA [51].

An expansion of CD4+CD25+ Treg has been demonstrated in mice during syngeneic and allogeneic pregnancy [53]. In healthy pregnant women, CD4+CD25+ Treg increase rapidly in peripheral blood peaking at midgestation and decreasing after delivery [54, 55]. Interestingly, expansion of Treg is driven by pregnancy levels of estradiol, which induce Foxp3 in CD4+CD25+ T cells [56]. One study found the suppression of proliferation of responder T cells by Treg markedly enhanced in the presence of estradiol [57].

HLA antigens, maternal–fetal incompatibility and microchimerism

The fetal cells coming into direct contact with maternal cells in the uterus do not express classical human leucocyte antigens (HLA) class I or class II genes. However, HLA-DR protein has been recently identified within the cytoplasm of the shed trophoblast [58]. To escape both cytotoxic T cells and attack by NK cells, trophoblast cells express nonclassical major histocompatibility complex (MHC) class I antigens: HLA-E, HLA-F, and HLA-G [22]. HLA-G exists in several isoforms, four membrane bound and three soluble, and seems to play a major role in promoting maternal tolerance to the fetus [59]. HLA-G inhibits activating signals on leucocytes by binding to leucocyte inhibitory receptors. Elevated levels of soluble HLA-G (sHLA-G) are found in maternal circulation during pregnancy. Functional studies of HLA-G have shown inhibition of NK cytotoxicity, down-regulation of IFN- γ and TNF α , and induction of a Th2 cytokine profile and of suppressive, regulatory T helper cells [60]. sHLA-G can also induce apoptosis of activated T cells.

Maternal–fetal incompatibility

A number of observations suggest that HLA incompatibility between mother and child is advantageous for the outcome of pregnancy [61]. Collagen-induced arthritis in mice improves much more in allogeneic than in syngeneic pregnancy [62]. Furthermore, HLA incompatibility induces a stronger Th2 cytokine response with more secretion of IL-4 and IL-10 [63].

In 1993, Nelson et al. [64] studied 46 pregnancies and found that disparity at the HLA-DRB1, DQA1, and DQB1 alleles between mother and fetus corresponded in 26 out of 34 pregnancies to amelioration or remission in RA. A Dutch study of 33 pregnancies in 1998 confirmed that maternal–fetal incompatibility at the DQA1 and DQB1 locus influenced the course of RA favorably during pregnancy [65]. A third study typed 118 maternal–fetal pairs from RA pregnancies for HLA-DRB1 and DQB1 but found no influence of HLA incompatibility on disease activity [66]. The disagreement between the studies may partly be based on different design and evaluation of disease activity of RA patients. Mechanisms proposed for the effect of maternal–fetal HLA disparity on disease activity of RA were: HLA class II molecules present foreign antigen but also self-antigens. In mothers with RA, peptides derived from class II HLA antigens of the fetus might compete with self-antigens and divert the mother's immune response away from an autoimmune response.

During pregnancy, fetal cells escape into the maternal circulation. Several studies have shown that they remain for decades in the mother, perhaps indefinitely. It has recently been established that fetal cells and cell-free DNA routinely traffic into the maternal circulation during normal pregnancy [67] and can be detected in the maternal serum as early as the first trimester. The concentration of fetal DNA increases over the course of pregnancy and declines rapidly after delivery [68]. The role of fetal cells or fetal DNA is not quite clear. Induction of tolerance to paternal antigens in the mother or the induction of a Th2 response could be possible results. The viewpoint has been put forward that altered peptide–MHC complexes can deviate development of T helper subsets away from Th1 and select for Th2 [69]. Interestingly, studies investigating the response of maternal peripheral blood mononuclear cells to trophoblast or paternal HLA antigens showed that paternal antigens stimulated the production of IL-4 [70].

In a recent study, a significant inverse correlation between arthritis activity and serum fetal DNA concentrations was found over the course of pregnancy and postpartum [71]. Arthritis amelioration occurred in 79% of patients with RA over a similar time course as rising serum fetal DNA levels, increasing as pregnancy progressed and dropping to undetectable or low levels after delivery, coincident with arthritis recurrence. In the third trimester, serum levels of fetal DNA were significantly greater in patients with amelioration as compared to those with active disease.

