Inflammatory arthritis

Benefit of pregnancy in inflammatory arthritis

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Pregnancy related hormones provide an anti-inflammatory milieu

Observations in the 19th century (Trousseau 1871, Charcot 1881, Bannatyne 1896) indicated that pregnancy is favourable in rheumatoid arthritis (RA). This was summarised in the Nobel Prize lecture of the rheumatologist Philip S Hench, 11 December 1950 (http://nobelprize.org/medicine/laureates/1950/hench-lecture.pdf, accessed 5 April 2005). This intriguing finding stimulated clinical and basic research into endocrine immune interactions and gender studies in rheumatic diseases, particularly in RA and systemic lupus erythematosus (SLE).

Philip S Hench wrote: ''…after 1931, records of these cases (of cases with RA) were more carefully made and assembled … because of my growing belief that this phenomenon of relief (from arthritic disability) was analogous to, if not identical with, that which may occur during jaundice, and that the same agent might be responsible for the relief both during pregnancy and jaundice, although the mechanism … might be different.''[1]

Until today, the sole and only factor during pregnancy responsible for the relief from arthritic disability is not known. However, the collection of important data, which might explain the positive effects of pregnancy in these diseases, has helped us to understand this interesting phenomenon. Østensen *et al* in this issue of the *Annals* make another important contribution to the field.[2]

Th1 VERSUS Th2 PREDOMINANCE IN ARTHRITIS

RA, psoriatic arthritis, and, to a lesser degree, ankylosing spondylitis are viewed as T helper type 1 (Th1) lymphocyte dominated inflammatory diseases, in which the balance between Th1 and Th2 responses is shifted towards Th1 pathways.[3] This paradigm was complemented by the finding that aggressive fibroblasts/macrophages/osteoclasts are important in destroying bone and cartilage in arthritis.[4 5] In addition, B lymphocytes were recently found to participate in the inflammatory process in RA; this finding was supported by the disease ameliorating effects of the B cell depleting antibody, rituximab.[6] In collagen type II arthritis the IgG2 isotype predominates and the B cell response is governed by Th1 pathways.[7]

These important cellular components of the destructive process in arthritic joint diseases are modulated by several steroidal hormones and neurotransmitters. The importance of hormonal factors and neurotransmitters in arthritis has been extensively reviewed recently.[8 9] Hormones and neurotransmitters, which support Th2 mediated immune responses and which inhibit fibroblasts and macrophages, are thought to counteract the arthritic process. Thus, any biological situation with a hormonally induced Th2 dominance will necessarily lead to improvement in Th1 dominated arthritic diseases.[10] If, in addition, these modulatory hormones have additive immune inhibiting effects on macrophages and fibroblasts, the arthritic disease will be further ameliorated.

Th2 DOMINANCE IN NORMAL PREGNANCY—AND BEYOND

As early as in 1993, Wegmann and colleagues proposed that successful pregnancy is a Th2 phenomenon.[11] Many subsequent studies in this field have shown that normal pregnancy is accompanied by Th2 dominated phenomena.[12]

> ''The factor during pregnancy responsible for the relief from arthritic disability is still not known''

Nowadays, a series of new studies have taken us well beyond the Th2 paradigm in pregnancy because, for example, it has been shown that cytokines such as interferon γ (IFNγ) at low concentrations are needed for successful implantation of the blastocyst (supported by placental neovascularisation). Cytokine effects at various stages during the course of pregnancy have to be considered and cytokines have a key role in local tissue remodelling, while not always being secreted by immune cells.[13] Although the Th2 paradigm is an oversimplification in reproductive immunology, it was initially useful but now needs to be complemented by several other important elements (for further reading see Chaouat *et al*[13]).

