Review Article

Recurrent Implantation Failure : Etiology, Treatment Strategies and Contemporary Clinical Perspectives

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Abstract

Background : Recurrent Implantation Failure (RIF) is a challenging clinical phenomenon characterized by the failure to achieve a clinical pregnancy after multiple embryo transfers as per good practice recommendations from the European Society of Human Reproduction and Embryology (ESHRE). The body further noted a cumulative predicted implantation probability of at least 60% in the failed cases. This review delineates the etiology of RIF, encompassing immunological, anatomical, embryonic, and microbiome factors, and outlines current approaches to treatment, including lifestyle modifications, immunotherapy, endometrial receptivity enhancement, and Assisted Reproductive Technology (ART) strategies. We covered recent evidence, including systematic reviews, umbrella reviews, and cohort studies, to provide an updated overview of RIF etiology and management. Recent advances emphasize the use of individualized diagnosis through endometrial receptivity assays and pre-implantation genetic testing. Current treatments range from evidence-based interventions, such as blastocyst transfer, pre-implantation Genetic Testing for Aneuploidy (PGT-A), to hysteroscopic evaluation with major findings suggesting that therapy should be tailored according to underlying etiology with immuno-modulatory treatments such as granulocyte colony-stimulating factor, intravenous immunoglobulin (IVIG), platelet-rich plasma (PRP) and peripheral blood mononuclear cells (PBMC). Contemporary perspectives increasingly emphasize the dynamic “biosensor” role of the endometrium, highlighting the integrated contribution of embryo competence and endometrial function. Standardizing the definition and management of RIF remains crucial for improving reproductive outcomes.

Key words : Recurrent Implantation Failure, Embryo Transfer, Endometrial Receptivity, PGT-A, Immunotherapy.

Implantation is a highly coordinated process that depends on the synchronized development of a competent blastocyst and a receptive endometrium[1]. Despite significant advancements in Assisted Reproductive Technology (ART), implantation remains a major limiting step, and the inability of embryos to implant continues to account for the majority of ART failures. Recurrent Implantation Failure (RIF) has long been defined by a fixed number of unsuccessful embryo transfers, typically three or more[2], but such a criterion does not reflect variations in maternal age, embryo viability, or center-specific success rates. The lack of a standardized definition complicates clinical diagnosis and management, as multiple factors, including maternal age, embryo quality, number of embryos transferred, and cycle characteristics, contribute to RIF. In response to these limitations, the 2023 ESHRE good practice recommendations introduced a probabilistic definition that considers RIF to be present when the cumulative predicted chance of implantation, based on embryo quality and patient characteristics, exceeds 60% without achieving pregnancy[3]. This patient-centered definition better reflects the multifactorial nature of implantation and encourages individualized evaluation.

RIF affects approximately 10-15% of couples who undergo IVF and often leads to emotional exhaustion, financial distress, and decreased confidence in treatment[2,3]. Although most implantation failures document a random nature, especially in the context of untested embryos, a proportion of patients consistently fail to achieve pregnancy despite the transfer of morphologically high-quality or genetically screened embryos. This pattern suggests that underlying biological dysfunction, whether embryonic, endometrial, immunological, or vascular, may be present[1,3,4]. Therefore, an understanding of the interplay between embryonic competence and endometrial receptivity is essential for optimizing outcomes.

Editor's Comment :

- Recurrent implantation failure is a multifactorial condition for which contemporary guidelines favour a probability-based, patient-centered definition over fixed cycle-count criteria.
- Successful management depends on individualized evaluation of embryo competence, endometrial receptivity, uterine factors, immune–vascular status, and microbiome.
- Evidence-based strategies (blastocyst transfer, PGT-A in selected cases, hysteroscopic correction, treatment of chronic endometritis, lifestyle optimization) should be prioritized over empirical add-ons.
- The embryo–endometrium “biosensor” concept highlights implantation as a dynamic dialogue, underscoring the need for dual-focus, personalized care.

