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New therapeutic approaches for improving the outcomes of assisted reproductive technologies

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ABSTRACT

Infertility is a global health problem that affects up to 17.5% of the world's population. The use of assisted reproductive technologies makes it possible to solve this problem; however, it is not adequately efficient in all observed cases. Implantation failure remains a serious and multifaceted problem faced by clinicians in reproductive technology, despite the significant advances that have been made in this area. This review highlights promising studies on medical and invasive intervention methods and their possible combinations, which potentially improve the clinical treatment of implantation failures. Nevertheless, further study is required to assess the effectiveness and safety of each therapeutic approach, which can introduce new prospects in the treatment of infertility and increase the chances of successful implantation and pregnancy.

Keywords: implantation failures; assisted reproductive technologies; new therapy approaches.

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Возможности новых терапевтических подходов, направленных на улучшение исходов вспомогательных репродуктивных технологий

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АННОТАЦИЯ

Бесплодие представляет собой глобальную проблему здравоохранения, которая затрагивает до 17,5% населения во всем мире. Использование методов вспомогательных репродуктивных технологий помогает решать данную проблему, однако не обладает достаточной эффективностью во многих наблюдаемых случаях. Неудача имплантации представляет собой серьёзную и многогранную задачу, с которой сталкиваются специалисты репродуктивных технологий, несмотря на значительные успехи, достигнутые в данной области. В представленном обзоре освещаются перспективные исследования, основанные на медикаментозных и инвазивных методах вмешательств, а также их возможные комбинации, которые потенциально смогут улучшить клиническое лечение неудач имплантации. Тем не менее требуется дальнейшее изучение эффективности и безопасности каждого терапевтического подхода, которое сможет открыть новые перспективы в лечении бесплодия и повышении шансов на успешную имплантацию и беременность.

Ключевые слова: неудачи имплантации; вспомогательные репродуктивные технологии; новые подходы терапии.

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旨在改善辅助生殖技术成果的新治疗方法的机遇

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摘要

不孕不育是一个全球性的健康问题，影响着全球高达17.5%的人口。辅助生殖技术的使用有助于解决这一问题，但在许多观察到的病例中效果并不理想。尽管生殖技术领域取得了重大进展，但植入失败仍是生殖技术专家面临的一个多方面的严峻挑战。这篇综述强调了基于药物和侵入性干预的前瞻性研究，以及它们可能的组合，有可能改善植入失败的临床治疗。然而，还需要进一步研究每种治疗方法的有效性和安全性，这将为不孕症的治疗开辟新的前景，并增加成功植入和怀孕的机会。

关键词：植入失败；辅助生殖技术；新治疗方法。

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Infertility is a serious health issue worldwide, affecting approximately 8%–13% of couples. Around 5% of women are expected to suffer from two consecutive pregnancy losses, almost 75% are due to an implantation failure, and therefore are never recognized as clinical pregnancies. Despite significant advances in assisted reproductive technologies (ART), in some cases, successful implantation cannot be achieved due to possible failure at one of the steps such as attachment, adhesion or invasion, which occurs in approximately 10% of cycles during in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) [1, 2]. In addition, 12%–46% of infertility patients experience recurrent implantation failure (failure to achieve pregnancy after three or more consecutive cycles of transferring 1–2 quality embryos in each cycle).

In addition to male factors, risk factors for embryo implantation failure when using ART include higher body mass index (BMI), smoking, alcohol consumption, stress (which may lead to changes in markers of uterine receptivity and decidualization, increased production of reactive oxygen species, changes in sperm microRNA content, and increased DNA fragmentation), as well as abnormal embryonic defects, abnormal embryo-endometrium interactions, dysregulation of immunological factors, and altered endometrial receptivity [3, 4].

Immunologic factors that may contribute to adverse pregnancy outcomes include dysfunction of innate lymphocytes, T cells, decidual dendritic cells, and macrophages [5]. T cells play an important role in the immune response during implantation. The primary role of T helper 1 (Th1) cells is to stimulate cell-mediated responses involving cytotoxic T cells and macrophages. T helper 2 (Th2) cells stimulate B cells to produce antibodies. With the onset and progression of pregnancy, the number of Th2 cells increases relative to Th1 cells, and this imbalance in favor of Th1 cells contributes to an increased immune response, which occurs in 37.7% of patients with implantation failure and is associated with increased levels of anti-inflammatory factors such as IFN-γ, tumor necrosis factor-alpha (TNF-α), and interleukin-2 (IL-2), suggesting immune rejection. T regulatory (Treg) cell depletion can also lead to adverse pregnancy outcomes and implantation failure due to reduced ability to control Th1 and Th2 cell balance and suppress activated T cells [6–8].

