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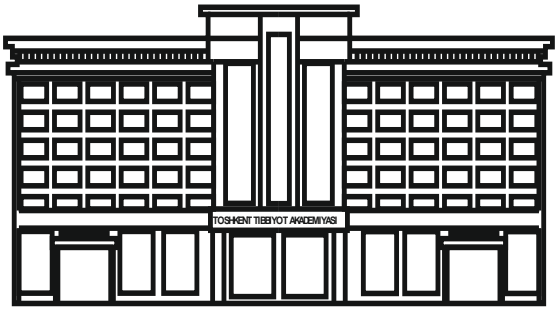

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IMMUNOLOGICAL INSIGHTS INTO EARLY REPRODUCTIVE LOSSES: THE CRUCIAL ROLES OF MATERNAL IMMUNITY, CYTOKINES, AND EMBRYO-MATERNAL INTERACTIONS

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ИММУНОЛОГИЧЕСКИЕ ИССЛЕДОВАНИЯ РАННИХ РЕПРОДУКТИВНЫХ ПОТЕРЬ: РОЛЬ МАТЕРИНСКОГО ИММУНИТЕТА, ЦИТОКИНОВ И ЭМБРИОНАЛЬНО-МАТЕРИНСКИХ ВЗАИМОДЕЙСТВИЙ

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ERTA REPRODUKTIV YO'QOTISHLARGA IMMUNOLOGIK NAZAR: ONA IMMUNITETI, SITOKINLAR VA EMBRION-ONA O'ZARO TA'SIRINI AHAMIYATI

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Представлено общее понимание иммунологических факторов, способствующие ранним потерям беременности, особенно в I триместре, который является ключевым периодом для развития эмбриона. Сложное взаимодействие между регуляцией материнского иммунитета, сигнальными путями цитокинов и эмбрио-материнским взаимодействием определяет исходы беременности и открывает перспективы для терапевтических вмешательств.

Ключевые слова: *ранние потери беременности, повторные потери беременности, материнский иммунитет, цитокины, регуляторные Т-клетки, маточные натуральные киллеры, взаимодействие эмбриона и матери.*

Erta reproduktiv yo'qotishlar klinik va emotsion jihatdan jiddiy muammo bo'lib, tan olingan homiladorliklarning taxminan 10 % uchraydi. Genetik va atrof-muhit omillari ushbu yo'qotishlarga hissa qo'shsa-da, so'nggi tadqiqotlar homiladorlik natijalarini belgilashda onaning immun tizimi tartibga solinishi muhim rol o'ynashini ko'rsatmoqda. Ushbu sharh erta reproduktiv homiladorlik yo'qotishlarida ishtirok etadigan immunologik mexanizmlarni tahlil qilib, onaning immun tizimi tartibga solinishi va embrion-onalik o'zaro ta'sirlarining homiladorlik natijalariga qanday ta'sir qilishi haqida muhim ma'lumotlar beradi.

Kalit so'zlar*: erta reproduktiv yo'qotishlar, takroriy homila yo'qotish, ona immuniteti, sitokinlar, regulyator T-hujayralar, bachadon tabiiy killer hujayralari, embrion-onalik o'zaro ta'siri.*

Обзоры

Early reproduction losses, generally defined as loss of pregnancy occurring during the first trimester, are a significant concern in obstetrics, affecting approximately 10% of recognized pregnancies [2]. These losses can have deep implications not only for maternal physical health but also for psychological well-being, often leaving lasting emotional scars on individuals and couples wishing to conceive. Above all, the etiology of the loss of early reproduction is multifactorial, encompassing genetic, maternal and environmental factors; However, emerging evidence highlights the critical role of immunological factors in modulating these reproductive results.

It is essential to understand the immunological landscape at the beginning of pregnancy because the maternal immune system must create a delicate balance which allows to accept the semi-allogenic embryo while protecting the mother from pathogens. The interaction between the maternal immune system and the embryo is facilitated by a variety of immune cells and cytokines, which contribute to the establishment of a tolerogenic environment necessary for successful implantation and early embryonic development [6]. T-Helper 1 (TH1) and T-Helper 2 (TH2) Cellular functions, characterized by their cytokine profiles, play a pivotal role in the orchestration of this immune tolerance. More specifically, a change towards a response to predominance TH2 is generally associated with a successful pregnancy because of its regulatory influence on local immunity [3].