Th2 DOMINANCE IN PREGNANT PATIENTS WITH INFLAMMATORY ARTHRITIS—AND BEYOND

The first indication that Th1 pathways are suppressed in pregnant patients with RA was provided by Russell *et al* in 1997.[14] Whole blood cultures stimulated by lipopolysaccharide were shown to release less interleukin (IL) 2 but more soluble tumour necrosis factor (TNF) receptor p55 and p75 during pregnancy. In their study serum TNF and IL1β concentrations were unchanged.[14]

In addition, other authors demonstrated decreased IFNγ, IL12 and increased IL6 production by lymphocytes after phytohaemagglutinin stimulation in third trimester pregnant women with RA as compared with healthy pregnant woman without RA.[15] This study was complemented by data in patients with RA (third trimester pregnancy) which showed that ex vivo monocytic IL12 production was about threefold and TNF production was approximately 40% lower than postpartum values.[16] In a prospective longitudinal study, increased levels of IL10 were found in pregnant women with RA or SLE as compared with healthy pregnant controls.[17] Interestingly, a similar phenomenon for IL10 was confirmed in patients with SLE, whereas a lower than expected increase of IL6 was found in third trimester pregnancy.[18]

In their study, Østensen *et al* longitudinally studied plasma and serum samples of pregnant patients with RA, with juvenile idiopathic arthritis, and with ankylosing spondylitis, and they compared these groups with samples from healthy pregnant women.[2] Clinical assessment and blood sampling in pregnant women was done once in each trimester and 6, 12, and 24 weeks post partum.

Significantly higher concentrations of the soluble TNF receptor p75 and IL1 receptor antagonist (IL1Ra) were measured in pregnant than in non-pregnant women.[2] An increase of IL1Ra from the second to the third trimester correlated with improvement of disease activity both in patients with RA and those with ankylosing spondylitis.

Compared with non-pregnant patients and with the other pregnant women, patients with RA had markedly raised levels of soluble CD30 during pregnancy.[2] CD30 (Ki-1) antigen has

been considered to be expressed on haematopoietic cells (for example, Reed-Sternberg cells of Hodgkin's disease) but also on non-haematopoietic cells such as human decidual cells.

It is thought that CD30 is a relatively specific marker for Th2 lymphocytes, which is not expressed on Th1 cells.[19]

All these data in pregnant women with inflammatory arthritis indicate a Th2 dominance which may be even more pronounced than in healthy pregnant women. In addition, the work by Østensen *et al* and Russell *et al* demonstrate that important anti-inflammatory factors, such as soluble TNF receptors and IL1Ra, are up regulated. Furthermore, these studies indicate that favourable changes during pregnancy reverse after delivery, leading to increased disease activity. The question is whether or not pregnancy is accompanied by hormonal changes which might modulate immune mechanisms.

Th2 DOMINANCE AND PREGNANCY HORMONES

During the course of normal pregnancy, hormones such as cortisol, dehydroepiandrosterone (DHEA), progesterone, oestrogens, and norepinephrine strongly increase (summarised by Kanik and Wilder[20]). For example, during pregnancy progesterone serum levels increase by a factor of four and oestriol serum concentrations increase by a factor of 20 (which can be regarded as a pharmacologically high dose). Of these hormones, cortisol, oestrogens, norepinephrine, and particularly, progesterone induce a Th2 pathway predominance (table 1). In addition, these hormones and the sex hormone precursor DHEA inhibit many proinflammatory macrophage functions (table 1). These hormones are needed to establish an immune tolerant milieu in the uterus in order to prevent the rejection of the semiallogeneic fetus.

The role of progesterone for inhibition of CD8+ lymphocyte mediated fetal rejection has recently been documented in a mouse model.[21] Other groups have demonstrated that oestriol altered the cytokine profile of human T lymphocytes towards a Th2 phenotype by up regulating the production of IL10 and inhibiting TNF secretion of T cells.[22]

> "Might pregnancy be accompanied by hormonal changes which modulate immune mechanisms?"

