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EDITORIALS

# Pregnancy and autoimmunity

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**ABSTRACT**

*Reproduction is intricately involved with the immune system. Pregnancy affects the immune system in such a way as to maintain the fetal-maternal allograft, which displays paternal antigens. The human uterus is generally considered to be an immunologically privileged site that isolates the implanted allogeneic embryo from an aggressive maternal immune response. Recent evidence suggests that maternal autoimmune or alloimmune aberrations may be involved in pregnancy rejection. Pregnancy seems particularly susceptible to immunologic interference during the very early and very late stages of gestation. During early pregnancy subclinical autoimmune processes seem capable of causing both pregnancy loss as well as congenital fetal abnormalities such as congenital heart block. Several, disorders that are historically associated with pregnancy loss – such as collagen vascular diseases (most notably systemic lupus erythematosus), chronic active hepatitis, inflammatory bowel disease, diabetes mellitus and thyroid disease – are autoimmune disorders. In women who suffer from rheumatic diseases the risk of repeated fetal loss, intrauterine growth restriction, and preterm birth remains higher than in the general population. At present, it seems that there are various antibodies associated with pregnancy loss. These include antiphospholipid antibodies, antithyroid antibodies and antinuclear antibodies. In this light, and because women are preferentially affected by a wide variety of autoimmune diseases, the subject of pregnancy and autoimmunity is of special interest.*

**Key words:** pregnancy, autoimmunity, connective tissue disorders

The inter-relationship between pregnancy and connective tissue disorders has been the important subject, now increasing, attention over the last half-century since. The dominance in women is associated with autoimmunity and recurrent miscarriage in the first trimester of pregnancy. The general effect of pregnancy on autoimmunity remains controversial. In the majority of cases, pregnancy may

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have no effect on the disease, while on other occasions, pregnancy induces exacerbations that may be especially pronounced in the immediate post-partum period. The reasons for this preponderance are still unclear.

Conversely, pregnancy tends to suppress the immune system, so the mother won't reject the new tissue she is growing. Some autoimmune diseases move into remission during pregnancy, only to rebound with sometimes violent flares when the mother is postpartum. Throughout the course of a pregnancy, a mother can develop autoimmune problems that can lead to recurrent spontaneous abortion. These autoimmune problems can be considered to be "self-immune" problems that the mother develops in response to pregnancy. Nowadays, with better treatment options and more understanding of how to control the disease process, many women with these conditions can look forward to successful, if somewhat complicated pregnancies. The application of an effective therapy has completely changed the prognosis the pregnancy in these patients. Some autoimmune diseases move into remission during pregnancy, only to rebound with sometimes violent flares when the mother is postpartum. Pregnancy is associated with improvement in the clinical signs and symptoms of rheumatoid arthritis (RA) in more than 70% of patients. RA tends to go into remission during pregnancy. The recent recognition that subclinical autoimmune processes may be causally related to repeated early-pregnancy loss has allowed for the conceptional connection between the fields of infertility and obstetrics. In order to cause pregnancy loss, autoimmune mechanisms might work by attacking the placenta or the epithelium of blood vessels and platelets which determine the maternal blood supply to the fetus. Very acutely occurring immune processes in late pregnancy can endanger both maternal and fetal life and need therefore to be clinicaly recognized as such (1).

Maternal tolerance of the fetal allograft could be the result of the integration of numerous mechanisms promoted by decidual natural killer (NK) cells, macrophages and T cells. Pregnancy is a condition in which profound immune-endocrine changes occur in order to achieve immunosuppression and tolerance by the immune system to paternal and fetal antigens. It is well known that estrogens progressively increase in maternal circulation during pregnancy, particularly in the third trimester. This increase is the result of a unique interchange between mother and fetus. Although less markedly an increase in cortisol and progesterone was also observed during pregnancy (2).

The placenta also secretes hormones that can suppress immune reactions. There is evidence that women also produce blocking antibodies, which may block their immune response to the fetus. It is known that glucocorticoids inhibit IL-1, TNF-α, IFN-γ and IL-2 production and stimulate IL-10, IL-4 and IL-13 synthesis, confirming a modulatory effect on the balance between anti-inflammatory/immunosuppressive responses during pregnancy. It has been demonstrated that during pregnancy IL-6 serum levels gradually increase in the maternal circulation and even more so during labor. TNF-α serum levels do not vary during pregnancy, whereas those of the TNF-α soluble receptors increase – probably to protect the fetus from the dangerous effects of TNF-α (3).

