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Editorial

Reproductive Immunology: Current Knowledge and New Perspectives

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Reproductive immunology is a field within reproductive medicine that remains largely underrecognized and insufficiently explored by most clinicians. Historically, the first immunological theory for non-embryo rejection by the maternal immune system was proposed by Peter Brian Medawar in 1953 [1]. At that time, he suggested that (1) maternal and fetal circulations should be separated, (2) fetal (placental) cells should evade maternal immune recognition, and (3) maternal immune system should be suppressed [1]. Over the last 70 years, with the help of different laboratory techniques, studies have helped elucidate the maternal immune response to the embryo, considered an allograft.

The maternal immune system basically develops an immune tolerance response during embryo implantation. This immune response (cellular and humoral) occurs in the uterine microenvironment and among other systems (in peripheral blood and other immune or nonimmune organs). Some adaptations of effector cells of the maternal immune system are essential for a successful pregnancy, such as increased uterine natural killer (NK) cells, reduced cytotoxicity of peripheral blood NK (pbNK) cells, increased regulatory T cells (Tregs), and predominant immune response of T helper (Th)-2 cells [2,3].

Although the pillars of reproductive immunology are already well consolidated, the diagnostic methods and immunotherapies proposed over the last decades are not yet part of the management guidelines for couples with reproductive failures (such as recurrent pregnancy losses [RPL] and recurrent implantation failures [RIF]) [4,5]. Gradually, the evidence is becoming more robust, and different scientific entities are changing their position on the importance of immune assessment in patients with adverse reproductive conditions [4,6].

The maternal immune response during pregnancy is a complex event, and abnormalities in uterine cellular immunity may occur. Lédée *et al*. [7] observed that women with reproductive failures present different endometrial immune profiles (EIP), such as normal immune activation, local immune overactivation, local immune low activation, and mixed pattern. The EIP evaluates the gene expression of five biomarkers: interleukin (IL)-15, IL-18, tumor necrosis factor-like weak inducer of apoptosis (TWEAK), fibroblast growth factor-inducible molecule 14 (Fn14), and NK cells (CD56). They reported improvements in reproductive outcomes occur when the choice of immunotherapy is based on a detailed diagnosis of the immune disorder [7,8].

Uterine NK (uNK) and pbNK cells play a key role in the immune response of pregnancy. Women with RPL and RIF present high CD56+ (endometrial tissue) uNK levels [9,10]. Recently, a systematic review and meta-analysis observed increased pbNK cell cytotoxicity both in the preconception period and during pregnancy in women with RPL. The Th1/Th2 immune response balance is also an important biomarker of gestational success. Studies demonstrate that an imbalance toward a predominantly Th1 response increases the risk of reproductive failure [11]. Although the extent to which peripheral blood immune markers reflect the uterine immune environment remains controversial, recent evidence suggests that pbNK cells can acquire a uterine-like phenotype under the influence of local cytokines such as transforming growth factor beta (TGF-β), supporting a potential link between systemic and uterine immune responses [11].

Autoimmune diseases increase the risk of reproductive complications, including infertility, RPL, and RIF. Several studies have observed the association between high autoantibody levels and reproductive failure. Antiphospholipid antibodies, antinuclear antibodies (ANA), and antithyroid antibodies (ATA) are the autoantibodies most commonly associated with reproductive failure [12–14]. Routinely, cellular and humoral immunity abnormalities, such as an imbalance between the Th1/Th2 immune responses, and increased NK cell cytotoxicity are frequently observed in patients with positive autoantibodies [14,15].

KIR (Killer-cell Immunoglobulin-like Receptor) genes, particularly the AB haplotypes on NK cells, interact with *HLA-C* ligands expressed by the embryo. The *KIR-HLA* interaction influences the immune response at the maternal-fetal interface and can lead to the activation or inhibition of NK cells. The interaction between maternal *KIR* AA and embryo *HLA-C2* is associated with inhibition of NK cells, resulting in an inadequate immune response

that may compromise trophoblast invasion and remodeling of spiral arteries. This combination is correlated with increased risks of RPL, RIF, and complications such as preeclampsia [16].

Immunotherapies for managing couples with reproductive failures have been proposed since the early 1980s [17]. Lymphocyte immunotherapy (LIT), intravenous immunoglobulin (IVIG), corticosteroids, and intravenous lipid emulsion (ILE) are examples of immunotherapies used in patients with RPL and RIF [18]. The vast majority of studies reported increased live birth rates in patients undergoing immunological interventions [18].

