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MINI REVIEW

Immunomodulation in Recurrent Miscarriage

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About the Author

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Abstract There are many etiological factors responsible for recurrent abortions. However, no explanation can be identified in approximately 40–50 % of women with recurrent miscarriage (RM). Several studies demonstrated that successful pregnancy is dependant on shifting of maternal immune response from (proinflammatory) Th1 toward (anti-inflammatory) Th2 phenotypes. It was suggested that unexplained RM might be due to immunologic factors. Recently, there is improved understanding regarding the role of the different immune cells and proteins that are important at each stage of a normal pregnancy. Various immune-based therapies with variable clinical evidences have been reported in women with RM with variable efficacy. Still there is lack of information about the mode of action and possible adverse effects of the treatment and a reliable marker for patient selection for immunopotentiation. Adequately powered placebo-controlled studies are required to study and treat couples with the so-called idiopathic recurrent miscarriage.

Keywords Immunomodulation · Pregnancy · Recurrent pregnancy loss · Immune system

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Spontaneous abortion is one of the most common complications of pregnancy, occurring in 15–20 % of pregnant women. In contrast, 0.5–2 % of women experience recurrent pregnancy loss (RPL) defined as the occurrence of

three or more clinically detectable pregnancy losses [1]. It is further stated that clinical evaluation may be undertaken after two first trimester miscarriages. Despite several well-established etiologic factors, the diagnosis can be made in almost 50 % of cases even after exhaustive investigations. Immunologic factors might be the causative factors responsible for unexplained RPL [2].

Immunomodulation

During normal pregnancy, there is cooperative interaction between maternal immune system and fetal antigen, and failure of this immune system adaptation leads to alloimmune rejection of the fetus resulting in loss of pregnancy [3]. Therefore, there is associated increase in tolerance-promoting T regulatory cell (Treg) activity and a commensurate decrease in the proinflammatory Th17-cell activity. Trophoblast acts as an allogenic tissue due to the parental genetic contribution during normal pregnancy. It induces an immunomodulatory effect, suppresses abortigenic maternal B and T cell responses leading to adaptation of the fetus. There is a shift toward a protective T helper (Th)-2 dominated cytokine balance (with interleukins 4, 6, and 10) and away from Th-1 cytokines like interleukin 2, interferon-gamma, tumor necrosis factor (TNF), alpha and IL-12 [4]. Progesterone-induced blocking factor (PIBF) prevents inflammatory and thrombotic reactions toward the fetus. PIBF, a protein synthesized by activated lymphocytes in the presence of progesterone, promotes this shift toward Th-2 cytokines. [5] In normal pregnancy, therefore, Th-2 type cytokine response mediated blocking antibodies mask fetal trophoblast antigens so as to prevent them from immunological recognition by a maternal Th-1 cell-mediated cytotoxic response. Women with recurrent miscarriage (RM) tend to produce a predominantly Th-1 type response both in the period of embryonic implantation and during pregnancy [4]. There are other proposed mechanisms of action of PIBF to prevent rejection of fetus. It also increases asymmetric non-cytotoxic blocking antibodies [6] and blocks natural killer (NK) cell degranulation [7]. Uterine NK cells appear to regulate placental and trophoblast growth, local immunomodulation, control trophoblast invasion, and enhance the changes in blood vessels which allow for adequate feto-maternal perfusion. However, if activated by TNF alpha, NK cells may induce apoptosis in the trophoblast possibly leading to miscarriage. It has been observed that that PIBF levels fail to increase in pregnancies that end in miscarriage [8]. In a mouse model, stress-induced miscarriage was associated with low levels of progesterone and PIBF. Treatment with dydrogesterone before the stress reduced the number of miscarriages, restored PIBF levels, and decreased uterine levels of Th-1 cytokines [9]. Progestogens also reduce the synthesis of prostaglandins directly, thereby relaxes uterine smooth musculature, and prevent inappropriate uterine contractions that may result in miscarriage [10].

The cellular and molecular mechanisms underlying the maintenance of normal pregnancy and the induction of abortion are still not clearly understood. It is possible that an early immune-mediated damage to the embryo may be playing an important role in a significant proportion of RM. Recently, modulation of the maternal immune response is proposed as one of the mechanisms of actions. [11] Impaired T regulatory cell function combined with increased activity of the newly described proinflammatory Th17 cells might be the underlying root in these cases of RM. An increased proportion of human leukocyte antigen sharing with their partner, a deficiency in maternal blocking antibodies or abnormal uterine and decidual suppressor NK cells is demonstrated in women with recurrent miscarriage. The relationship between uterine NK cell numbers and future pregnancy outcome in patients with RPL is still being investigated.

Granulocyte colony-stimulating factor (G-CSF) is an important regulatory cytokine responsible for embryo implantation and subsequent development. G-CSF deficiency in pregnancy adversely impacts on fetal and placental development [12] and it may be effective in the treatment of unexplained RPL. Human chorionic gonadotropin (hCG) is also of critical importance in the establishment of the early embryo in the endometrium. Its role has been defined in promoting angiogenesis and placentation and in recruiting and promoting maternal Treg cell function. hCG is important in maintaining pregnancy by promoting a down regulation of harmful maternal immunity [13]. While progesterone has been found to be important in encouraging Treg proliferation and activity, the role and importance of hCG have been gaining increased recognition.

