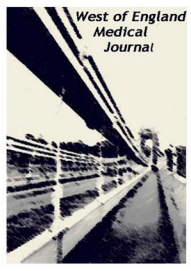

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Pregnancy in Rheumatoid Arthritis and Systemic Lupus Erythematosus

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INTRODUCTION

Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) are both auto-immune diseases, but with contrasting immune pathophysiology. RA is described as a predominately T cell-mediated immune disorder, characterised by a type 1 (pro-inflammatory) cytokine environment (see table 1), also known as a T-helper1 (Th1) immune response. SLE, however, is associated with a Type 2 (anti-inflammatory) cytokine environment (see table 1) synonymous with a T-helper2 (Th2) immune response. It is therefore described as a predominately antibody-mediated immune disorder [1, 2].

Type 1 cytokine environment	Type 2 cytokine environment
Tumour necrosis factor (TNF)-alpha and beta	Interleukin-4 (IL-4)
Interferon (IFN)-gamma	Interleukin-5 (IL-5)
Interleukin-2 (IL-2)	Interleukin-10 (IL-10)
Interleukin-1 (IL-1)-alpha and beta	Interleukin-13 (IL-13)
Interleukin-8 (IL-8)	
Interleukin-12 (IL-12)	

Table 1: Type1/2 cytokine profiles Source: Information adapted from: Mosmann T R & Subash S. 1996. The expanding universe of T-cell subsets: Th1, Th2 and more. Immunol. Today 17:138-146

CLINICAL RECOGNITION OF RA AND SLE

The majority of patients with RA present with pain and swelling of the small joints of the hand and feet, particularly the metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints respectively. This can be summarised as a symmetrical polyarthritis of the small joints of the distal limbs . Pain and swelling of other joints such as the wrist, elbow, shoulder, knee and the ankle can also be present. Although the pattern of inflammation of the joints is usually polyarticular, approximately 10% of cases can present with monoarthritis of the knee or shoulder or carpel tunnel syndrome. The patient may also complain of stiffness that is significantly worse in the morning but reduces during the day as mobility increases. Reduced movement and muscle wasting can also be found on examination of the affected area [3].

With SLE clinical presentation varies between patients but the majority will present with fatigue and arthralgia. A butterfly shaped rash over the malar area and bridge of the nose can occur, characteristic of SLE's dermatological manifestation. Joint involvement is the most common clinical feature and patients usually have symmetrical small joint arthralgia resembling RA, although the joints can appear clinically normal. Connective tissue disorders are also associated with SLE in a number of cases affecting the muscles (50%), skin (85%), lungs (50%), cardiovascular system (25%), kidney (30%), nervous system (60%) and eyes (15%). [4]

EFFECT OF PREGNANCY ON RA AND SLE

During pregnancy it has been observed that the clinical manifestations of these diseases change. More than three-quarters of patients with RA improve during the first and second trimester of pregnancy with reports of remission during the third and last trimester [5-7]. Hench first observed this phenomenon in 1938, when he reported that eighteen out of the twenty-two women with RA involved in his study had diminished symptoms during pregnancy[8]. In 1997, further studies supported Hench's findings with an estimation that amelioration of RA during pregnancy was between 54-86% with an average of 75% [9]. However, the basis for these values has been shown to be limited retrospectively, due to the lack of standardised measurements of disease progression to support such figures[10]. In 2008, a prospective study looked into this occurrence, measuring disease activity using the DAS28 and DAS28 derived European League Against Rheumatism (EULAR) response criteria. Results showed a decrease in RA disease activity during pregnancy with statistical significance (P = 0.035)[11].

Conversely, SLE has been shown to flare during pregnancy, particularly the cutaneous and articular manifestations [12,13, 14-16]. Between 5%-46% of patients will have a severe flare with major organ involvement such as lupus nephritis [17,18]. Observational studies have shown that those with active disease at the time of, or around conception, have a higher risk of a flare and the reverse is true [12, 16, 19, 20]. Findings from some prospective studies report that the incidence of flares is highest during the second trimester and lowest in the third [12, 13, 21, 22].

Such findings may reflect the fact that during pregnancy women with SLE show no peak in progesterone and oestrogen in the third trimester compared to healthy individuals [12,23], possibly due to placental damage that occurs during pregnancy in a mother with SLE[12].

EFFECT OF RA AND SLE ON PREGNANCY

The effect of RA on pregnancy is still inconclusive. Although it has been shown that women with RA do not have an increased rate of spontaneous abortions [24,25,26] there are uncertainties as to whether or not there is an association between RA and premature delivery and also reduced birth weight. A prospective study investigating disease activity in RA and the effect on pregnancy concluded that women with well-controlled RA have a comparable outcome of pregnancy with the general population. The use of prednisone to manage RA was found to cause a significantly lower gestational age at delivery however (P = 0.001), often with premature delivery (<37 weeks, P= 0.004). High level of disease activity showed an independent negative correlation with birth-weight suggesting an immune-mediated mechanism [27].

Increased rate of foetal loss has been reported in patients with SLE in both retrospective and prospective studies [28], with some retrospective studies concluding that foetal loss is 1.5-2.5 times higher compared to the healthy population. It has been identified that factors such as past renal disease, active SLE, presence of anti-phospholipid antibodies and a previous history of foetal loss all increase the risk [29,30]. In addition, pre-term birth, foetal growth restriction and pre-eclampsia have also been associated with SLE [31].

However, the focus of my internal student selected component (iSSC) will be looking in greater depth at the immunological changes that occur in RA and SLE during pregnancy, particularly changes in immune response. This may give some explanation as to the changes in disease activity observed clinically. RA and SLE both have a higher prevalence in women than men and therefore issues surrounding pregnancy are common. An awareness and understanding of the changes that occur during pregnancy are important to recognise for any clinician involved with the management of these patients, especially concerning medication during pregnancy. It is for this reason that I have decided to explore this topic for my iSSC.