Etiology of Recurrent Implantation Failure (Tables 1&2):

Embryonic Factors :

Embryo quality is arguably the primary determinant of implantation success[5,6]. A substantial proportion of embryos, even those appearing morphologically normal,

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Table 1 — *Definition/s of recurrent implantation failure from different perspective*

Definition Approach	Key Elements Considered	Key Years	Typical Threshold	Strengths	Limitations
Cycle-count based	Number of failed ET cycles	2004- 2021	≥2-3 failed ET cycles	Simple, easy to apply clinically	Ignores embryo quality, maternal age
Embryo-number based	Total good-quality embryos transferred	2011- 2021	≥4-6 high-grade embryos	Accounts for cumulative exposure	Arbitrary quality cutoffs, no ploidy data
Euploid-ET based	Failed euploid blastocyst transfers	2021- 2023	≥2-3 failed euploid SETs	Focuses on "true" RIF	Requires PGT-A access, expensive
Probability-based (ESHRE)	Cumulative predicted implantation chance	2023	>60% predicted success without achievement	Age/embryo stage adjusted	Complex calculation needed

Table 2 — *Optimized embryo transfer strategy in recurrent implantation failure*

ET Parameter	RIF-Optimized Approach	Rationale/Evidence	Practical Implementation
Embryo Stage	Single/double blastocyst >cleavage	Higher IR/LBR	Day 5/6 euploid where possible
Fresh *versus* Frozen	Frozen-thawed preferred	Better synchrony, higher CPR (19-24%)	HRT-FET cycles
Embryo Transfer	Single euploid blastocyst (good prognosis)	Minimize multiples, maximize per-transfer success	Double blastocyst if indicated
Luteal Support	Individualized duration	ERA-guided if indicated	Progesterone optimization
Adjuncts	ERA/PGT-A in selected	Addresses specific defects	After 2+ unexplained failures

are chromosomally abnormal. Aneuploidy increases significantly with maternal age and is a major contributor to implantation failure[5]. Evidence from recent meta-analyses indicates that euploid embryo transfer significantly increases implantation and live birth rates, particularly in women aged 35 years and above[4-6]. From the paternal side, contributions, including sperm DNA fragmentation, epigenetic abnormalities, and mitochondrial dysfunction, may further compromise embryo development[7]. Although techniques such as Intracytoplasmic Sperm Injection (ICSI) circumvent fertilization barriers, do not fix intrinsic sperm defects that affect early embryogenesis[2,5,6]. However, preimplantation genetic testing for aneuploidy (PGT-A) improves implantation rates by selecting euploid embryos, offering potential benefit in RIF cases[6]. In summary, optimization of both oocyte and sperm quality remains foundational in the evaluation of RIF.

Uterine and Anatomical Factors :

Structural abnormalities of the uterine cavity constitute a well-recognized cause of implantation failure[7-9]. The septate uterus remains one of the most strongly implicated congenital anomalies with recent evidences consistently shows improvement in reproductive outcomes following septum resection[8]. Similarly, acquired pathologies such as intrauterine adhesions, submucosal fibroids, and endometrial polyps have been associated with reduced implantation rates[8,9]. Hysteroscopy used to be considered the gold standard for diagnosing and correcting cavity abnormalities and is recommended in women with RIF, particularly if prior imaging was inconclusive[7,9]. Even minor irregularities of the cavity may adversely affect endometrial receptivity by disrupting vascular supply, altering cytokine expression, or interfering mechanically with embryo apposition.

Endometrial Receptivity and the Biosensor Concept :

Beyond anatomical considerations, the functional state of the endometrium plays a pivotal role in determining implantation success. Emerging evidence suggests that the endometrium functions as a "biosensor," capable of assessing embryo competence and modulating its receptivity accordingly[4]. In healthy cycles, endometrial stromal cells undergo a process of decidualization that facilitates embryo invasion, immune tolerance, and placental development. When decidualization is impaired due to hormonal imbalance, inflammation, or genetic predisposition the embryo–endometrium dialogue becomes disrupted[1].

