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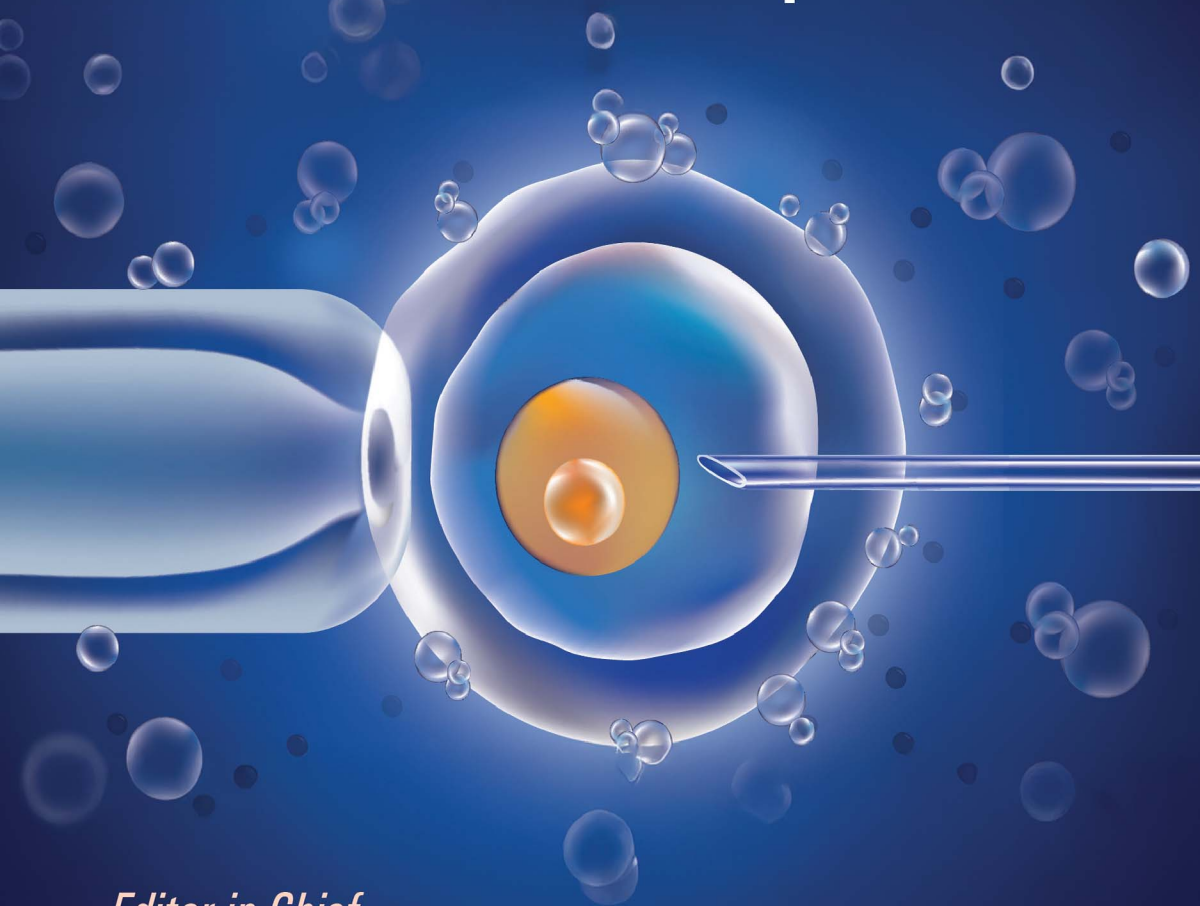
Current Clinical Perspectives



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CURRENT BURNING ISSUES IN ART

CHAPTER 33

Recurrent Implantation Failure

Jayesh S Amin, Ripal S Patel, Rudri A Patel

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INTRODUCTION

Implantation failure refers to the term where an embryo fails to reach the stage where it can be seen as a gestational sac on ultrasound. Again, this refers to two situations, one in which there has been no recordable beta-human chorionic gonadotropin (hCG) and the other in which there was recorded beta-hCG. However, it did not progress to the stage of gestational sac. In the present era, where the field of assisted reproductive technology (ART) has been so advanced, unexplained recurrent implantation failure poses a great challenge. However, there are so much of debates regarding the ideal approach toward these cases that there is no definite evidence-based proven approach to dealing with these cases. In this chapter, authors have tried to simplify the approach toward recurrent implantation failure (RIF) cases and to reach to possible conclusion keeping in mind the current treatment options available.

DEFINITION

The term RIF applies to only those patients undergoing ART. There is no universally accepted definition of RIF. Table 1 depicts various definitions of RIF in the literature.

The European Society of Human Reproduction and Embryology (ESHRE) definition of RIF describes the scenario in which the transfer of embryos considered to be viable has failed to result in a positive pregnancy test sufficiently often in a specific patient to warrant consideration of further investigations/interventions.

Regardless of the variability in definitions, the diagnosis of RIF is a difficult reality for many couples undergoing infertility treatment. There is as yet no universally accepted definition for RIF, despite many publications on this topic.

INCIDENCE

Due to variability in the definition of RIF, there are no accurate data available on the exact incidence or prevalence of RIF. Biochemical pregnancy is reported to vary from 8% to 33% in the general population, which includes spontaneous conception as well.

Table 1: Definitions of RIF in the literature.

