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# AUTOIMMUNE ASPECTS OF PREGNANCY AND INFERTILITY

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## 3.1 Background

Autoimmune diseases affect more women than men. For example, it has been estimated that 75 % of roughly 8.5 million people who suffer of an autoimmune disorder in the United States are female. The precise reasons for this gender bias are unclear, but sex hormones and / or sex hormone related genes my modulate susceptibility.

Distinct immune environments in males and females underlie many of the sex differences in autoimmunity. These environments are established by the cytokines released by immune cells, particularly T helper ($T_H$) lymphocytes. Females are more likely to develop a $T_H1$ response (dominated by interleukin-2 (IL-2), interferon-g (IFN-g), and lymphotoxin) after challenge with an infectious agent or antigen, except during pregnancy when a $T_H2$ environment prevails (dominated by IL-4, IL-5, IL-6, IL-10 and TGF-b). Furthermore, the degree of immune response also differs between men and women. As androgens seem to be primarily suppressive on cellular and humoral immunity, immune responses tend to be more vigorous in females, resulting in greater antibody production and increased cell-mediated immunity after immunisation. There are several possible ways in which sex hormones could affect the immune system. They may modulate T cell receptor signaling, expression of activation molecules on T lymphocytes and antigen-presenting cells, transcription or translation of cytokine genes, or lymphocyte homing.

## 3.2. Effects of pregnancy on the course of autoimmune disorders

Pregnancy in healthy women does not seem to increase the prevalence of autoantibodies in comparison with non-pregnant control groups, but may differently affect the clinical course of several autoimmune disorders, with important consequences for both mother and offspring. In multiple sclerosis and rheumatoid arthritis, there is a decrease in disease severity during the 9 months of gestation, with a return to pre-pregnancy levels after birth. This is in contrast to lupus where the disease may worsen during pregnancy. Thus, as the particular hormone environment during pregnancy favours a $T_H2$ response, the progression of the $T_H1$ immune response associated with multiple sclerosis and rheumatoid arthritis may be halted. In contrast, pregnancy may further enhance the ongoing $T_H2$ (antibody-promoting) response associated with SLE.

The following part of the presentation will focus on common autoimmune disorders that can be regarded as typical examples for clinically relevant autoimmune aspects of pregnancy and infertility.

### *3.2.1 Rheumatoid arthritis*

Pregnancy is associated with improvement in the clinical signs and symptoms of rheumatoid arthritis in more than 70% of patients. Maternal-fetal disparity in alleles of HLA-DRbeta1, DQalpha, and DQbeta has been reported to be associated with pregnancies characterised by remission or improvement, possibly by induction of maternal-regulatory T cells, or by affecting the maternal T cell receptor repertoire via fetal presentation of associated peptides.

### *3.2.2 Systemic lupus erythematosus (SLE)*

The course of SLE is more variable. Whether flare rates increase during or after pregnancy is unsettled, since individual patient series vary in the characteristics of patients accepted for study and in definitions of flare. Despite a high overall flare rate in some series approaching 60%, recorded flares were usually not severe. More recent prospective studies indicate that pregnancy is safe for the majority of mothers - even with lupus nephritis - if pregnancy is planned when SLE is quiescent. Scoring systems for SLE related disease activity have been adapted as diagnostic tools for lupus flares during pregnancy and the puerperium. Pregnant lupus patients seem to be susceptible to pre-eclampsia, especially if they suffer lupus nephritis, and to steroid-induced hypertension and hyperglycemia.

Oral contraceptives containing oestrogens and hormone replacement therapy are generally not prescribed for women with systemic lupus erythematosus (SLE). The concern regarding estrogens is based on the greater incidence of SLE in women, abnormalities of oestrogen metabolism, murine models of lupus, several anecdotes of patients having disease flares while receiving hormones, and one retrospective study in patients with pre-existing renal disease. A 12-months hormone replacement therapy was recently shown to be associated with a small risk of increasing the natural flare rate (relative risk 1.34, $p = 0.01$), but most of the flares were mild to moderate, and hormone replacement did not significantly increase the risk for severe flares compared to placebo.

### *3.2.3 Scleroderma*

Only limited data are available regarding the incidence or outcome for either the mother with scleroderma or her fetus. The extent of diffuse skin disease and systemic involvement, particularly pulmonary, cardiac and renal, may be more important than the duration of the disease; limited disease carries a better prognosis for the mother and fetus.

## 3.3 Effects of maternal autoimmune disorders on the offspring

Transplacental transfer of autoantibodies is common, and autoantibodies can be readily demonstrated in newborn serum. Only a small proportion of infants with circulating

autoantibodies exhibit clinical symptoms. The transient neonatal manifestations of maternal autoimmune disease disappear over a time course consistent with the catabolism of IgG, providing no permanent damage occurs. Thus the pathogenic role of transferred autoantibodies seems well established. However, maternal-autoantibody-mediated tissue damage appears to depend on factors other than the mere passage of the antibody to the fetal compartment.