Conditions such as chronic endometritis have gained renewed attention herein, with studies demonstrating improved reproductive outcomes following targeted antibiotic therapy[9,10]. Similarly, thin endometrium, typically defined as endometrial thickness below 7 mm, may indicate inadequate proliferation or vascularization, although its causal role in RIF remains debated. Molecular receptivity tests such as Endometrial Receptivity Array (ERA) evaluate gene expression profiles to facilitate personalized embryo transfer timed to optimal WOI. However, current evidence does not support routine use of these assays in RIF, as discrepancies in study design and outcome reporting limit their clinical applicability[11].

Immunological Factors :

Maternal-fetal immune tolerance to the semi-allogenic embryo is necessary for embryo implantation[1]. Dysregulation of uterine Natural Killer (uNK) cells, macrophages, regulatory T cells and altered dendritic cell and macrophage activity has been implicated in implantation failure[6]. Recent studies suggest polymorphisms in Killer cell Immunoglobulin-like Receptors (KIR) and Human Leukocyte Antigen (HLA) interactions may affect uNK cell activity and vascular remodeling at the implantation site[12]. However, the interpretation of immunologic findings is challenging due to methodological variability across studies. Excessive activation of NK cells, imbalanced Th1/Th2 responses, or aberrant HLA/KIR interactions have been proposed as possible mechanisms[1,2,12], yet their predictive value

remains inconsistent. Consequently, immunologic testing is not universally recommended[3]; nevertheless, targeted immunomodulatory therapies may benefit selected individuals whose clinical presentation and laboratory findings suggest immune-mediated implantation failure.

Thrombophilic and Vascular Influences :

Vascular dysfunction and impaired endometrial perfusion have also been proposed as contributors to RIF. Inherited thrombophilias, including hyperhomocysteinemia, Factor V Leiden and prothrombin gene mutations, and acquired disorders such as antiphospholipid syndrome can increase microthrombotic events within the endometrium[7,9], potentially impairing implantation. However, current evidence does not support routine thrombophilia screening in RIF patients unless clinically indicated[3]. The vascular hypothesis also encompasses impaired spiral artery remodeling or endothelial dysfunction[1], which may influence decidualization and early placentation.

Microbiome and Infectious Contributors :

The uterine microbiome has recently emerged as an additional determinant of reproductive success[4,6]. A microbiota dominated by Lactobacillus species is generally considered favorable, whereas dysbiosis characterized by increased Gardnerella, Atopobium, or anaerobic species has been associated with lower implantation rates. Altered vaginal and endometrial microbiota, including decreased Lactobacillus species and chronic endometritis, have been linked to RIF[13,14]. Hysteroscopic evidence of micropolyps, stromal edema, or abnormal vascular patterns prompts biopsies that can identify plasma cell infiltration, thereby guiding antibiotic therapy[14]. Although microbiome profiling is promising, its role in routine RIF evaluation remains exploratory.

Lifestyle and Psychosocial Influences :

Lifestyle factors exert significant effects on implantation and ART success. Obesity alters endocrine function, reduces endometrial receptivity, and increases inflammatory markers[15]. Cigarette smoking impairs oocyte competence and increases sperm DNA fragmentation[2,4]. Alcohol consumption and exposure to environmental toxins have also been implicated[8]. Additionally, the psychological stress associated with repeated ART attempts may adversely influence endocrine and immune function[3]. Therefore, lifestyle modification forms an essential component of comprehensive RIF management.