Many women with autoimmune disorders, such as systemic lupus erythematosus (SLE), have an increased risk of miscarriage. In contrast, 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 (4).

If a woman suffers from autoimmune disease, several factors can affect pregnancy or neonatal outcome: repeated spontaneous pregnancy losses (frequently related to antiphospholipid antibodies, neonatal lupus with complete congenital heart block linked to transplant passage of IgG anti Ro/SS-A antibodies) and the disease activity itself that can affect the mother, the pregnancy and fetal outcome (5).

Autoimmune rheumatic diseases affect young females in their childbearing years. It is noteworthy that some autoimmune diseases (such as SLE), which are mainly mediated by Th2 cytokines, tend to occur or relapse during pregnancy, whereas Th1-mediated diseases (such as RA) tend to improve in both cases there is a flare or onset of disease during the postpartum period, when the anti-inflammatory Th2 cytokines collapse due to a modification in the balance between estrogens and androgens and to an increase in prolactin levels. Lupus carries a high risk of miscarriage, as it can promote blood clots that may interfere with placenta function (6).

Patients with SLE have an increased frequency of disease flares during pregnancy, compared to nonpregnant SLE patients. Transplacental passage of IgG anti-Ro/SS-A antibodies is linked to neonatal lupus (2%). Transplacental passage of antiplatelet antibodies, in about 10% of mothers with SLE, can induce thrombocytopenia in the fetus or the neonate (7,8).

Data on pregnancy outcome in other autoimmune diseases such as ankylosing spondylitis, Sjögren's syndrome, undifferentiated connective tissue diseases, systemic sclerosis, polymyositis/dermatomyositis and systemic vasculitis, are limited mainly because most of them are rare and their onset occurs after the age of 40. Adult women with type 1 diabetes may have successful pregnancies, but they tend to fare better if their disease is well controlled, with no heart, eye, or kidney problems. Diabetic women must be extremely vigilant about their blood sugar, especially for the first eleven weeks. One special caution for pregnant women with multiple sclerosis is that they may lack the muscular strength to deliver the baby without surgical intervention. A combination of pregnancy and scleroderma isn't common, because this disease is typically diagnosed between age forty and fifty – a time when most women have completed their childbearing. When a woman with scleroderma does get pregnant, the possible complications are serious (1,9).

Several different autoimmune abnormalities exist, which include antiphospholipid antibodies (aPL) that have been clearly associated with recurrent pregnancy loss, as well, as antinuclear antibodies, which are still being investigated as to the possible effects they have on reproductive failure. Antiphospholipid antibodies are frequently observed in patients with SLE. Little is known about the genetic mechanisms involved in antiphospholipid antibodies or antithyroid antibodies. Antiphospholipid antibodies are associated with recurrent pregnancy losses that may occur at any age of gestation. The pathogenesis of pregnancy failures is linked to the thrombophilic effect of a antiphospholipid antibodies but also to different mechanisms including a direct effect of antibodies on the throphoblast differentiation and invasion. Thus, antiphospholipid syndrome and SLE carry a miscarriage rate of 7-8 and 22%, respectively, with a higher risk for fetal death after the first trimester (7,10).

Women with Crohn's disease are usually counseled to wait for a year after abdominal surgery before starting a pregnancy (11). There is a known association of miscarriage with the presence of autoantibodies against the thyroid gland; women found to have such antibodies were statistically more likely to experience spontaneous abortions. Most studies have shown a significant positive association between the presence of thyroid autoantibodies and miscarriage rate. Pregnancy loss among patients with thyroid antibodies could be induced by several putative mechanisms including thyroid dysfunction, as seen in Hashimoto's thyroiditis. However, the higher prevalence of anti-thyroid antibodies in women with miscarriages may reflect a predisposition for an underlying autoimmune disease, rather than overt thyroid hormone abnormalities (12). ❑

## CONCLUSION

The relation of autoimmunity to miscarriage is an important issue that has attracted the interest of many investigators.

The outcome of pregnancy is dependent upon two immunological reactions: alloimmune reactions, reaction to and with antigens from a genetically non-identical individual of the same biological species, and autoimmune reactions, reaction to and with self-tissues.

Pregnancy is a physiological condition that affect the course and severity of numerous autoimmune diseases.

Systemic lupus erythematosus and diabetes mellitus are two autoimmune diseases which have been associated with pregnancy loss.

The considerable progress in the clinical immunology of pregnancy made over the last few years needs to be continued by defining the clinically observed processes immunologically and biochemically in more detail. ❑

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