The observed adaptations of the immune system during pregnancy are, in general, thought to result from hormonal changes associated with pregnancy. In this respect the effect of oestrogens, progesterone and cortisol have been most widely studied. Briefly, in high concentrations, compatible with pregnancy, oestrogens inhibit T-cell function; in particular, Th1 cells, inhibit the production of interleukin (IL)1, IL6, IL12 and tumour necrosis factor by monocytes/macrophages and dendritic cells, but stimulate (auto)antibody production. Progesterone inhibits production of IL1, IL6 and IL12 and stimulates Th2 effects, whereas cortisol is thought to have a general immunosuppressive effect.

That pregnancy hormones exert both immunostimulatory and immunosuppressive properties has often been used as an explanation for the different impact that pregnancy may have on various autoimmune diseases, depending on the pathogenic mechanisms involved. Despite all the conflicting results there is some agreement that the frequency of flares is higher in pregnant than in non-pregnant women with systemic lupus erythematosus.14 15 The role for oestrogens in the suppression of the immune system during pregnancy or whether these changes are also responsible for the ameliorating effect of pregnancy on RA.

Radboud J E M Dolhain

In this issue of the Annals of the Rheumatic Diseases 'Wallenius et al' report an increase in the occurrence of pregnancy-RA on RA disease activity, including, for example, an increase in regulatory T cells, a shift from Th1 to Th2 cells and changes in glycosylation of IgG. However, owing to the difficulty in performing a prospective study in pregnant RA women, the majority of these studies are small and hence do not allow a comparison of patients with RA who improve during pregnancy with those who do not. Therefore, it can often not be concluded from these studies whether the observed changes only represent a general adaptation of the immune system during pregnancy or whether these changes are also responsible for the ameliorating effect of pregnancy on RA.

In the well-known ameliorating effect of pregnancy on RA, the flare of RA after delivery is often explained by a gradual returning of the immune system to a pre-pregnancy state after delivery. Owing to the lack of studies, it is not known whether such a gradual returning of the immune system to this pre-pregnancy state occurs. On the contrary, it might very well be that like pregnancy also the postpartum period represents a specific state of the immune system that differs from the state before pregnancy. In this respect, a role for high prolactin levels, associated with breastfeeding, has been suggested. Prolactin is thought to be involved in the breakdown of B-cell tolerance, enhancing cell proliferation and the development of antigen presenting cells. It promotes immunoglobulin production and the production of proinflammatory cytokines.16 In RA, breastfeeding has been associated with the occurrence of the postpartum flare.17 The interpretation of this association, however, is difficult, since women who breastfeed are in general not receiving medication and hence are more likely to flare.

We have recently found that the postpartum period has a specific influence on the levels of mannose binding lectin (MBL). MBL is a complement factor that initiates the lectin pathway of complement. During pregnancy MBL levels are increased, but after delivery MBL levels decline to such an extent that some women even become MBL deficient, before returning to normal in the next few months.18 Although a role for MBL in the pathogenesis of RA has been questioned,19 this finding clearly illustrates that the changes of the immune system in the postpartum period do not simply reflect a gradual returning of the immune system to its pre-pregnancy homoeostasis, but may rather reflect a specific situation. Such a specific situation could, from an immunological point of view, be an explanation for the increased incidence of RA and other forms of chronic arthritides in the postpartum period. However,
more epidemiological data are needed to determine whether this is a true increased incidence or whether rather the incidence of RA and other forms of arthritis is postponed to after delivery. Unfortunately, this question is not answered in the article of Wallenius et al.1

What can we learn from studies on pregnancy and RA? Our concept of the syndrome that we call RA has changed dramatically during the past decade. One of the most revolutionary concepts is that RA is not a fixed entity that just occurs, but has a long preclinical period.22 This is supported by the finding that RA-specific antibodies like ACA and rheumatoid factor can be found years before the actual onset of RA.23 Although these autoantibodies are thought to be important in the pathogenesis of RA, their actual presence does not seem to be sufficient to result in arthritis.24

All these findings have led to a new pathogenic model for RA. According to this model RA results from a complex gene–environment interaction, in which RA only develops after the immune system has been triggered by several environmental factors, a process which may take years.25 One of the environmental factors that has been clearly shown to trigger RA is smoking.25 Besides predisposing environmental factors, protecting environmental factors might postpone the onset of clinical signs. The immunological mechanisms responsible, however, may be identical.

Viewed in such a way, the impact of studies like that of Wallenius et al.1 goes beyond the field of rheumatologists interested in female health issues, but these studies may contribute to a better understanding of the fundamental question why one person gets RA and another does not. The Norwegian situation in which two national health registers are linked, offers unique opportunities for more research in this particular field and more interesting data can hence be expected.

Competing interests: None.

Provenance and peer review: Commissioned; externally peer reviewed.

Accepted 30 November 2009


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