Diagnostic Evaluation in RIF :

A structured evaluation is essential to identify reversible contributors and avoid unnecessary interventions. Current consensus emphasizes embryo quality assessment, review of laboratory parameters, and reconsideration of ovarian stimulation strategies[3]. Uterine evaluation through Transvaginal Ultrasound and hysteroscopy is recommended to identify structural abnormalities or signs of chronic endometritis. Basic endocrine tests, including thyroid function and prolactin levels, should be considered, as should semen analysis with optional sperm DNA fragmentation assessment. More advanced tests, such as receptivity assays, immune profiling, or thrombophilia screening, should be reserved for select cases where clinical suspicion is high. A stepwise, evidence-based approach helps balance diagnostic yield with avoidance of over-testing.

Therapeutic Strategies in Recurrent Implantation Failure (Figs 1-3) :

Lifestyle Modifications :

Optimizing Body Mass Index (BMI), discontinuing smoking and alcohol intake, and implementing effective stress-management strategies are recommended to enhance IVF outcomes, with even stronger emphasis in women with RIF.

Improving Implantation Potential : Selection, Transfer, and Adjuvant Measures in RIF

Optimizing embryo selection and refining transfer strategies are central to improving outcomes in women with RIF[4]. Blastocyst-stage transfer enhances physiologic selection by allowing only embryos with higher developmental competence to progress to transfer, while PGT-A further improves selection by identifying euploid embryos[5]. Numerous studies report higher implantation and live birth rates following euploid transfer, particularly in women of advanced maternal age or those with previous failed cycles, though considerations such as cost, accessibility, and potential biopsy-related risks remain important[2,6,8]. Alongside embryo selection, adjustments in ovarian stimulation protocols, luteal phase support, and prioritizing blastocyst over cleavage-stage transfer can enhance implantation efficiency. Assisted hatching may provide benefit in selected patient cohort, especially those with prior failures or older maternal age though evidence remains mixed. Frozen–thawed blastocyst transfer may also offer advantages over fresh cycles in RIF[3]. However, the benefits must be weighed against procedural costs, accessibility, and potential biopsy risks. Low-molecular-weight Heparin (LMWH) can improve live birth rates in RIF patients with confirmed thrombophilia[7,9], but its routine use for all RIF cases is not universally recommended[3].

Correcting Uterine Factors :

Hysteroscopic treatment of uterine abnormalities such as septa, fibroids, adhesions, and polyps is supported by moderate- to high-quality evidence demonstrating improved clinical pregnancy rates[2,4,16]. Even subtle intrauterine lesions may disrupt implantation and warrant correction. Endometrial injury or “scratch”, prior to embryo transfer historically proposed to improve receptivity[16] by inducing local inflammation thereby provoking decidualization and increasing cytokine release, has

shown inconsistent results in unselected IVF populations but may offer benefit in strictly defined RIF cases[3], thus requires further standardization.

Immunomodulatory Therapies :

A growing number of RIF patients are being offered immuno-modulatory therapies, although evidence supporting their use remains heterogeneous. Granulocyte colony-stimulating factor (G-CSF) has gained interest following studies reporting improved implantation rates (2, 4), including a recent 5-year cohort where intrauterine G-CSF was associated with significantly higher implantation compared with controls[12]. However, effects on clinical and chemical pregnancy rates were less conclusive. Intralipid infusion, believed to modulate NK-cell function, has shown favorable results in several meta-analyses, although the quality of evidence varies[17]. Similarly, glucocorticoids, intravenous immunoglobulins (IVIG) may reduce uNK cells cytotoxicity and improve Treg cell function in selected patients but require cautious use due to limited definitive evidence[18]. Platelet-rich Plasma (PRP) and Peripheral Blood Mononuclear Cell (PBMC) infusions have demonstrated improvements in implantation and clinical pregnancy in multiple small trials and systematic reviews[19], but standardization of preparation and administration protocols remains lacking. LMWH may be considered in patients with documented thrombophilia or antiphospholipid syndrome, though routine use in RIF is not supported[3].