Cytokines, as fundamental regulators of immune responses, operate as key mediators in dialogue between maternal tissues and developing embryo. Studies have stressed how high levels of pro-inflammatory cytokines, such as the factor of tumor-alpha necrosis (TNF-α) and interleukines (IL-1, IL-6), can create unfavorable conditions contributing to the early failure of pregnancy [18]. These cytokines can disrupt the implantation process or interfere with subsequent development stages, illustrating the way in which immune dysfunction can precipitate reproductive failures. Conversely, anti-inflammatory cytokines such as IL-10 support a favorable maternal environment that promotes the survival of embryos. Thus, a complex balance of these signaling molecules is essential to support early pregnancy.

In addition, the complexity of the maternal immune response is further improved by the interaction of various immune cells, including regulatory T-cells (TREG) and natural killer cells (NK). TREGs, known for their immunomodlative functions, are particularly crucial in removing excessive inflammatory responses and ensuring the acceptance of the implanted embryo [6]. The deficiencies or malfunctions of these regulatory frameworks were involved in the loss of recurring pregnancy, enlightening how maternal immune deregulation can lead to unfavorable reproductive results.

In the end, an in -depth understanding of immunological factors that influence early reproduction losses is essential to develop effective clinical interventions. More in-depth research is justified to elucidate the specific mechanisms by which maternal immunity, the signaling of cytokines and embryo-maternal interactions contribute to successful pregnancy results, thus potentially attenuating the incidence of early reproductive failures. By advancing our knowledge of these immunological foundations, we can better meet the challenges posed by the first reproductive losses and improve reproductive health strategies. The maternal immune system plays an essential role in the establishment and maintaining pregnancy, balancing between immune de-

fense and tolerance to promote an appropriate environment for embryonic development. At the heart of this balance are various immune cells, in particular natural killer cells and regulatory T-cells, which operate at the maternal-fetal interface. NK cells, an innate immune cell type, are disproportionately represented in the deciduous, the uterine mucosa at the start of pregnancy. It is believed that they play a central role in the reshaping of maternal blood vessels to ensure an adequate infusion of the placenta, thus facilitating an exchange of appropriate nutrients [16]. In addition, these NK cells can release cytokines which not only contribute to a conducive uterine environment, but also modulate the activity of other immune cells. An imbalance in the activity of NK cells, due to hyperactivity or dysfunction, was involved in complications such as preeclampsia and loss of early pregnancy [12].

TREGs, on the other hand, are essential to promote immune tolerance towards the semi-allogenic fetus. They operate by removing the responses from the actors039; T cells that could potentially harm the embryo. During pregnancy, the number of TREG increases considerably within the maternal circulation and on the site of implantation, reflecting their essential role in the prevention of maternal immune rejection of the development fetus [3]. The literature indicates that a depletion or dysfunction of TREGs can lead to a failure to establish and maintain pregnancy, as evidenced by an increase in spontaneous abortion rates in animal models without TREG populations.

The complex interaction between these immune components is crucial not only for a successful implantation but also for the subsequent progression of pregnancy. Cytokine profiles in the maternal environment further illuminate the balance between tolerance and immune activation. For example, pro-inflammatory cytokines such as the factor of tumor-alpha necrosis and interferon-Gamma (IFN-γ), although essential for maternal defense against pathogens, can have a negative impact on trophoblastic function and placement if they are excessive during early gestation [16]. Conversely, anti-inflammatory cytokines, such as interleukin-10, are essential in the promotion of a tolerogenic environment which promotes the survival of embryos.

The interaction between the embryo and the maternal immune system is also characterized by the expression of specific molecules on trophoblastic cells. The trophoblasts express non-classic human leukocyte antigen molecules (HLA) which facilitate immune escape. These HLA molecules engage with inhibitory receptors on NK cells, effectively preventing cytotoxic activity against invasive trophoblast [12]. In addition, the engagement of the factors derived from trophoblasts with maternal immune cells more modulates local immune responses. The differential expression of these immunomodlative factors must be closely regulated, because deregulation can cause inadequate immune protection against maternal infections or excessive immune responses which could compromise the viability of embryos [5].