The important role of macrophages in implantation, placentation, and embryonic development has been suggested by their effects on vascular remodeling at the mother-fetus interface and on trophoblast invasion in the spiral arteries [9]. For example, in patients with implantation failure, proportions of $CD56^+$ uNK, $CD16^+$ NK cells and $CD16^+$ macrophages were significantly increased, which is thought to increase cytotoxicity and lead to immune rejection of the embryo [10].

Uterine NK cells (uNK cells) represent more than 70% of all endometrial leukocytes detected in the decidua stroma early in pregnancy. They produce cytokines, express receptors mediating maternal-fetal immunity, and are the major source of angiogenic growth factors (placental growth factor, vascular endothelial growth factor, and VEGF-A) that can drive angiogenesis during embryo implantation and remodel spiral arteries. Studies show that aberrant activity of uNK cells during trophoblast invasion can lead to undesirable outcomes (local ischemia and oxidative stress) that negatively affect the implantation process [11–13].

In patients with infertility, changes in the vaginal microbiome (decrease in lactobacilli counts, increase in opportunistic microflora) is identified, suggesting a negative effect on gametogenesis, implantation, and delivery [14, 15]. The endometrium contains fewer bacteria than the vagina (10^6–10^7), and changes in its microbiota can potentially lead to chronic endometritis, with a prevalence of 2.8% in patients with infertility and 7.7% to 66.0% in patients with implantation failure. Chronic endometritis affects the immune status of the endometrium by increasing the synthesis of lipopolysaccharides, counts of immune cells in the endometrium ($CD83^+$ mature DC, $CD68^+$ macrophages, $CD8^+$ T cells and $Foxp3^+$ Treg cells), which may affect the endometrial susceptibility and induce recurrent implantation failure [14, 16, 17].

Inherited/acquired thrombophilia (genetic mutations in factor V Leiden, proteins S and C, prothrombin and methylenetetrahydrofolate reductase [MTHFR], V34L [factor XIII polymorphism], G20210A [prothrombin gene mutation] and 4G/L33P [ribosomal polymorphism of MTHFR enzyme], a/b L33P [ribosomal polymorphism of MTHFR enzyme] and 4G/5G [plasminogen activator inhibitor-1, PAI-1], antiphospholipid syndrome) may also contribute to implantation failure through impaired embryo vascularization and decidual blood flow [18].

In addition to the above, impaired endometrial receptivity is also one of the reasons for implantation failure in IVF and embryo transfer (ET) in two out of three cases, possibly due to changes in the differential expression of key genes (PTGS2, FGB, MUC1, SST, VCAM1, MMP7, ERBB4, FOLR1, C3) and impaired prostaglandin synthesis [19].

Congenital uterine anomalies, uterine fibroids, polyps, intrauterine adhesions, adenomyosis, and hydrosalpinx affect the implantation rate not only by mechanical obstruction but also by altering endometrial secretion of cytokines (protein binding insulin-like growth factor 1, TNF-alpha). The literature shows that the proportion of undiagnosed disorders in patients with implantation failure ranges from 14% to 51% [20].

The studies show that after three attempts of IVF and ET, the overall pregnancy rate did not increase significantly, suggesting the need for timely identification of potential etiological factors of this condition for the development of potential individualized therapeutic solutions that would help improve the results of the ARTs used.

Non-medical measures to reduce the risk of implantation failure in IVF and ET include reducing BMI to normal levels

through low-calorie diets, medications, and bariatric surgery; quitting smoking; reducing alcohol consumption to one unit per day or abstaining from alcohol altogether; eating a balanced diet; exercising regularly; and consulting a psychologist to reduce psychological distress if needed [21, 22].

Other treatment options include the use of Intralipid, a 20% intravenous lipid emulsion consisting of soybean oil, glycerin, egg yolk phospholipid, and water. Intralipid may provide the body with essential fatty acids, including omega-3 fatty acids and alpha-linolenic acid [23]. Studies suggest that Intralipid may have immunomodulatory properties, possibly through mitochondrial-dependent reduction in platelet aggregation, reduction in hepatic apolipoprotein M secretion, increased insulin sensitivity, changes in platelet composition, reduction in platelet aggregation, reduction in secretion of IL-2, tumor necrosis factor alpha, IL-1 beta, and Th1 cells, increased production of TH2 cytokines, and long-term inhibition of NK cell activity and their modification to a phenotype more compatible with pregnancy [24].

A meta-analysis found that intravenous fat emulsion significantly improved pregnancy outcomes in IVF/ICSI cycles in patients with implantation failure (higher clinical pregnancy rates and live birth rates), but had no effect on miscarriage rates. In addition, the combined use of Intralipid and prednisolone has shown better results in terms of pregnancy rate [23, 25, 26]. However, it should be noted that some studies show conflicting results regarding clinical pregnancy, miscarriage, and live birth rates, so further evaluation of this option is needed before it can be introduced into clinical practice [27].