Microbiome Management and Infection Treatment :

Treatment of chronic endometritis with targeted antibiotics has consistently improved reproductive outcomes and is now considered a critical component of RIF management when diagnosed. Restoration of normal microbiota through probiotics, antibiotics; in single or in combination or other microbiome-modulating interventions[20] is under investigation and may become a future therapeutic avenue.

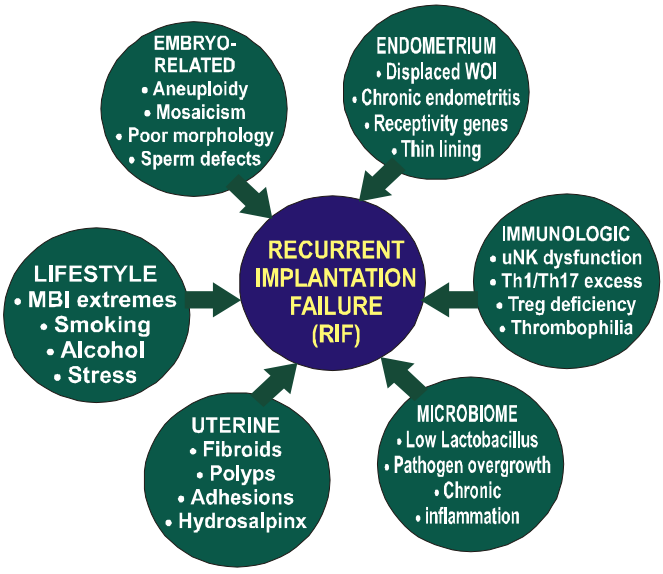

Fig 1 — Conceptual Map of RIF Etiologies. Conceptual framework showing major etiologic domains contributing to recurrent implantation failure and their interactions

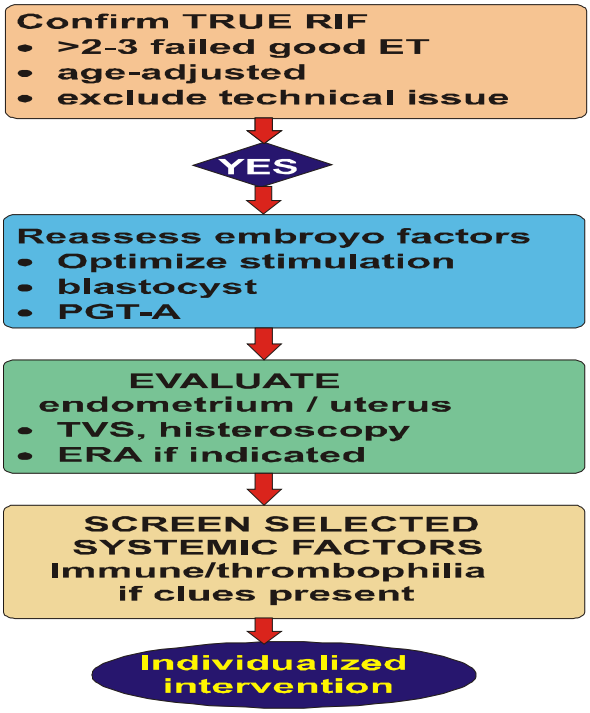

Fig 2 — Stepwise RIF Management Pathway. Clinical algorithm for evaluation and management of recurrent implantation failure

Male Factor Interventions :

Management of male factor infertility includes optimization of lifestyle habits, antioxidant supplementation, correction of varicocele when indicated, and refinement of sperm selection techniques[3]. Although these interventions may improve sperm DNA integrity and embryo development, their specific impact on RIF requires further study.

Psychosocial Support :

Recognition of the psychological burden of RIF is important, as stress can influence endocrine signaling, immune function, and treatment adherence. Counselling, stress-reduction techniques, and structured support programs contribute significantly to patient well-being and may indirectly improve cycle outcomes[2,3].

