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# IMMUNOMODULATORY APPROACHES IN RECURRENT IMPLANTATION FAILURE (RIF): REVIEW OF CLINICAL AND THERAPEUTIC EVIDENCE

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**Abstract:** Recurrent implantation failure (RIF) represents one of the main challenges in contemporary reproductive medicine, especially in cases where immunological factors interfere with endometrial receptivity and the establishment of pregnancy. Among the most investigated therapies are intravenous immunoglobulin (IVIG) and intralipids, which act by modulating the maternal immune response, particularly in patients with alterations in the profile of natural killer (NK) cells and inflammatory cytokines. This study aimed to analyze the main immunomodulatory approaches used in RIF, with an emphasis on the efficacy and safety of IVIG and intralipids in assisted reproduction protocols. To this end, an integrative literature review was conducted between February and May 2025, searching the PubMed and SciELO databases, including articles in English that addressed the immunological mechanisms and clinical outcomes of these therapies. The findings show that both IVIG and intralipids can favor implantation and live birth rates in subgroups of patients with specific immunological profiles. However, the lack of standardization in diagnostic criteria and therapeutic protocols limits the generalization of results. It should be noted that advances in reproductive immunology and the integration of professionals, such as biomedical scientists, are fundamental for the development of personalized strategies based on scientific evidence. It is concluded that the careful application of immunomodulatory therapies, combined with prior immunological evaluation and multidisciplinary action, is a promising way to optimize results in reproductive medicine and promote ethical and safe conduct in clinical practice.

**Keywords:** Recurrent Implantation Failure, Immunotherapy, Intravenous Immunoglobulin, Intralipids, Assisted Reproduction.

## INTRODUCTION

Recurrent implantation failure (RIF) is a significant challenge in reproductive medicine, directly affecting the hope and resilience of couples seeking pregnancy through in vitro fertilization (IVF). This condition compromises the success of reproductive treatments and has a significant emotional and psychological impact on patients. Understanding RIF requires recognizing embryo implantation as a complex process that depends on the precise interaction between the embryo and the maternal endometrium (Wang *et al.*, 2023).

In general, RIF is defined by the absence of clinical pregnancy after the transfer of multiple good-quality embryos in consecutive IVF cycles (Ma J; Gao W; Li D, 2023). The causes of this condition are multifactorial, including embryonic, endometrial, and, increasingly, immunological aspects. In this context, the role of the biomedical scientist is essential. According to the Regional Council of Biomedicine of the 5th Region (CRBM5), the biomedical specialist in assisted reproduction plays a fundamental role in investigating factors that interfere with implantation, contributing to the analysis of immunological profiles and the development of individualized therapeutic strategies.

Embryo implantation occurs through a coordinated sequence of biological events that require synchrony between the embryo and the endometrium. Repeated failure of this communication, even with morphologically viable embryos, characterizes RIF, generally defined as the absence of clinical pregnancy after at least three IVF cycles with the transfer of good-quality embryos. Recent evidence indicates that maternal immune imbalances significantly influence the implantation process, highlighting the importance of understanding these mechanisms to optimize clinical practice (Ghaebi *et al.*, 2017).

Recurrent implantation failure (RIF) is a significant challenge in reproductive medicine, impacting not only the success rates of in vitro fertilization (IVF), but also the emotional and psychological health of couples. Although multiple factors may contribute to RIF, recent evidence highlights the influence of maternal immune imbalances as a significant determinant of this condition. Among the therapeutic alternatives, intravenous immunoglobulin (IVIG) and intralipids have been studied for their ability to modulate the maternal immune response, promoting embryo tolerance and pregnancy success. Advances in these therapies show promising potential in reducing implantation failure, especially in patients with previously identified immune disorders. Given the clinical and emotional relevance of RIF and the growing adoption of immunomodulatory therapies in assisted reproduction protocols, it is necessary to gather and critically analyze the available scientific evidence on the efficacy and safety of IVIG and intralipids. ly consolidating this knowledge contributes to supporting clinical practices based on specific immunological profiles, improving interdisciplinary performance and strengthening the role of biomedical professionals in evidence-based reproductive medicine. Thus, the objective of this study was to evaluate, through an integrative review, the main immunomo-

dulatory therapies used in the treatment of RIF, focusing on IVIG and intralipids, comparing their clinical efficacy and outlining guidelines based on specific immunological characteristics, contributing to evidence-based clinical practice and future research in the area.