PREGNANCY AND IMMUNOLOGY

Physiological immunological changes:

In theory, the maternal immune system should not be able to support a semi-allogenic foetus due to the presence of paternal antigens. Therefore, in order to prevent rejection accommodative changes must occur. However, these changes most occur without compromise to the maternal immune system. Instead a system must be achieved where there is immune 'mutualism' between the mother and the foetus [32].

Trophoblast cells are involved in the development of maternal immune tolerance by the expression of membrane molecules on their cell surface [32]. However, more significant to this essay, are the changes made to maternal cytokine profile peripherally and at the maternal-foetal interface:

1. Increases in cortisol, progesterone, oestradiol and testerone during pregnancy have been shown to be associated with an increased production of Type2 cytokines and a reduction in type1 (see table1). As a result,

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an antibody-mediated immune response is favoured and a cell-mediated immune response dampened [33,34,12]. This is in order for the trophoblast cells to invade and attach onto the decidua [35].

2. Serum levels of cytokines and cytokine receptors change throughout the trimesters of pregnancy. In the systemic circulation serum levels of type 2 cytokines have been shown to progressively increase throughout pregnancy whereas Type 1 cytokines significantly decrease in the third trimester compared to the first [36,37,38].

Immunological changes in RA during pregnancy:

Through animal and human studies, evidence has been gathered which shows that pregnancy is involved with a shift in the Th1/Th2 immune response and hence a subsequent alteration in the cytokine environment [39-41]. Peripheral blood cells from pregnant women support this, showing a down-regulation of IFN-gamma and IL-2, characteristic of a type 1 cytokine environment, and an increase in the production of the type 2 cytokines, IL-4 and 10 (table 1, p1) [42-44]. These alterations in immune response create a shift from a T cell-mediated immune response, associated with the immune pathology of RA, to an antibody-mediated immune response. Soluble receptors of IL-6 and TNF-alpha, alongside soluble IL-1 receptor antagonist increase during pregnancy [45,46, 47], elevating a Th1 immune response in favour for a th2 response. However, the majority of these changes are dependant on an increased serum cortisol concentration as well as the sex hormones oestrogen and progesterone. Glucocorticoids have been shown to suppress many pro-inflammatory cytokines, many of which are mentioned in table 1 (page 1). During pregnancy lymphocytes develop progesterone receptors which, when activated, release a protein known as progesterone-induced blocking factor (PIBF) [48]. PIBF positive lymphocytes secrete IL-10, and in addition, PIBF has strong anti-natural killer cell activity [44] once again, favouring a shift from a T-cell mediated response to an antibody-meditated response. A change from the production of type 1 cytokines to type 2 cytokines, as well as inhibition of the type 1 cytokines by soluble receptors, shifts the immune system to an antibody-mediated immune response (Th2) that may contribute to the remission of RA observed clinically.

Immunological changes in SLE during pregnancy

Pregnancy is associated with elevated concentrations of progesterone and oestrogens. Oestrogens have been shown to support B-Cell maturation as well as antibody formation [49] therefore favouring an antibody-mediated immune response. This is predominately the cause of the autoimmune pathophysiology of SLE and hence a possible mechanism behind the exacerbation observed during pregnancy. The shift created by pregnancy from a cell-mediated immune response to an antibody-mediated immune response, theoretically could also explain the exacerbation and new development of lupus nephritis that can develop during a flare [50]. Peripheral blood cells from patients with SLE have been shown to respond to oestrogen treatment with a reduction in TNF-alpha. As TNF-alpha is one of the factors that regulate apoptosis, a reduction in its production during pregnancy may cause a disruption of programmed cell death of activated immunocompetent cells in SLE, propagating the autoimmunity [51,52].
Progesterone, on the other hand, has been shown to increase the production of IL-4 and IL-10 in human T-cells hence assisting T-cell differentiation from a Th1 immune response to a Th2 immune response [44], again showing the favouring of the antibody-mediated immune response during pregnancy. However, other studies have noted a significant decrease in the levels of IL-4 mRNA expression during all trimesters of pregnancy compared to healthy pregnant women [53], adding some controversy to the picture.
Pregnant women with SLE do have higher serum levels of IL-10 during each trimester of pregnancy compared to healthy pregnant individuals. However, patients with SLE generally have a constant level of raised IL-10 serum levels, regardless of pregnancy, therefore suggesting a constitutional rather than steroid-induced hyper production of IL-10 [12, 13].

CONCLUSION:

In order for the maternal immune system to accept the semi-allogenic foetus, adaptive changes most occur. These changes are associated with a decrease in disease activity in RA but an increase in SLE. The foetus promotes a polarisation of the maternal immune system to a Th2 immune response, which relieves the mother from the autoimmune Th1 response of RA but exacerbates the autoimmune Th2 response in SLE. In terms of clinical relevance, understanding the changes that occur in pregnancy in these autoimmune diseases must be taken into account when giving advise on family planning including: the implications of pregnancy for both the mother and the foetus and also the changes to management and medication, and their subsequent effects on the mother and foetus. In terms of understanding the underlying pathophysiology more work needs to be conducted. On average only 75% of women with RA get better during pregnancy, leaving an unexplained 25% of cases. Likewise, some prospective studies have shown that there are no differences in flares between pregnant and non-pregnant women with SLE [54-57].
Further research to try to understand the immunological changes that occur during pregnancy and the factors which govern these changes may possibly reveal further subdivision of RA and SLE, leading to an explanation of the clinical differences experienced by patients during pregnancy as reported in studies. It may also provide better ways of managing the disease by knowing where to intervene more accurately and effectively pharmacologically.

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