Contemporary Perspectives :

Recent literature challenges the notion of RIF as a distinct clinical entity[21]. With the increasing use of euploid single embryo transfer, many cases previously labeled as RIF now appear to reflect random biological variation. In present times, individualized assessment including maternal age, embryo quality, endometrial status, and immunological profile is essential for effective management. Immunomodulatory approaches and endometrial receptivity optimization represent the forefront of therapeutic strategies[22]. Nonetheless, persistent implantation failure

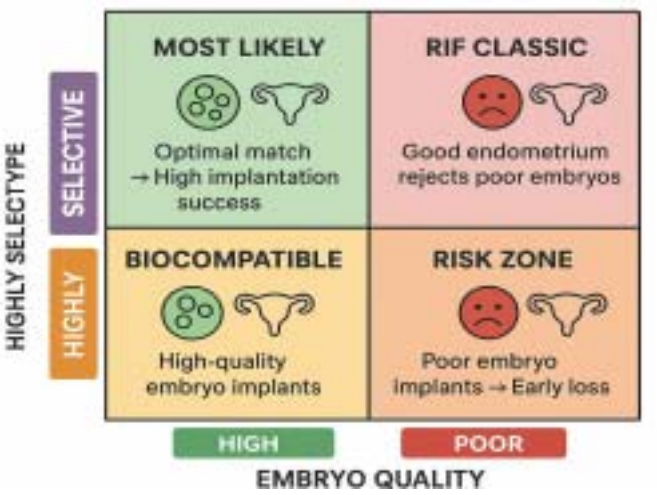

Fig 3 — Schematic of the embryo–endometrium "biosensor" concept
X-axis: embryo genomic/functional quality from "high" to "poor".
Y-axis: endometrial phenotype ranging from "highly selective/low receptivity" to "highly receptive/low selectivity"

after transfer of high-quality or genetically normal embryos suggests that underlying pathological mechanisms do exist for a subset of patients. The emerging biosensor model reframes implantation not as a one-sided failure of the embryo or endometrium but as a dynamic interplay between both. This conceptual shift encourages dual-focus reproductive management, emphasizing both embryonic competence and endometrial health.

Conclusion

RIF remains one of the most challenging conditions in reproductive medicine. Its multifactorial etiology necessitates a comprehensive, individualized approach that balances evidence-based diagnostics with judicious therapeutic selection. High-quality embryos, a receptive uterine environment, optimal maternal health, and well-regulated immune function form the cornerstones of successful implantation. Although several adjuvant treatments such as G-CSF, intralipids, PRP, and PBMC infusions show promising results, the current evidence is insufficient for universal recommendation. As the field moves toward a more precise understanding of embryo–endometrium interactions, future research must focus on improving prognostic models, validating targeted therapies, and minimizing empirical use of interventions. Ultimately, careful patient-centered evaluation and evidence-driven management offer the best opportunity to improve outcomes and reduce the burden of RIF on affected couples.