## MATERIALS AND METHODS

This study consists of an integrative review of the literature, designed to identify, analyze, and synthesize current knowledge on immunomodulatory therapies applied to RIF. Searches were conducted in the PubMed (National Library of Medicine) and SciELO (Scientific Electronic Library Online) databases between February and May 2025. The keywords "immunotherapy," "recurrent implantation failure," "intralipids," and "intravenous immunoglobulin" were used, associated with terms such as "treatment," "clinical application," and "immune system." Articles published in English from scientific journals and recognized institutions that were directly related to the subject of the study were included. Publications not relevant to the topic were excluded from the analysis.

## DEVELOPMENT

Embryo implantation failure is a multifactorial condition that has a significant impact on the results of assisted reproduction techniques. Among the various factors involved, immunological factors stand out for directly influencing endometrial receptivity and maternal-embryonic interaction, making it essential to investigate therapies capable of reducing pregnancy failure rates.

In this scenario, different immunomodulatory approaches have been studied with the aim of optimizing clinical outcomes in patients with recurrent implantation failure. Among the main interventions described in the literature are the administration of intravenous immunoglobulin (IVIG), paternal lymphocyte infusion (PLI), the use of corticosteroids, granulocyte colony-stimulating factor (G-CSF), hydroxychloroquine, immunosuppressants such as tacrolimus and sirolimus, as well as intralipids, low molecular weight heparin, and aspirin (Ma J; Gao W; Li D, 2023). Currently, the most widely used therapies in reproductive immunology are IVIG and intralipids, which stand out for their ability to modulate the maternal immune response and restore the balance between pro- and anti-inflammatory mechanisms, favoring embryo implantation. These strategies will be detailed below.

### INTRAVENOUS IMMUNOGLOBULIN (IVIG) THERAPY

Intravenous immunoglobulin (IVIG) is a concentrate of antibodies obtained from the plasma of multiple healthy donors and is widely used in different immunological contexts (Abdolmohammadi-Vahid *et al.*, 2019). Its main action is related to the modulation of the maternal immune response, with a reduction in *Natural Killer* (NK) cell activity, neutralization of autoantibodies, and regulation of the inflammatory cytokine profile, which contributes to an endometrial environment more receptive to embryo implantation (Velikova *et al.*, 2023). Thus, IVIG has shown promising results both in recurrent implantation failure (RIF) and in other conditions associated with immune dysfunction that compromise assisted reproduction outcomes.

Clinical studies reinforce the therapeutic potential of IVIG. Moraru et al. (2012) observed a significant improvement in clinical pregnancy and live birth rates in women with high NK cell levels treated with IVIG. Similarly, the meta-analysis conducted by Abdolmohammadi-Vahid et al. (2019) showed that treatment can increase pregnancy and live birth rates in patients with immune disorders related to implantation failure. However, the authors caution that these benefits cannot be generalized to all women undergoing assisted reproductive technology (ART).

Shu et al. (2023) corroborate these findings, reporting better outcomes in women under 40 years of age. In a recent study, Peero et al. (2024) evaluated patients with severe implantation failure—characterized by more than five unsuccessful viable embryo transfers—and found a live birth rate of 65% in the IVIG-treated group, compared to 20% in the control group, with no reports of relevant adverse effects. These results indicate that the therapy may benefit specific subgroups of patients with altered immune profiles.

On the other hand, Polanski et al. (2014) warn of methodological heterogeneity among the available studies, highlighting the need for caution regarding the generalized indication of IVIG. The guidelines of *the American Society for Reproductive Medicine* (ASRM) and the *Korean Society for Reproductive Immunology* reinforce this position, pointing to the lack of robust evidence and recommending the use of therapy only in patients with proven immune alterations, such as elevated levels of inflammatory cytokines or NK cell hyperactivity (Penzias *et al.*, 2018; Sung *et al.*, 2017).