An increased understanding of these immunological dynamics is essential to elucidate the mechanisms behind the first reproductive losses. It is clear that alterations in the function or regulation of maternal immune cells can result in alteration of maternal-fetal interactions, resulting in failure to maintain pregnancy. The development of targeted therapeutic strategies aimed at modulating these immune responses is promising to improve results in women undergoing early reproduction losses linked to immunological factors. Cytokine signaling during pregnancy is a complex and strongly regulated process that plays a crucial role in mediating maternal immune responses. These small proteins, produced predominantly by immune cells, serve as signaling molecules that facilitate communication between the embryo and maternal tissues. Proinflammatory cytokines, such as tumor-alpha necrosis factor and interleucine-6, are whole during the early stages of pregnancy, as they contribute to the process of implantation and the establishment of maternal-fetal interface. However, excess of these proinflammatory cytokines can lead to unfavorable conditions for embryo development, thus increasing the risk of loss of pregnancy [1].

On the other hand, anti-inflammatory cytokines, especially interleucine-10 (and transforming-bead growth factor, play a protective role in pregnancy. These cytokines support the tolerance of the maternal immune system in relation to semi-Logenic fetus, ensuring that the embryo is not rejected by maternal immunological defenses [15]. Deregulation in the balance between proinflammatory and anti-inflammatory cytokines has been associated with an increase in the incidence of early reproductive losses. For example, a hyperactive maternal immune response characterized by high levels of proinflammatory cytokines has been associated with conditions such as abortion and premature birth [10].

Environmental factors and nutritional stators significantly influence cytokine profiles during pregnancy, adding another layer of complexity to the dynamics of cytokine signaling. Several studies have shown that maternal nutrition, including a balanced intake of micro and macronutrients, can modulate cytokine production and subsequently affect pregnancy results [9]. For example, deficiencies in essential fatty acids and certain vitamins may lead to a response to increased proinflammatory cytokine, making successful implantation and placement difficult. In addition, exposure to environmental toxins, such as endocrine pollutants and disruptors, can also distort cytokine production, potentially resulting in adverse reproductive results [15].

The interaction between cytokines, along with maternal immune cells, such as Natural Assassin Cells and Macrophages (NK), provides critical information on the pathophysiology of early reproductive loss [10]. It is important to emphasize that research indicating that local immune responses in deciduity (the uterine coating during pregnancy) are modulated by the presence and activity of these cytokines highlights the potential targets for therapeutic interventions aimed at improving the outstanding results. For example, improving the expression of beneficial anti-inflammatory cytokines may promote a more favorable immune environment for im-

plantation and fetal development, thus reducing the risk of early pregnancy loss.

In addition, longitudinal studies that track cytokine levels throughout pregnancy can elucidate the time and nature of pro and anti-inflammatory responses, providing a clearer understanding of their contributions to success or reproductive failure. This research area remains dynamic, with continuous efforts designed to identify specific cytokine profiles that correlate with successful pregnancies versus those that precede reproductive losses. The findings will be crucial for the development of personalized therapeutic strategies for women at risk for loss of early pregnancy, promoting clinical practices in reproductive health [7]. The interaction between the embryo and the maternal immune system is a critical aspect of reproductive success, especially during the early stages of pregnancy. These interactions are complex and involve a delicate balance between immune tolerance and response, which is necessary for the successful system and the continuation of gestation. The embryo is not simply a passive entity but actively engages with the maternal immune system through various mechanisms, thus significantly influencing maternal immunity [11].

The embryonic development starts a series of immunological adaptations within the maternal body that promote a favorable environment for the system. One of the key components in this process is the expression of specific antigens of the trophoblast, which helps the embryo to evade maternal immune surveillance. The trophoblast cells play a crucial role in this immunological dance by secreting immunomodulants and cytokines that can alter the local immune environment [13]. These factors, including human chorionic gonadotropin (HCG), placiar lactogen and the various cytokines, contribute to an anti -inflammatory environment that encourages the maternal acceptance of the embryo [18].

The cytokines, in particular, are essential in mediating the interaction between the embryo and the maternal immune system. Various cytokines produced by trophoblasts and decidual cells, such as interleuchin-10) and the transformation of the growth-bet factor, have anti-inflammatory properties that help to establish and maintain immune tolerance [19]. These cytokines suppress the activity of the effective T cells and promote the differentiation of the regulatory T (Treg) T-circle in maternal circulation, thus promoting a more immunosuppressive environment in favor of pregnancy [16].