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References

1 Koot YE, Teklenburg G, Salker MS, Brosens JJ, Macklon NS — Molecular aspects of implantation failure. *Biochim Biophys Acta* 2012; **1822(12):** 1943-50.
2 Ma J, Gao W, Li D — Recurrent implantation failure: A comprehensive summary from etiology to treatment. *Front Endocrinol (Lausanne)* 2023; **13:** 1061766.
3 Cimadomo D, de Los Santos MJ, Griesinger G, Lainas G, Le Clef N, McLernon DJ, *et al* — ESHRE Working Group on Recurrent Implantation Failure ESHRE good practice recommendations on recurrent implantation failure. *Hum Reprod Open* 2023; **3:** hoad023.
4 Macklon N — Resolving recurrent implantation failure. *Reprod Biomed Online* 2025; **50(4):** 104827.
5 Almohammadi A, Choucair F, Khan KS, Bueno-Cavanillas A, Cano-Ibáñez N — Interventions for recurrent embryo implantation failure: An umbrella review. *Int J Gynaecol Obstet* 2025; **169(2):** 539-56.
6 Bulletti FM, Sciorio R, Conforti A —. Causes of embryo implantation failure: A systematic review and metaanalysis of procedures to increase embryo implantation potential. *Front Endocrinol (Lausanne)* 2025; **15:** 1429193.
7 Simon A, Laufer N — Assessment and treatment of repeated implantation failure (RIF). *J Assist Reprod Genet* 2012; **29(11):** 1227-39.
8 Coughlan C, Ledger W, Wang Q — Recurrent implantation failure: definition and management. *Reprod Biomed Online* 2014; **28(1):** 14-38.
9 Margalioth EJ, Ben-Chetrit A, Gal M, Eldar-Geva T — Investigation and treatment of repeated implantation failure following IVF-ET. *Hum Reprod* 2006; **21(12):** 3036-43.
10 He Y, Shi S, Su X, Chen G Zhao X — Incidence of pregnancy outcomes among patients with recurrent implantation failure: a systematic review and meta-analysis. *BMC Pregnancy and Childbirth* 2025; **25(1):** 1184.
11 Lessey BA, Young SL — What exactly is endometrial receptivity? *Fertil Steril* 2019; **111(4):** 611-7.
12 Elkhateb I, Fahmy R, Ramadan W, Mourad A, El-Demiry NM, Shohayeb A — Granulocyte colony-stimulating factor for recurrent implantation failure: the results of a 5-years cohort study. *Sci Rep* 2025; **15(1):** 40390.
13 Moustafa S, & Young SL — Diagnostic and therapeutic options in recurrent implantation failure. *F1000Research*, *9*, F1000 Faculty Rev-208.
14 Eslami M, Naderian R, Ahmadpour A, Shushtari A, Maleki S, Mohammadian P, *et al* — Microbiome structure in healthy and pregnant women and importance of vaginal dysbiosis in spontaneous abortion. Frontiers in Cellular and Infection Microbiology 2025; **14:** 1401610.
15 Lessey BA, Young SL — What exactly is endometrial receptivity? *Fertil Steril* 2019; **111(4):** 611-7.
16 Nastri CO, Polanski LT, Raine-Fenning N, Martins WP — Endometrial scratching for women with repeated implantation failure. *Hum Reprod* 2014; **29(12):** 2855-6.
17 Kumar P, Marron K, Harrity C — Intralipid therapy and adverse reproductive outcome: is there any evidence?. Reproduction & fertility 2021; ***2*(3):** 173-86.
18 Cai QY, Tang WZ, Li ZM, Li JZ, Zhi XQ, Yang QH, *et al* — Efficacy of glucocorticoids treatment in recurrent embryo implantation failure. *Cell Death Discovery* 2025; **11(1):** 461.
19 Huang C, Ye X, Ye L, Lu L, Liu F — Platelet-Rich Plasma Intrauterine Infusion as Assisted Reproduction Technology (ART) to Combat Repeated Implantation Failure (RIF): A Systematic Review and Meta-Analysis. *Iranian Journal of Public Health* 2023; **52(8).**
20 Zhang H, Zou H, Zhang C, Zhang S — Chronic endometritis and the endometrial microbiota: implications for reproductive success in patients with recurrent implantation failure. Annals of Clinical Microbiology and Antimicrobials 2024; **23(1):** 49.
21 Lu JK, Law YJ, Zhang N, Katsika ET, Kolibianakis EM, Venetis, C — A. Variability and implications of recurrent implantation failure definitions used in the scientific literature: a systematic review. Human Reproduction Open 2025; **3:** hoaf033.
22 Liu M, Yuan Y, Qiao Y, Tang Y, Sui X, Yin P, *et al* — The effectiveness of immunomodulatory therapies for patients with repeated implantation failure: a systematic review and network meta-analysis. Scientific reports. **12(1):** 18434.