The lack of adequate investigation for the diagnosis of immune disorders associated with reproductive failure, lack of patient selection criteria to indicate immunotherapy, and no standardization of treatment protocols are the main flaws detected in studies that do not observe benefit from immunotherapy in the management of couples with RPL and RIF [19–21]. However, an improvement in the methodological quality of recent meta-analyses that evaluated the effectiveness of some immunotherapies can be observed [18].

Recently, a British multicenter study evaluated the impact of immunomodulatory treatment (corticosteroids, low-molecular-weight heparin, and ILE) in 27,163 cycles of assisted reproductive techniques (ART), of which 5083 received immunotherapy and 22,080 did not. Women who received immunomodulatory therapy—administered only to those with laboratory evidence of immune dysregulation, including high titers of autoantibodies, increased numbers or proportions of T or B lymphocytes, elevated activity or proportion of peripheral blood NK cells, or an altered Th1/Th2 cytokine profile skewed toward a pro-inflammatory response—had a significantly higher live birth rate (LBR) (20.9% *vs.* 15.8%, odds ratio (OR): 1.4, $p < 0.001$) compared with those who received standard ART alone. Multivariate analysis confirmed that immunomodulation was an independent predictor of live birth, with an adjusted OR of 1.33. Furthermore, the cumulative LBR rate was higher in the treatment group (adjusted HR = 1.78, $p < 0.001$) [22].

Recent evidence reinforces the potential of IVIG as an immunomodulatory therapy in reproductive failure, with retrospective data demonstrating improved live birth rates in women with severe unexplained recurrent implantation failure and a systematic review supporting its benefit in selected patients with unexplained recurrent pregnancy loss [23,24].

Another recent study evaluated the effect of immune therapy with granulocyte colony-stimulating factor (G-CSF) in 79 patients with RIF and *KIR/HLA-C* incompatibility, of whom 30 received subcutaneous G-CSF. The results showed no significant differences in univariate analysis. However, logistic regression analysis controlled for confounders indicated that the G-CSF-treated group had significantly higher rates of ongoing pregnancy (adjusted OR = 3.808) and live birth (adjusted OR = 4.998), as well as a lower rate of miscarriage (adjusted OR = 0.057). G-CSF has shown promise in modulating NK cell-mediated immune responses, improving trophoblast invasion and reproductive outcomes in women with *KIR/HLA-C* incompatibility [25].

Recommendations of the main international guidelines for managing patients with reproductive failure are still controversial. A recent update of the European Society of Human Reproduction and Embryology (ESHRE)'s RPL guidelines includes recommendations for the investigation of immune biomarkers (such as antiphospholipid antibodies, ATA, and ANA) [4]. Also, a group of The International Federation of Gynecology and Obstetrics authors suggested that laboratory tests to detect autoantibodies (such as ANA, anti-thyroid peroxidase antibody [TPO-Ab], and gliadin antibodies), NK cell levels and cytotoxicity, and cytokine levels should be considered in RPL workup when the reproductive medicine center has a specialist with experience in reproductive immunology [6].

Women being monitored for an autoimmune disease must control the disease activity before becoming pregnant to reduce the risk of obstetric complications. Antiphospholipid syndrome is another autoimmune condition that must be appropriately treated to prevent pregnancy losses. Recently, ESHRE recognized that IVIG may improve the live birth rate in females with 4 or more unexplained RPL [4].

New biomarkers are being studied to accurately identify immune abnormalities and individualize the treatment for women with reproductive failure [26]. The endometrial decidualization score is a promising omics-based biomarker that evaluates the expression of 6 genes involved in this decidualization process, especially in the implantation immune response [27]. Omics studies in decidua, villus, and maternal peripheral blood can help identify new, more sensitive, and specific biomarkers for better management of patients with pregnancy loss [26]. New anti-obesity drugs have immune properties that can help treat patients with reproductive failure [28]. Furthermore, the therapeutic use of miRNA mimics (replacement of depleted miRNAs) or miRNA antagonists (inhibition of overexpressed miRNAs) can modulate the immune response during embryonic implantation and, consequently, become a new therapeutic tool [28].

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MBC, EAJ, and RG designed the editorial. MBC wrote the editorial. EAJ and RG performed critical review. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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