Recent studies have shown that the balance of specific cytokines is crucial; For example, altered levels of pro-inflammatory cytokines, such as the Alfa tumor necrosis factor and interferon-gamma, can lead to a hostile uterine environment that can cause early pregnancy loss [1]. In addition, the times of the release of Cytokines are an integral part; An inappropriate temporal expression can stop the delicate balance necessary for the system and the vitality of the embryo [14].

In addition, the maternal immune response depends on the recognition and response to embryonic signals. The activation of innate maternal immune cells, including cells and natural killer macrophages, is modulated by the presence of specific factors secreted by the embryo [2]. The NK cells, in particular those located in the deciduous Hardino, are crucial to establish the early placental circulation and the supply of nutrients; However, an excessive activation of these cells can cause damage to tissue and reproductive insufficiency. The embryos can also influence the recruitment and polarization of the macrophages, which have double roles in the promotion of the system and subsequently in the production of inflammatory mediators who can influence the placental development [12].

The crosstallk between the embryo and the maternal immune system highlights a unique evolutionary adaptation, in which the embryo can orchestrate a protective response from the maternal side. Understanding these interactions is fundamental in clarifying the immunological factors that contribute to early reproductive losses. The interaction of maternal immunity, cytokine profiles and embryonic signaling lays the foundations for a successful pregnancy, underlining the importance of a balanced immune response in the early stages of gestation., Understanding the immunological factors that contribute to early reproductive losses is crucial to the development of effective clinical strategies to support women suffering from recurring loss of pregnancy (RPL). Current literature emphasizes the complex interaction between maternal immunity, cytokine profiles and embryonic signs that interact with the maternal immune system. A significant focus on the roles of various cytokines emerged, as these molecules can influence maternal tolerance in relation to the semi-elogenic embryo. For example, an imbalance in the medium of proinflammatory and anti-inflammatory cytokines has been observed in women with RPL, suggesting that the cytokine environment can directly affect the success of implementation and early maintenance of pregnancy [4].

Despite the knowledge acquired about cytokines, such as tumor-alpha necrosis factor, interleucine-6 and interleukin-10, more research is needed to delineate specific limits and interactions that generate harmful immune responses. Examination of cross conversation between deciduous immune cells and trophoblasts can reveal critical information on how maternal immune responses can facilitate or prevent embryo implantation and early development. Investigating regulatory T-cells, which play a central role in maintaining pregnancy, could provide understanding in their dysfunctional pathways that lead to RPL [8].

From a clinical perspective, there is an urgent need to translate these immunological ideas into actionable treatment strategies for RPL women. Current interventions, such as corticosteroids, aim to modulate the immune system, but its effectiveness remains variable. Therefore, it is essential for future research to explore more targeted immunotherapies that can accurately address underlying immunological deregulation. Such therapies may include monoclonal antibodies that inhibit specific proinflammatory cytokines involved in RPL pathophysiology. In addition, understanding of time and dosage of such interventions will be critical to minimize possible side effects, maximizing therapeutic effectiveness.

In addition, recent studies have highlighted the potential benefits of micronutrients in modulating immune responses during pregnancy. Vitamin D has gained attention for its role in promoting an immunologically favorable environment, conducive to successful implant and fetal development [20]. Investigating the impact of vitamin D supplementation on cytokine profiles and immune tolerance can open new paths for preventive care in RPL women. In addition, an examination closer to maternal eating habits and their association with immunological markers can provide information on how maternal nutrition influences reproductive results [17].

In short, the intricate relationship between maternal immunity, cytokines and embryo interaction with the maternal immune system has a rich landscape for future investigations. As researchers deepen their exploitation in these immunological dimensions, it remains essential to translate discoveries into clinical practice. Approaching gaps in understanding mediated immune factors associated with early reproductive losses will not only improve our theoretical structure, but also potentially lead to new therapeutic strategies adapted to support women who face the challenges of recurring loss of pregnancy.

The list of references is available at the editorial office

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Early reproductive losses, particularly those occurring within the first trimester, represent a major clinical and emotional burden, affecting approximately 10% of recognized pregnancies. This review provides a comprehensive understanding of the immunological factors contributing to early pregnancy loss, particularly during the first trimester, which is a critical period for fetal development. The complex interplay between maternal immune regulation, cytokine signaling, and embryo-maternal communication underpins pregnancy outcomes and offers insights into potential avenues for therapeutic interventions.

Key words: *early pregnancy loss, recurrent pregnancy loss, maternal immunity, cytokines, regulatory T-cells, uterine natural killer cells, embryo-maternal interaction.*

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