Polyclonal immunoglobulin G (IgG) is a donor plasma product that acts by neutralizing pathogenic antibodies to HLA/autoantibodies, suppressing the production of Th1 cytokines with a shift toward Th2 responses, increasing the counts of Treg cells, and suppressing the cytotoxicity of NK cells to protect from the maternal immune system [28].

Studies show that low doses of polyclonal IgG (0.4–0.5 mg/kg intravenously) increase live birth rates in patients under 40 years of age with four or more implantation failures, provided that treatment is initiated before the sixth week of gestation. Intravenous injection of polyclonal IgG at 0.6–0.8 mg/kg once mid-cycle and then 3 months or 5–10 days prior to ET in IVF cycles and at 16–20 weeks of gestation also increased live birth rates in patients with five or more implantation failures [29, 30]. In addition, the combined use of intravenous polyclonal IgG, acetylsalicylic acid, and sodium heparin may increase peripheral blood Treg cell levels and pregnancy rates in patients with implantation failure compared to patients receiving acetylsalicylic acid and sodium heparin alone. However, further studies are needed to understand the exact mechanism of IgG action in order to improve treatment criteria and develop a standard protocol for treatment with IgG [8, 31, 32].

A corticosteroid (prednisolone) is an immunoregulatory agent that stimulates trophoblast proliferation and invasion, normalizes cytokine expression and uterine NK cell activity by binding to glucocorticoid receptors on uNK cells and reducing their counts, and stimulates human chorionic gonadotropin (hCG) secretion [33].

Studies report that in patients with a history of two or more implantation failures with elevated uNK cell levels, prednisolone monotherapy may reduce concentrations of these cells, but without a significant effect on pregnancy outcomes. This is also consistent with a large multicenter trial and a Cochrane meta-analysis that found no beneficial effect of corticosteroids on live birth, clinical pregnancy, and miscarriage rates. In addition, an increased risk of preterm birth and biochemical pregnancy loss is reported in patients receiving prednisolone [34].

The use of oral antibacterial agents alone and in combination for the treatment of chronic endometritis may be effective against a wide range of pathogens, but does not appear to improve pregnancy outcomes. In contrast, a regimen combining oral doxycycline with topical antibiotics or intrauterine dexamethasone is shown to significantly improve implantation and pregnancy rates and may improve endometrial receptivity. Therefore, the concomitant administration of doxycycline and prednisolone acetate (200 mg and 5 mg per day, respectively) for 14 days is shown to increase implantation and progressive pregnancy rates, and this combination was more effective in managing chronic endometritis than doxycycline monotherapy [35–37]. The combination of doxycycline (100 mg orally twice a day for 14 days) and metronidazole (400 mg concomitantly) and intrauterine perfusion (gentamicin 80 mg and dexamethasone 5 mg) with ET within 3 months of this treatment was shown to provide higher implantation, pregnancy, and live birth rates than oral antibiotics alone [37, 38].

Immunosuppressants such as tacrolimus (a calcineurin inhibitor), currently used to reduce the risk of organ rejection in transplant recipients, may also help improve implantation rates. Calcineurin is a cytoplasmic protein involved in activating, proliferating, and differentiating T cells and mediates the transcription and translation of inflammatory factors. It may help suppress immune rejection by blocking communication between Th1 cells and macrophages or cytotoxic cells, inhibiting cytotoxic T cell generation, alloantigen-induced lymphocyte proliferation, and IL-2 and IFN-γ production [39, 40]. Therefore, in patients with a history of implantation failure and an increased ratio of Th1 or Th2 cells, administration of tacrolimus at a dose of 2–4 mg per day at the beginning of pregnancy or 2 days prior to ET may help prevent immunologic rejection and increase the implantation rate, as well as reduce the risk of pre-eclampsia (due to a decrease in Treg cells and an increase in Th1 cells). Studies show that the combined use of tacrolimus and low-molecular-weight heparin can improve the clinical picture of pregnancy, live birth rates, and reduce the risk of spontaneous abortion in patients with a history of implantation failure and an increased coefficient of NK cells in the peripheral blood [41, 42].

Cyclosporine is also an immunosuppressant and calcineurin inhibitor that increases the production of IL-4, Th2 cells, and the chemokine CXCL12 at the maternal–fetal interface. Studies show that cyclosporine also helped increase live birth and clinical pregnancy rates and decrease miscarriage rates. However, tacrolimus is shown to be more effective in reducing miscarriage rates and has a more favorable lipid profile [43, 44].