### *3.3.1 SLE*

The rate of loss in SLE pregnancies has decreased from a mean as high as 43 % before 1975 to 17 % and 14 % in two recent series and was found to be similar to the general US population. However, the rate of preterm delivery in mothers with SLE was still around 33 % and thus nearly the triple of what would be expected. Furthermore, fewer life births occurred among women with high-activity lupus compared to those with low-activity SLE, with high disease activity during the first and second trimesters being associated with a 3-fold increase in pregnancy loss. Especially, the survival of the fetus is strongly in doubt when cyclophosphamide is required to treat lupus in the mother. Therefore, the old dogma, that women with SLE are advised to consider pregnancy only when disease is stable, seems still to be valid. Maternal SLE does not seem to impair intelligence levels of the children, but learning disabilities have been described especially in male offsprings, and may be associated to maternal anti-Ro/La antibodies.

### *3.3.2 Neonatal lupus syndromes (NLS)*

The neonatal lupus syndromes (NLS), while quite rare, carry significant mortality and morbidity in cases of cardiac manifestations. Anti-SSA/Ro-SSB/La antibodies are detected in > 85% of mothers whose fetuses are identified with congenital heart block in a structurally normal heart. However, the risk for a woman with the candidate antibodies to have a child with congenital heart block was described to be at or below 2 %. While the precise pathogenic mechanism of antibody-mediated injury remains unknown, it is clear that the antibodies alone are insufficient to cause disease and fetal factors are likely contributory, including apoptosis of cardiocytes, surface translocation of Ro and La antigens, binding of maternal autoantibodies, and a scarring process that involves TGFbeta and cardiac myofibroflast. The spectrum of cardiac abnormalities continues to expand, with varying degrees of block identified in utero and reports of late onset cardiomyopathy.

Moreover, there is now clear documentation that incomplete blocks can progress postnatally, despite the clearance of the maternal antibodies from the neonatal circulation. Furthermore, cutaneous, hematologic, hepatic abnormalities and serositis have been described, but are usually transient. Mothers of affected infants are often asymptomatic, and when symptomatic, the clinical features are frequently characteristic of Sjögren's syndrome

### *3.3.3 Immunosuppressive drugs during pregnancy*

The management of pregnancy in patients with autoimmune disorders includes the treatment of disease flares, using drugs effective but safe for the fetus. Corticosteroidsare

routinely used to control maternal disease. Some immunosuppressive drugs such as azathioprine may also be regarded as relatively safe, whereas others such as cyclophosphamide and methotrexate are clearly contraindicated. The last 10-year experience shows that fetal exposure to antimalarial drugs should not be regarded as an important risk factor for gestational nor neonatal complications. However, information about long-term outcome of children exposed to immunosuppressive drugs "in utero" are still lacking and more efforts are needed in this research area.

### 3.4 Autoimmune aspects of infertility

Both anti-phospholipid and anti-thyroid antibodies have been linked to infertility and pregnancy loss. The anti-phospholipid syndrome (APS) is a non-inflammatory disease characterised by the presence of anti-phospholipid antibodies in the plasma of patients with venous or arterial thrombosis or obstetric complications such as recurrent abortions and miscarriage. APS is usually diagnosed in the setting of maternal SLE, but may present as a primary syndrome. An overwhelming activation of complement triggered by antibodies deposited in the placenta seems to be pathogenetically important. Recent data indicate that only a subpopulation of the heterogeneous population of anti-phospholipid antibodies is pathogenic, antibodies against β2-glycoprotein I being especially important. In patients who fulfil criteria for APS, recent papers advocate combined treatment with aspirin (75-100 mg/d) and low molecular weight heparin, rendering obstetric APS to a treatable condition in most patients.

The association between thyroid autoimmunity and adverse fetal outcome has been described repetitively and was recently confirmed in a meta-analysis, that found a clear association between the presence of anti-thyroid autoantibodies and miscarriage in case control (odds ratio 2.7; 95 % CI 2.20 - 3.40) and longitudinal studies (odds ratio 2.3; 95 % CI 1.80 - 2.95). In a study investigating anti-thyroid antibodies and anti-phospholipid-antibodies in women with recurrent spontaneous abortions, anti-thyroid antibodies were found in 27 % of patients and were associated with a significantly lower percentage of spontaneous pregnancies and life births when compared with women who were tested positive for anti-phospholipid antibodies and negative for anti-thyroid antibodies. The underlying pathogenetic mechanisms are unclear.

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