Christiansen et al. (2019) report that the efficacy of IVIG is more evident when treatment is started before conception, especially in women with early signs of autoimmunity. Similarly, Banjar Shorooq, Almasri Walaa, and Genest Geneviève (2022) emphasize that therapeutic success depends on the timing of administration and the careful selection of patients who are candidates for therapy (Banjar Shorooq; Almasri Walaa; Genest Geneviève, 2022). Although the findings are significant for the use of IVIG, there is still a lack of consensus on the criteria for indication and duration of therapy.

Despite encouraging results, there is still no consensus on the criteria for indication, optimal dose, and duration of treatment. Velikova et al. (2023) emphasize that the future of IVIG in reproductive immunology depends on the accurate identification of the immune profiles that benefit most from this intervention. Danieli et al. (2025) add that, although the therapy is biologically safe and feasible, the lack of standardization of therapeutic protocols makes it difficult to compare studies and limits the consolidation of clinical guidelines.

Table 1 presents a summary of the main scientific studies that investigated the use of intravenous immunoglobulin (IVIG) as a therapeutic intervention in women with reproductive failure, including recurrent miscarriage and recurrent implantation failure, organized according to study type, target population, main results, and conclusions.

The studies analyzed indicate the potential of intravenous immunoglobulin (IVIG) as a therapeutic adjuvant in cases of reproductive failure associated with immune dysfunction, especially in the presence of

| Article (Author and Title) | Type of Study / Population Studied | Main Results | Conclusion |
|---|---|---|---|
| **Moraru et al., 2012**<br>***Intravenous Immunoglobulin Treatment Increased Live Birth Rate in a Spanish Cohort of Women with Recurrent Reproductive Failure and Expanded CD56+ Cells*** | Observational study / Women with reproductive failure and $CD56^+$ NK cell expansion | Clinical pregnancy rate of 92.5% and live birth rate of 82.5% with IVIG | IVIG modulated NK cells and significantly improved reproductive outcomes |
| ***Danieli et al., 2025***<br>***Intravenous immunoglobulin as a therapy for autoimmune conditions*** | Narrative review / Various autoimmune and reproductive diseases | IVIG demonstrated effective and safe immunomodulatory effect, even outside of medical prescription | The article advocates its use but emphasizes the need for further clinical trials |
| ***Christiansen et al., 2019***<br>***Treatment with intravenous immunoglobulin in patients with recurrent pregnancy loss: An update*** | Systematic review and meta-analysis / Women with recurrent pregnancy loss (RPL) | IVIG before conception increased live birth rates in secondary RPL | IVIG is effective in specific subgroups with immunological abnormalities |
| ***Banjar et al., 2022***<br>***Use of intravenous immunoglobulin in unexplained reproductive failure*** | Retrospective cohort / Women with RPL and unexplained RIF | Live birth rates greater than 60% with preconception IVIG | The study recommends IVIG for patients with unexplained reproductive failure |
| ***Polanski et al., 2014***<br>***Interventions to improve reproductive outcomes in women with elevated natural killer cells undergoing assisted reproduction techniques: A systematic review*** | Systematic review / Women with elevated NK cells undergoing ART | Inconsistent benefits and high heterogeneity of data | Does not recommend routine use of IVIG for all patients |
| ***Shu et al., 2023***<br>***Reproductive Outcomes of in Vitro Fertilization and Embryo Transfer in Women with Unexplained Repeated Implantation Failure are Significantly Improved with Intravenous Immunoglobulins*** | Retrospective observational study / Women with FRI | IVIG increased live birth rates in women <40 years old | IVIG was effective in young patients with FRI |
| ***Velikova et al., 2023***<br>***Intravenous Immunoglobulins as Immunomodulators in Autoimmune Diseases and Reproductive Medicine*** | Theoretical review / Focus on the immunological mechanisms of IVIG | IVIG regulated immune pathways, such as Tregs and NK cells | The review highlights immunological bases but reinforces the need for a personalized approach |

