

Spotlight on the Role of Natural Killer Cells in Recurrent Spontaneous Abortion

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Introduction to recurrent spontaneous abortion

The uterus is an enigma. Despite a full complement of immunocompetent cells, it allows the fetal allograft to thrive for 40 weeks.

During pregnancy, the fetoplacental unit orchestrates immune mechanisms via T and B lymphocytes, natural killer (NK) cells, a variety of soluble immunoregulatory factors (cytokines), and antibodies. To a significant degree, the interaction between maternal and fetoplacental tissue and the immune system will determine whether a pregnancy succeeds¹. Many theories explain the decreased cell-mediated immunity in pregnancy (decrease in CD4 cells; increase in CD8 cells; and defective cytotoxic activity of NK cells). So-called IgG (blocking antibodies of pregnancy) have been implicated, along with other proteins (e.g., macroglobulin pregnancy associated β_2 -glycoprotein), and altered balance between helper and suppressor T cells².

Differences between major histocompatibility complex (MHC) of mother and fetus may be beneficial to the fetus but as a potential graft it must be protected against transplantation attack by the mother. Undoubtedly, the most important factor is the well-documented lack of both conventional class I and class II MHC antigens on the placental villous trophoblast, which protects the fetus from allogeneic attack. These fundamental changes in the regulation of MHC genes also lead to the unique expression of the non classical MHC class I protein. HLA-G on the extravillous cytotrophoblast. The HLA-G may act to inhibit cytotoxicity of trophoblast (killing) by maternal NK cells³.

Spontaneous abortion is the most common complication of pregnancy. It can repeat itself, starting a clinical picture known as recurrent spontaneous abortion (RSA) or habitual abortion which is defined as the loss of three or more pre-viable (less than 500 gm or before the 24th week) pregnancies in succession. It occurs in about 0.4- 0.8% of all pregnancies⁴.

Causes of RSA

The following causes are considered in evaluating patients with a history of RSA: Infection (1%): toxoplasmosis, herpes simplex & cytomegaloviruses, mycoplasma; Anatomic abnormalities (5% to 10%); Low progesterone levels or luteal phase defect (5% to 20%); Chromosomal abnormalities (7% to 50%); Immune mechanisms (50%) and Unknown (15%)¹.

The majority of recent research work has focused on potential autoimmune and alloimmune causes as: Inadequate maternal antipaternal leukocyte antibodies; Anti phospholipid antibodies; Antinuclear antibodies; Antithyroid antibodies; Natural killer cells; Cytotoxic T cells and Embryotoxic factors⁵.

Role of NK cells in RSA

NK cells are large granular lymphocytes that arise from the bone marrow and circulate peripherally before localizing to specific tissues⁶. They are the most prevalent lymphocyte population in secretory endometrium and the decidua of early pregnancy and are believed to play a role in regulating trophoblast invasion⁷ and trophoblast protection, as women with alloimmune abortions have a limited inhibitory killer immunoglobulin-like receptors (KIRs) repertoire and so, RSA may occur because trophoblastic HLA class I molecules are recognized by decidual NK cells lacking the appropriate inhibitory KIRs⁸.

NK cells seem to have a key role in immunosurveillance of the invading trophoblast. However, if activated by tumor necrosis factor alpha (TNF-), NK cells may induce apoptosis in the trophoblast possibly leading to miscarriage. This action is inhibited by transforming growth factor beta (TGF-). Early ultrasound scanning and embryoscopy have revealed structural anomalies in karyotypically normal embryos which have terminated in first trimester missed abortion⁹.

Elevated NK cell activity in the peripheral blood may be a reflection of increased NK cell killing at the tissue level. Increased peripheral and endometrial NK cell activity has been demonstrated in in-vitro fertilization (IVF) patients who experienced spontaneous pregnancy loss⁷. Moreover, pre-conceptional NK cell abnormalities

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were predictive of spontaneous abortion with normal fetal karyotype¹⁰. Therefore, functional or quantitative analysis of NK cells could be used to identify alloimmune causes of RSA⁵.

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