There is a correlation between endometrial thickness and the number of live births; patients with endometrial thickness less than 7 mm had lower clinical pregnancy rates than patients with endometrial thickness greater than 7 mm. Estradiol (oral, transdermal, vaginal) is one of the main treatment options for this condition. However, some studies confirm the efficacy of intrauterine infusion of platelet-rich plasma and granulocyte colony-stimulating factor (G-CSF) [45, 46].

Intrauterine infusion of platelet-rich plasma is an autologous concentrate of platelets in plasma injected into the uterine cavity that has a regenerative effect on tissues and cells, including the endometrial mucosa, through cytokines and growth factors, angiogenesis, cell proliferation, differentiation, and modification of the local immune response. Studies show that this treatment option promotes the expression of tissue remodeling genes and reduces fibrosis in Asherman's syndrome in animal models [46, 47]. Positive results were also obtained in terms of increase in clinical pregnancy rates and endometrial thickness in patients with thin endometrium and a history of implantation failure, and this treatment option was the most effective of the immunomodulatory treatments for implantation failure [48, 49].

Granulocyte colony-stimulating factor (G-CSF) is a cytokine produced by endothelial, stromal, macrophage, decidual, and other immune cells. Infusion of G-CSF at 60 to 300 mg on the day of hCG administration or embryo transfer can temporarily suppress the immune response by acting on lymphocytes, macrophages, and Th2 cells, stimulate dendritic cell renewal, secretion of Th2 cytokines, activation of Treg cells, and remodeling of endometrial vessels, which could improve endometrial receptivity and the implantation process [50]. However, some studies show both positive and conflicting results in terms of increasing the likelihood of pregnancy. It should be noted that the use of G-CSF is associated with side effects and adverse events (mucositis, splenomegaly, hepatomegaly, transient hypotension, epistaxis, urinary disorders, osteoporosis, flare-ups of rheumatoid arthritis, anemia, and pseudogout) [51, 52]. Therefore, further studies are needed to evaluate the efficacy and safety of these treatment options with larger populations before implementation in clinical practice.

Intrauterine infusion of autologous peripheral blood mononuclear cells (monocytes, T and B cells) can induce the production of interleukins and growth factors that appear to have a beneficial effect on endometrial thickness and receptivity and may also promote embryo implantation and invasion. The literature [53, 54] reports an increase in the number of pregnancies and live births following this infusion, although its empirical use is not recommended.

Intrauterine injection of hCG may help initiate and control blastocyst invasion and improve maternal immune tolerance by binding to the endometrial luteinizing hormone receptor, inducing cytokine production during the implantation window, and regulating endometrial receptivity and embryo implantation. Increased implantation and pregnancy rates are reported when administered at 500 to 1000 U 0.25 to 72 hours prior to ET [55, 56]. Although the evidence suggests a benefit, it is primarily derived from small, uncontrolled studies. There is no precise definition of the required dose and timing of hCG administration or the volume of perfusion fluid, which requires further research.

Personalized ET after assessment of endometrial receptivity using transcriptome analysis of gene expression at different stages of endometrial development was found to result in higher implantation and live birth rates in the first cycle of ET in infertile patients, suggesting a potential improvement in implantation failure outcomes [57].

Endometrial scratching, which is scraping of the uterine mucosa, promotes decidualization and prepares the endometrium for implantation by increasing the levels of LIF and IL-11 cytokines involved in endometrial receptivity and delaying endometrial maturation to establish synchrony between the endometrium and the embryo. In patients with two or more unsuccessful ICSI cycles, performing this procedure at hysteroscopy on day 7 of the previous cycle and on day 7 of the IVF cycle or the cycle preceding ICSI improved implantation rates. However, some studies show that this procedure does not significantly increase pregnancy rates, and no significant difference is found in the clinical course of pregnancy, miscarriage of singleton or multiple pregnancies [58, 59], so further studies are needed to determine the number, depth of endometrial scrapings, and timing of the procedure.

Therefore, to reduce the prevalence and improve the outcomes of ART, etiological factors of this condition should be identified and personalized treatment options should be developed. The above options are in some cases not included in routine practice, but show promising results in improving ART outcomes. This requires careful consideration and further studies with larger populations to confirm or refute the existing data with an assessment of their tolerability and safety before implementation in clinical practice.

ADDITIONAL INFO

Authors' contribution. S.A. Levakov — editing the article; T.A. Gromova — literature review, collection and analysis of literary sources, writing the text and editing the article; E.A. Rudiakova — literature review, collection and analysis of literary sources, writing the text of the article. All authors confirm that their authorship meets

the international ICMJE criteria (all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work).

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