| | | | |
|---|---|---|---|
| ***Penzias et al., 2018***<br>***The role of immunotherapy in IVF: A guideline*** | International guideline (Israel, US, Europe) / Women with reproductive failure | Weak to moderate evidence; benefit limited to specific subgroups | IVIG should only be used in clinical studies or in cases with multiple failures and altered immune profiles |
| ***Sung et al., 2017***<br>***The Korean Society for Reproductive Immunology Guideline*** | National guideline (South Korea) / Women with RPL and/or RIF | Improvement in live birth rate and reduction in miscarriage | IVIG should be recommended in cases with proven immunological abnormalities |
| ***Peero et al., 2024***<br>***Intravenous immunoglobulin for patients with unexplained recurrent implantation failure: a 6-year single center retrospective review of clinical outcomes*** | Multicenter, randomized, double-blind, placebo-controlled clinical trial / Women with unexplained infertility undergoing IVF | No statistically significant difference in pregnancy rates | IVIG showed no clear benefit for women with unexplained infertility |

elevated levels of *Natural Killer* (NK) cells. The evidence points to consistent benefits in well-defined subgroups, such as women with a history of recurrent pregnancy loss (RPL), recurrent implantation failure (RIF), and proven immune disorders.

On the other hand, international guidelines and high-quality clinical trials warn of the heterogeneity of the available data and the absence of significant benefits in unselected populations. In this context, the need for a personalized therapeutic approach based on individual immunological profiles is reinforced, as well as the importance of new randomized controlled clinical trials that allow for a robust assessment of the efficacy and safety of IVIG in the field of reproductive medicine.

## INTRALIPID THERAPY

Intralipid therapy has stood out in the field of immunomodulatory therapies, emerging as a promising approach for patients with recurrent implantation failure (RIF) and recurrent pregnancy loss (RPL). This therapy consists of an intravenous lipid emulsion originally used in parenteral nutrition, but which has been investigated as an immunomodulatory strategy, especially for its ability to suppress the activity of natural killer (NK) cells, whose elevated levels are associated with RIF and RPL (Bespalova *et al.*, 2022). Several clinical studies have analyzed the therapeutic potential of intralipids in patients with reproductive immune dysfunction.

Check and Check (2016) evaluated the use of intralipids in women aged 40 to 42 years who had a history of implantation failure or miscarriage in in vitro fertilization (IVF) cycles. The research, conducted without defined immunological criteria, showed no pregnancies among the treated women, while the control group had pregnancy rates of 40% and live birth rates of 30%.

In contrast, Al-Zebeidi, Lary Sahar, and Al-Jaroudi (2017) observed a pregnancy rate of 43.3% in a group of 30 women with multiple implantation failures treated with intralipids. The authors emphasized that the efficacy of the therapy seems to be restricted to specific cases, and the conditions that favor its positive response remain uncertain. Similarly, Peivandi et al. (2022) identified a significant increase in the clinical pregnancy rate in women with a history of two implantation failures who underwent intralipid infusion before embryo transfer, pointing to the need for a better understanding of the mechanisms involved.

Other studies reinforce the immunomodulatory effects of therapy on NK cells. Coulam (2019) reported an increase in live birth rates of up to 60% in women diagnosed with RIF or PGR and NK cell hyperactivity. In a later publication, the author emphasized that the therapy's effectiveness is limited to patients with proven immune dysfunction and is not recommended indiscriminately (Coulam, 2021). Similar results were reported by Canella et al. (2021), who found significant modulation of the NK cell-mediated immune response, although the pathophysiological mechanisms involved still need to be elucidated.

Recent meta-analyses corroborate these findings. Kumar, Marron, and Harrity (2024) identified a significant increase in clinical pregnancy, live birth, and implantation rates, as well as a reduction in miscarriage rates. However, the authors recommended the use of therapy exclusively in patients with diagnosed immune disorders and a history of recurrent reproductive failure. Rimmer et al. (2021) held a similar position, recognizing the potential of intralipids but highlighting the lack of robust evidence to justify their routine use in clinical practice.