Immunomodulatory Therapy

Both immunomodulation and hormonal support (progesterone or hCG supplements) have been used to improve the live birth rate in recurrently aborting women. Therefore, immune-based therapies such as glucocorticoids, intravenous immunoglobulin, anti-TNF alpha drugs, and many others are being utilized in the management of RPL with the objective to positively modulate the maternal immune system or to dampen an excessive harmful immune response.

Prednisolone has been shown to reduce raised endometrial NK cells in women with recurrent miscarriage [14]. In a placebo-controlled randomized study, Laskin et al. showed that the use of steroids to suppress autoantibody

titers does not improve the live birth rate. Further, it can increase the risk of preterm delivery [15]. In a study by Reznikoff-Etievant et al. [16], prednisone and low-dose aspirin were significantly helpful in 214 women with RM compared with 63 RM women receiving aspirin alone. It is possible that the reduced T regulatory cell activity and raised prothrombotic mechanisms were corrected in the prednisone and aspirin group, while only the prothrombotic problems were reduced in the aspirin only group. A Cochrane review reported that use of prednisolone along with aspirin in RM associated with antiphospholipid antibody (APA) resulted in significant increase in prematurity and gestational diabetes, but without improvement in outcome. [17]. It is suggested that early and perhaps preconception steroid therapy that is restricted to the early pregnancy and to women with non-APAS autoimmunity may be beneficial in improving the outcome. However, glucocorticoids during pregnancy are associated with a risk of preterm delivery secondary to rupture of membranes and the development of preeclampsia and gestational diabetes [15].

RM is possibly due to autoimmunity to trophoblastic, fetal, or placental antigens. Therefore, these auto-antibodies may be neutralized or decreased by the antibodies in the intravenous immune globulin (IVIg). It has been suggested by Bansal et al. [18] that IVIg may be playing its beneficial role in RM by reducing Th17 cell differentiation as well as by increasing FoxP3 expression, which promotes Tregs. Ata et al. [19] analyzed 6 RCTs involving 272 women with unexplained RM and concluded that there is no beneficial effect of IVIG in treatment of RM. Moreover, intravenous immunoglobulin is a pooled-blood product and is associated with anaphylactic response, fever, flushing, muscle pains, nausea, and headache [20]. In a review of 20 trials of various forms of immunotherapy for RM, IVIg, paternal white blood cell immunization, third-party donor cell immunization, and trophoblast membrane infusion were found to be ineffective for primary RM and are not recommended for treatment. [21].

TNF alpha is produced by uterine NK cells and trophoblast cells and inhibits trophoblast invasion through increased trophoblast apoptosis and decreased trophoblast proliferation, thereby impairing the nutrient supply for the developing embryo. To minimize the deleterious inflammatory effects on fetal viability, TNF alpha inhibitors have been used to reduce the action of the proinflammatory TNF alpha. When used in conjunction with IVIg, the TNF alpha inhibitors like etanercept or adalimumab were found to be significantly helpful in improving the live birth rate in women with RM compared with those receiving anticoagulation alone. [22]. However, TNF alpha inhibitors have been found to be responsible for the development of lymphoma, granulomatous diseases such as tuberculosis, demyelinating disease, congestive cardiac failure, and syndromes similar to systemic lupus erythematosus. [23].

Dydrogesterone was also able to reduce TNF alpha and decrease the Th1/Th2 ratio (Raghupathy 2005). Raghupathy [24] reported that the dydrogesterone treatment significantly reduces secretion of the Th1 cytokines (IFN-γ & TNF-α) and elevates the secretion of the Th2 cytokines (IL-4 & IL-6) ($p < 0.05$), thereby decreasing the Th1/Th2 ratio. This has been used to prevent miscarriage with variable efficacy. A randomized study by El-Zibdeh [25] showed significantly less abortions in the dydrogesterone group (who received till 12th week of gestation) (13.4 %) than the control group (29 %). In a double-blind, prospective randomized, placebo-controlled study, the author has observed the occurrence of having another abortion after three consecutive abortions is as high as 16.76 % in placebo group. However, the administration of dydrogesterone from early pregnancy to 20 weeks of gestation reduced the occurrence of miscarriage to 6.86 % in RSM group. The mean serum cytokines levels between women who aborted and who continued their pregnancy among the three groups (controls, placebo and dydrogesterone groups) did not differ significantly either at time of recruitment or at second sampling (even after dydrogesterone administration). At the time of abortions, the levels of Th1 and Th2 cytokines fail to show any significant difference among the women who aborted in all the three groups (unpublished data from ICMR funded project -Modulation of cytokine production in women with recurrent pregnancy loss). Further studies are required to show clear-cut benefits by selective use of dydrogesterone in RM and demonstrable alterations in the Th1/Th2 ratio. Similarly, salbutamol, salmeterol, and formoterol may be of some benefit in promoting materno-fetal tolerance in RPL by reducing Th1 and increasing Th2 activity. [26].

Conclusion

It is imperative to have thorough understanding of modulation of the maternal immune system and factors that encourage intolerance fetal allograft through excessive activation in RM. Natural killer cells seem to have a key role in immunosurveillance of the invading trophoblast. The subsequent down regulation of maternal antitrophoblastic T- and NK-cell immunity is critical in preventing rejection of the fetus. The judicious use of immunomodulatory therapy even before implantation in women demonstrating excessive peripheral blood T cell activity altered ratios of Th1/Th2 or increased NK cell numbers; activation or cytotoxicity represents the most rational approach. However, further translation trials are needed to generate

evidence-based benefits and clinical application of immunomodulation.

Conflict of interest The author reports no conflicts of interest.

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