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Review

Novel immunotherapeutic approaches for treatment of infertility

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ABSTRACT

One of the most important reasons of infertility and human reproductive failure is related to uncontrolled immunological response of maternal immune system to early embryo or fetus, that cause rejection of this semi-allograft. Therefore, a tolerance in the immune system is essential to modulate the reactions against the fetus to avoid rejection. The immune system imbalance during implantation or pregnancy may lead to implantation failure or miscarriage. So, use of immunosuppressive or immunomodulator agents can be helpful to prevent immunological attack. Initially, there was a focus on steroids like prednisolone or intralipids in treatment of miscarriage that suppressed the activity of most immune cells, Intravenous Immunoglobulin (IVIG) was then introduced with various mechanisms. Nowadays, novel and specific strategies are established such as monoclonal antibodies and cytokines. More recently, Tacrolimus and Cyclosporine, which were utilized in prevention of transplantation reject, are used as immunosuppressive factors in modulation of immune responses against the fetus. This review is focused on the main immunotherapeutic methods of infertility treatment.

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1. Introduction

It is estimated that infertility affects as about the 186 million people and 8–12% of reproductive-aged couples in the world and is a global problem. Although this problem up to %50 is related to male infertility, however, it is usually a woman's social burden. It is evident that unavailability of assisted reproductive techniques (ARTs) in some regions of the world causes much more complications in management and treatment of infertility [1,2].

The blastocyst with the products of paternally inherited genes as a foreign graft, induces the maternal immune response. A tolerance in mother immune system is needed to prevent the rejection or immune-mediated damage. Therefore, emerging evidence indicates that immunological factors like anti-sperm antibodies (ASA), antiphospholipid antibody (APA), cytokines and uterine natural killer (uNK) cells in reproduction are of the reasons of infertility and miscarriage [3]. Subsequently, any disruption in this immunological tolerance causes miscarriage or pregnancy loss, so different strategies of immunotherapies have been introduced to treat couples experiencing these kinds of problems in order to improve the pregnancy outcome and increase the rate of live birth.

The term "Infertility" means inability to conceive [1], it is classified into primary or secondary based on the etiology. Failing to achieve pregnancy is called primary infertility while complications after the achievement of pregnancy are known as secondary infertility [3]. Infertility includes almost all kinds of reproductive failures such as Recurrent Pregnancy Loss (RPL), Recurrent spontaneous Abortion (RSA), and Recurrent Implantation Failure (RIF).

1.1. Recurrent pregnancy loss (RPL)

Recurrent pregnancy loss (RPL) is defined by $\geq$2 failed clinical pregnancies [4]. The etiology of RPL in almost 50% of cases is unknown [5], however, anatomic, genetic, endocrine, autoimmune, and infectious factors are suggested [6].

1.2. Recurrent spontaneous abortion (RSA)

RSA is identified by three or more consecutive loss of pregnancy before the 20th week of gestation, which occurs in 1–5% of women of reproductive age [7–9]. Although the exact reason of RSA remains unknown, chromosomal, anatomic, endocrinologic, infectious and autoimmune problems have been suggested. It has been proposed that unexplained RSA (URSA) is usually related to the failure of immunologic tolerance of mother immune system to fetus, and it usually occurs in the first trimester of pregnancy [10,11].

1.3. Repeated implantation failure (RIF)

Repeated Implantation Failure (RIF) is characterized with the failing of implantation after transferring at least three high quality embryos in the IVF (in-vitro fertilization) process. In each cycle of IVF, one or two embryos of good-quality are transferred [12].

Focusing on definitions, we can understand that these disorders are closely related and in some cases even can be converted to each other.

In order to avert the infertility, multiple treatment methods are studied such as low molecular weight heparin (LMWH), aspirin and progestin. Regarding the pivotal role of immunological factors in reproductive problems, there is much more attention on the biologic and immunologic based treatment options. In this study, we are going to explain the new approach of management and treatment of infertility based on immunotherapy.

2. Immunotherapy of infertility

There is now more attention on critical role of immune system in pregnancy, therefore different types of immunotherapies have been introduced to treat couples experiencing infertility [13]. It is essential to understand the mechanisms involved in these kinds of complications to choose and utilize the best and most specific treatment strategy [14].

Immunotherapy is classified into two groups:

- Active: like paternal leukocyte injection, that stimulates maternal immune system to activate and response.
- Passive: like intravenous infusion of immunoglobulin or IVIG that modulates the immune system with different mechanisms [15].

3. Types of immunotherapy

Several types of immunotherapies were used earlier in management of miscarriage such as prednisolone, paternal lymphocyte immunization (PLI), intralipids and IVIG. After these methods, more specific strategies like Anti-TNF (Tumor Necrosis Factor) agents (Etanercept and Adalimumab) were introduced to reduce the side effects. Moreover, granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) were utilized as critical factors in human reproductive process. Recently, tacrolimus and cyclosporine are used in the immunotherapy of infertility. Indeed, these two agents suppress and modulate maternal immune system to prevent immunological damage or rejection of embryo or fetus as a semi-allograft (Fig.1).

There is a classification for these immunotherapy methods according to their structure including small molecule-based therapies (e.g. prednisolone, tacrolimus and cyclosporine); large molecule based therapies such as IVIG, anti-TNF agents (Adalimumab and Etanercept), G-CSF and GM-CSF and cell-based therapies (e.g. paternal lymphocyte immunization).

3.1. Small molecule-based therapies

3.1.1. Prednisolone

Prednisolone is an anti-inflammatory and immunomodulatory agent, which can reduce the production of inflammatory mediators and is beneficial in treatment of autoimmune diseases and immune-mediated conditions in pregnancy [16–18]. Prednisolone is a steroid with the lowest side effect, because only a little part (about%10) will reach the fetus and its major part will be disintegrated in the placenta [19,20].

The action mechanism of prednisolone is not fully determined but some studies suggest that it may inhibit placental tissue Th1