Convergently, Akar et al. (2022) reported high rates of clinical pregnancy (41.5%) and live births (29.2%) in women with RIF treated with intralipids, compared to the control group, emphasizing, however, the need for careful indication.

In a more recent study, Dayer, Menshawey, and El-Damaty (2025) identified a 20% increase in the clinical pregnancy rate in 112 women with unexplained reproductive failure undergoing intracytoplasmic sperm injection (ICSI). The treated group had a clinical pregnancy rate of 51.1%, compared to 37.5% in the control group. Although the results indicate potential benefit, the authors highlighted the persistence of gaps in understanding the immunological mechanisms responsible for the observed therapeutic effects.

Table 2 presents a summary of the main scientific studies that evaluated the effects of intravenous lipid emulsion therapy (intralipids) on reproductive outcomes in women with recurrent implantation failure and repeated pregnancy loss, categorizing them according to study type, population investigated, interventions, and main findings.

Therapy with intravenous lipid emulsions (intralipids) has established itself as a promising adjuvant approach in the management of reproductive failure, especially in patients with immune dysfunction characterized by elevated levels of natural killer (NK) cells. Randomized clinical trials, such as those conducted by Peivandi et al. (2022) and Dayer, Menshawey, and El-Damaty (2025), have demonstrated a significant increase in clinical pregnancy rates after the

| Article (Author and Title) | Type of Study / Population Evaluated | Intervention / Main Results | Conclusion |
|---|---|---|---|
| ***Check, Check (2016)*** ***Intravenous intralipid therapy is not beneficial in having a live delivery in women aged 40-42 years...*** | Case-control study / Women aged 40-42 years with FIR and/or PGR | Infusion of 4 mL of Liposyn II at 20% in 100 mL of intravenous saline solution. Result: 0% pregnancy in the treated group vs. 30% in the control group. | Intralipid therapy showed no benefit; possible adverse effect in older women. |
| ***Al-Zebeidi et al. (2018)*** ***The Effect of Fat Emulsion Intralipid 20% in Reproductive Outcome...*** | Retrospective study / Women with multiple implantation failure | Infusion of 20% intralipids in IVF-ICSI cycle. Result: 43.3% had a positive pregnancy test. | Promising results, but without clearly established statistical significance. |
| ***Peivandi et al. (2022)*** ***Effect of Intralipid Infusion on Pregnancy Outcome...*** | Single-blind randomized clinical trial / Women with two implantation failures | Infusion of 2 mL of 20% intralipids in 250 mL of physiological solution. Result: 30% clinical pregnancy in the treated group vs. 10% in the control group. | Statistically significant evidence of efficacy in improving the clinical pregnancy rate. |
| ***Coulam (2020)*** ***Intralipid treatment for women with reproductive failures*** | Critical review / Women with FIR and NK cell abnormalities | Intravenous intralipid therapy in patients with immune disorders. Live birth rate between 33% and 91% , depending on the diagnosis. | Better response observed in patients with identified immune alterations. |
| ***Canella et al. (2021)*** ***Lipid emulsion therapy in women with recurrent pregnancy*** | Narrative review / Women with RPL, FIR, and NK cell abnormalities | Various protocols for the use of intralipids. | Promising results, but still controversial and without methodological standardization. |
| ***Rimmer et al. (2021)*** ***Intralipid infusion at time of embryo transfer...*** | Systematic review and meta-analysis / Women with RIF | Infusion of 20% intralipids on the day of embryo transfer. | The review showed a significant increase in clinical pregnancy and live birth rates. |
| ***Kumar, Marron, Harrity (2021)*** ***Intralipid therapy and adverse reproductive outcome...*** | Systematic review and meta-analysis / Women with PGR and FIR | Comparison between intralipids and placebo/no intervention. | Evidence of benefits in specific cases, especially with immune disorders. |
| ***Akar et al. (2022)*** ***Effect Of Intravenous Lipid (Smoflipid®) Use...*** | Case-control study / Women with RPL despite good embryo quality | Infusion of SMOFlipid® until the 10th week of pregnancy. Result: 29.2% live births vs. 10.3% in the control group. | Positive results, but efficacy needs to be confirmed by randomized clinical trials. |
| ***Dayer, Menshawey, El-Damaty (2025) Efficacy of Intralipid Administration to Improve Pregnancy Rates...*** | Randomized controlled clinical trial / Women with unexplained recurrent miscarriage | Infusion of 100 mL of 20% intralipids diluted in 500 mL of physiological solution, between 7 and 10 days before embryo transfer. | Intralipid therapy was considered safe and effective, with a significant improvement in the clinical pregnancy rate. |