A recent review has suggested that shed trophoblast and apoptotic fetal cells in the maternal circulation may be crucial players in the remission of RA observed during pregnancy [72]. Apoptosis of fetal cells or placental trophoblast cells will release fetal HLA alloantigens. The uptake and cross-presentation of soluble fetal paternally

inherited HLA peptides and self-HLA class II peptides in the environment of pregnancy could modulate the maternal autoimmune response of RA. Suppression of autoreactive T cells could be achieved by T cell deletion, anergy, or by induction of Treg. With the removal of the placenta after parturition, the source of trophoblast debris or fetal DNA disappears resulting in the reappearance of an autoimmune response. As shown in the study by Yan et al. [71], the drop of serum fetal DNA after delivery was coincident with the relapse of arthritis.

Innate immunity

The mother is not systemically immunosuppressed nor immunodeficient. However, specific immune responses are weakened during pregnancy. The suppression of the adaptive immune response is compensated by activation of the innate immune system. Granulocytes and monocytes are increased in number during gestation [73]. It has been shown that monocytes get activated through phagocytosis of debris shed from the trophoblast, but in contrast to phagocytosis of other particles, increased secretion of IL-10 and decreased secretion of IL-1 β follows [74]. Studies some 25 years ago and several recent investigations explored the effect of pregnancy on cells of the innate immune system. Results of studying the activation status of granulocytes and monocytes from pregnant women differ, some showing enhanced activation, others demonstrating reduced activity during pregnancy. A study of pregnant healthy women and of pregnant patients with rheumatic disease found enhanced metabolic activity and migration of granulocytes and monocytes in pregnancy [75]. Another study observed an increase in the expression of CD11b, CD14, and CD64 and CD32 on monocytes [76] in pregnancy with a peak in the third trimester [77]. Enhanced production of IL-12 was demonstrated in monocytes from pregnant women [76]. Monocytes also displayed an increased capacity for phagocytosis [77]. By contrast, several studies of neutrophil function in pregnant women and pregnant RA patients found decreased phagocytosis and reduced neutrophil superoxide anion release in pregnancy [73, 78]. Similar reduction in neutrophil responsiveness to external stimuli was found in studies incubating neutrophils with supraphysiological levels of estradiol [79]. The contradictory results in regards to neutrophils are partly related to the method used to measure superoxide anion production and to the definition of neutrophil activation. As has been pointed out, different results are obtained depending on whether extracellular release of reactive oxygen metabolites (ROM) or intracellular release is measured [80]. Neutrophils of pregnant women show enhanced spontaneous intracellular ROM release [80]. This can be defined as “activation,” whereas stimulated extracellular ROM release has been found

diminished, and this could be labeled as “suppression” of neutrophil function [80].

Conclusion

The spontaneous improvement or remission of RA during pregnancy remains an intriguing phenomenon that inspires continuous research. The beneficial effect of pregnancy on a disease that affects different organ systems must be mediated by circulating factors, either proteins or trafficking cells. Because the etiology of RA at present is not known, one can only speculate on the importance of the possible candidates presented in this review.

The crucial event of pregnancy is the implantation of the fertilized egg and the resulting presence of a semiallogeneic graft in the mother for 9 months. In spite of contact with fetal cells, maternal T cells are tolerized to paternal antigens. The presence of HLA antigens that differ from maternal HLA class II antigens at the DQ loci have been proposed as beneficial for the course of RA during pregnancy. However, at present, the mechanisms by which the ameliorating effect is achieved remains unclear. It seems unlikely that HLA disparity between mother and fetus promotes the expansion of Treg because the study of Aluhivare et al. [53] showed the gestational increase in CD4+CD25+ Treg both in syngeneic and allogeneic pregnancies. Thus, expansion of Treg is not driven by fetal alloantigens. However, maternal–fetal disparity could come into play through induction of Th2-type cytokine secretion in T cells, which is supported by the work of Chaouat et al. [63]. The beneficial effect of counteracting the predominance of Th1-type cytokines has been convincingly shown by the success of TNF-blocking agents in inflammatory rheumatic disease. This suggests that any condition that suppresses Th1 pathways can ameliorate activity of RA. In pregnancy, the concerted action of hormones and of fetal cells including the trophoblast promotes an anti-inflammatory milieu not only at the maternal–fetal interface but also systemically. The tolerizing effect of pregnancy is not limited to adaptive immunity. Furthermore, monocytes and neutrophils undergo changes that support their vigilance but counteract a proinflammatory milieu.

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