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Inflammation and Immunity in Recurrent Pregnancy Loss: A snapshot

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Commentary

Recurrent pregnancy loss or RPL is defined as a failure of two or more clinical pregnancies [1]. The incidence of RPL is estimated to be <5% with about 1 % of reproductive aged women facing three or more consecutive miscarriages. The major etiopathogenesis of RPL is idiopathic in almost 50% of cases while others include anatomic, genetic, autoimmune, endocrine and infections. When the evaluation of the patient in the above known factors is completed, the lesser known factors such as inflammation and coagulation are considered [2]. In many developing countries, anecdotal treatment of idiopathic causes are instituted without any actual evidence of inflammation. Hence, this commentary is focussed towards the role of mediators of inflammation in patients with recurrent miscarriages.

The complete understanding of the complex interaction between maternal immunological response and fetal tissue is still open to research [3]. Inflammation plays a vital role in both implantation and miscarriage [4]. This leads us to the critical period of blastocyst-endometrium crosstalk in the implantation window. Specific cytokines, and adhesion molecules are expressed by both parties at this time leading up to implantation or miscarriage [5]. During the period that the endometrium is preparing itself to implant the blastocyst, cAMP mediated decidualization occurs in a progesterone controlled environment, an event that can occur even in the absence of a conceptus [5,6]. IL-6 family of cytokines comprising of LIF, IL-6, IL-11, neurotrophic factor, oncostatin M, and cardiotrophin 1 plays an important role in embryonic implantation. These factors have an effect on both endometrium and the implanting blastocyst. Adhesion molecules such as L-selectin, integrins mucin 1 and E-cadherin play a vital role in apposition and adhesion, followed by trophoblast invasion through pinopod formation [7]. There is also a notable controlled interaction between immune cells, complements and MHC complexes in establishing a successful pregnancy. T regulatory cells, rather than the T helper cells have been shown to help establish allotolerance [8]. It is important to be aware that while the fetus

carries all the MHC complexes derived paternally, it remains 'shielded' from the maternal immune system, through a 'cushion' of no MHC expression carrying villous syncytiotrophoblasts [9].

In women with idiopathic recurrent pregnancy loss, an imbalance of proinflammatory and anti-inflammatory mediators combined with a higher thrombophilic tendency leads to possibly another miscarriage [10]. Evaluation in research studies of women with recurrent spontaneous abortion noted that there is a difference in chain composition of gamma/delta TCR-bearing lymphocytes in peripheral blood which may have a role in progesterone-dependent immunomodulation [11]. Increased cytotoxicity mediated by elevated levels of activated NK cells in RPL has also received attention from researcher's worldwide [11,12]. Pro and anti-inflammatory T helper cell mediated release of cytokine imbalance in RPL is a matter of debate since there are many studies out there contradicting one another. Maternal HLA polymorphisms in RPL is subject to further investigation.

There remains an unmet need to further the research in this arena of immunological evaluation of RPL patients. As a result, treatments to induce immunological tolerance in these patients have already been extended to this population with debatable success. Immunotherapy with paternal peripheral blood mononuclear cell, third-party donor leukocytes, trophoblast membranes, and intravenous immunoglobulin do not provide any significant benefit over placebo treatments unless in primary RPL with numerous miscarriages [13,14,15]. On behalf of the editorial board at the Reproductive Immunology Open Access, I invite the researchers in various fields to contribute to this topic and others, to advance our understanding of this field.

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