Table 2 – Comparison of studies on the use of Intralipid Therapy in reproductive failures

administration of intralipids. Complementarily, systematic reviews and meta-analyses conducted by Kumar, Marron, and Harrity (2021) and Rimmer et al. (2021) reinforced the benefits of therapy on reproductive outcomes, including increased clinical pregnancy and live birth rates.

However, methodological heterogeneity among studies, variability in patient clinical profiles, and the lack of standardization in therapeutic protocols described in retrospective and narrative analyses still compromise the extrapolation and universal applicability of the results.

The available findings indicate that the beneficial effects of intralipid therapy are predominantly manifested in patients with previously identified immune disorders, highlighting the importance of detailed immunological diagnosis as a criterion for therapeutic eligibility.

Thus, although the current results are promising, it is essential to conduct new randomized clinical trials with robust methodological designs and uniform diagnostic criteria in order to consolidate the efficacy and safety of intralipid therapy in the context of assisted reproduction.

## IMMUNOLOGICAL ASPECTS AND THE ROLE OF THE BIOMEDICAL PROFESSIONAL IN RECURRENT IMPLANTATION FAILURE

Reproductive medicine has made significant advances, driven by improvements in embryo culture techniques, ovarian stimulation protocols, and pre-transfer embryo screening methods. Despite these advances, embryo implantation failure remains a significant challenge in in vitro fertilization (IVF) cycles (Amjadi et al., 2020). In this context, studies aimed at understanding the influence of the immune system on recurrent implantation failure (RIF) have broadened our understanding of the mechanisms involved, although there is still no consensus on the exact role of immune responses in this condition (Franasiak & Scott, 2017; Hashimoto et al., 2017).

Recent research indicates that different components of the immune system, such as uterine natural killer (uNK) cells, regulatory T lymphocytes (Tregs), cytokines, and autoantibodies, exert a relevant influence on endometrial receptivity and the success of embryo implantation. Evidence suggests that uNK cell hyperactivity, Treg dysregulation, cytokine secretion imbalance, and the presence of autoantibodies are associated with maternal immune dysfunction, constituting critical factors that can compromise embryo attachment.

In this scenario, the role of the biomedical scientist is fundamental in laboratory research and in understanding the immunological aspects related to RIF. Through the application of advanced techniques, such as flow cytometry, immunological assays, and molecular analyses, biomedical scientists contribute to the identification of altered immunological profiles, including the quantification of immune cells, the detection of pro- and anti-inflammatory cytokines, and the evaluation of autoantibodies and genetic markers.

The scientific training of biomedical professionals enables the integration of laboratory research and clinical practice, allowing for the individualization of therapeutic approaches and support for the multidisciplinary team in choosing personalized strategies for each patient. Thus, biomedical professionals play an essential role in the

interface between diagnosis, prognosis, and therapy, contributing significantly to the improvement of clinical outcomes in reproductive medicine.

## CONCLUSIONS

Embryo implantation depends on coordinated interaction between the immune system, the endocrine system, and endometrial receptivity. Although assisted reproduction techniques have advanced, immunological factors still play a central role in recurrent implantation failure (RIF). Among the immunomodulatory therapies studied, intravenous immunoglobulin (IVIG) and intralipids show promising results in patients with specific immunological alterations, such as elevated NK cells and cytokine imbalance. However, the absence of standardized protocols and robust evidence limits their widespread clinical application. It is therefore essential to develop controlled clinical trials to confirm their efficacy and safety. In this context, biomedical scientists play a strategic role in investigating immunological mechanisms and individualizing therapeutic approaches, contributing to scientific advancement and the safe practice of reproductive medicine.

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