Further characterisation indicated that oestriol inhibited nuclear transcription factor κB (NF-κB).[22] Interestingly, these effects are only observed at a very high concentration of oestriol of 20 ng/ml, which is similar to the serum concentration in late pregnancy. Normally, oestriol is not measurable in the serum of men and women, and only low concentrations of oestriol are expected in peripheral tissues as there is little conversion of precursor hormones. Low concentrations may be proinflammatory, whereas typically higher pregnancy oestriol levels can be regarded as anti-inflammatory. The important effects of high doses of oestriol were further supported in a pilot clinical trial with oral oestriol treatment of patients with relapsing remitting multiple sclerosis[23]: peripheral blood mononuclear cells collected longitudinally during the trial were given different stimuli, and it was demonstrated that supernatant levels of IL5 and IL10 increased, whereas levels of TNF decreased during oestriol treatment.[23]

In addition, norepinephrine stimulates a Th2 phenotype through the β_2 adrenoceptor.[24 25] Norepinephrine is supported by cortisol owing to cooperative effects of the two hormones, which lead to an increase in glucocorticoid receptors, β adrenoceptors, intracellular cyclic AMP, protein kinase A, and cAMP responsive, element binding protein, a sequence of events which has been demonstrated in various cell types.[26–34] Similar cooperation between norepinephrine and cortisol has recently been demonstrated in mixed synovial cells of patients with RA.[35] Owing to an increase of norepinephrine and cortisol in pregnancy, these two hormones may additionally support a Th2 predominance and a macrophage suppressive environment.

The question appears to be whether or not hormones during pregnancy in patients with RA or ankylosing spondylitis are normal as compared with those in healthy subjects. The present data do not indicate a large difference in typical pregnancy hormones in patients with RA or ankylosing spondylitis as compared with healthy controls.[2 16] Interestingly, recent studies in pregnant patients with SLE showed different hormonal changes than in healthy pregnant subjects.[36] Oestradiol and progesterone showed the most relevant alterations because both were significantly lower than expected in pregnant women with SLE in the second and to a greater extent in the third trimester, periods in which these hormones are predominantly secreted by the placenta. Thus, the decrease in their serum concentration might suggest placental dysfunction. In fact, placental alterations related to a decidual vasculopathy/coagulopathy and/or chronic villitis of unknown aetiology are frequently reported in SLE pregnancies, even in the absence of known risk factors, such as antiphospholipid antibodies. These problems seem to be specific to SLE as they were not reported in inflammatory arthritis.

Table 1 Immunomodulation by adrenal/gonadal hormones and sympathetic and sensory neurotransmitters.[37]

Hormone	Modulation of innate and adaptive immune functions
Cortisol	Inhibition of oxidative burst, phagocytosis, collagenase production, antigen presentation, COX-2, IL1, IL2, IL6, IL12, IFNγ, TNF etc, support of Th2 pathways (together with norepinephrine)
DHEA	Inhibition of oxygen radical production, IL1, IL6, TNF
Oestrogen	Inhibition of IL1, IL6, TNF (pharmacologically high concentration), stimulation of immunoglobulin production (physiological concentration)
Progesterone	Inhibition of T helper 1 pathways, increase of T helper 2 pathways, increase of CD30 expression on T cells, inhibition of TNF, IL1β, and IL6
Norepinephrine (via β adrenoceptors)	Inhibition of oxygen radicals, phagocytosis, NK cell activity, HLA class II expression, IL2, IFNγ, IL12, TNF, increase of Th2 pathways (together with cortisol)

COX-2, cyclo-oxygenase type II; DHEA, dehydroepiandrosterone; HLA, human lymphocyte antigen; IL, interleukin; IFN, interferon; NK, natural killer cell; TNF, tumour necrosis factor.

CONCLUSION

The present data led to the hypothesis that pregnancy related hormones provide an anti-inflammatory milieu. This is (*a*) supportive for successful reproduction, and (*b*) also positively influences inflammatory arthritis. Pregnancy-specific immune changes occur predominantly at the maternal-fetal interface, but these changes also elicit systemic effects in the maternal circulation and at sites distant from the uterus. Although all studies in humans are associative in nature, this hypothesis is based on relatively good clinical evidence. Future therapeutic studies with pharmacologically high doses of oestriol or progesterone in RA, ankylosing spondylitis, or psoriatic arthritis may

shed new light on this intriguing question. The accidental finding that pregnancy is favourable in these diseases suggests that hormonal factors and neurotransmitters are important players in modulation of the arthritic process.

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