Polanski et al., 2014b	Absence of implantation after two consecutive cycles of fresh or frozen IVF embryo transfers with a cumulative number of transferred embryos of four or more cleavage-stage embryos or two or more blastocysts, all of good quality
Coughlan et al., 2014	Failure to achieve a clinical pregnancy after the transfer of at least four good-quality embryos in a minimum of three fresh or frozen cycles in a woman under the age of 40 years
El-Toukhy et al., 2016	Two to four previous fresh or frozen IVF treatment cycles ending in an embryo transfer but no pregnancy
Mariee et al., 2012	Failure of three fresh IVF cycles or two fresh IVF and two frozen embryos transfer cycles
Ledee et al., 2016	Failure to have an ongoing pregnancy >10 weeks after at least six embryos were transferred on day 3 or day 5 in women aged <43 years
Mitri et al., 2016	Failure to have a clinical pregnancy after four or more blastocysts (fresh or frozen) after ruling out malformed uterine cavity, hydrosalpinx, abnormal karyotype, or persistently thin endometrium in women aged 38 years or younger
Kitaya et al., 2017	Serial negative pregnancy tests following the transfer of three or more morphologically good cleavage-stage embryos and/or blastocysts
Lensen et al., 2019	Two previous implantation failures, no precision on the number of embryos
Olesen et al., 2019	Implantation failure despite top-quality embryo or blastocyst transfer(s)
Greco et al., 2014	Three to nine previous implantation failures after IVF (mean 4.9)
Huang, Wei and Li, 2017	Two or more failed transfers of good-quality embryos
Koot et al., 2019	Three failed IVF or ICSI treatments, each with at least one fresh good quality embryo per transfer, or failure to achieve pregnancy after transfer of 10 good quality embryos

ICSI: intracytoplasmic sperm injection; IVF: *in vitro* fertilization.

CAUSES

The causes of RIF can be broadly divided into maternal factors, embryonic factors, and paternal factors as described in Table 2.

INVESTIGATIONS

There are 'n' number of investigations that are offered to cases of RIF worldwide.

Practically speaking, if the patient arrives after even one *in vitro* fertilization (IVF) failure in today's era, it is always advisable to counsel the patient to undergo preimplantation genetic testing (PGT). The decision of endometrial receptivity array (ERA) is a dynamic one. It depends on the number of PGT normal embryos one has. If there are less number of PGT normal embryos, it is always beneficial to go for a hysteroscopy and ERA testing and then go for transfer.

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Table 2: Causes of recurrent implantation failure (RIF).

Maternal factors	
Maternal age	As age increases so do the chances of aneuploidy leading to more implantation failures or abortions
BMI	The patients having class 1, 2, and 3 type of obesity have the highest rates of implantation failure
Smoking	Smoking disturbs the luteal phase by disturbing the function of the corpus luteum thus leading to implantation failure
Stress	Elevated levels of cortisol due to stress lead to more chances of early abortions
Uterine factors and endometrial factors	Uterine fibroids, endometrial polyps, congenital uterine anomalies, intrauterine synechiae, adenomyosis, and hydrosalpinx
Thrombophilias	Antiphospholipid antibody syndrome
Connective tissue disease	Some of the disorders associated with RIF are systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, primary Sjogren syndrome, inflammatory myositis
Immunological factors	Dysregulation of uterine NK cells, untreated hypothyroidism, cytokine imbalance
Embryonic factors	
Chromosomal abnormalities	Translocations, mosaicism, inversions, and deletions are more common in patients with RIF. The most common abnormality in patients with RIF is translocation abnormalities in the hatching process
Paternal factors	
Paternal factors associated with RIF are varicocele, infections, leukocytospermia, testicular torsion, testicular cancer, systemic infections, diabetes sperm chromosomal aneuploidy, and sperm DNA fragmentation	

BMI: Body mass index; NK: Natural killer.

How to proceed in the case of RIF?

- Counseling: The counseling should be stressed on the following important points in previous one or more IVF failure:
  - Possibility of multiple ovum pick-up in borderline ovarian reserve
  - PGT-A should be recommended
  - Hysteroscopy as and when required
  - The decision of ERA will be based on the number of PGT normal embryos
  - The possibility of donor oocytes in case of previous embryo arrest, consistently aneuploid embryos, and consistently empty follicle syndrome can be considered
  - The possibility of surrogacy in idiopathic RIF can be considered
- Ovarian stimulation: Regarding ovarian stimulation, if the history of previous stimulation is available, we can modify the dose accordingly. We will prefer to do genetic polymorphism testing of follicle-stimulating hormone and luteinizing hormone receptors before deciding the dose of stimulation. Otherwise, we will give the standard dose of gonadotropins depending on whether the patient belongs to the normal, hyper, or hyporesponder group. We will prefer adding adjuvants in hyporesponders along with gonadotropins. For further details, kindly refer to the chapter on ovarian stimulation
- Embryo transfer: The current trend is toward blastocyst frozen embryo transfer (ET) in the case of patients with RIF. According to the current study published in 2019, the

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clinical pregnancy rate, implantation rate, and ongoing pregnancy rate were higher in the single frozen/thawed blastocyst-stage transfer group compared with the double-cleavage-stage embryo transfer group (41.15% vs. 27.11%, $p<0.001$; 41.15% vs. 19.28%, $p<0.001$; 40.03% vs. 25.9%, $p<0.001$). They concluded that the blastocyst stage transfer could be a preferred strategy in patients with RIF

- Role of PGT: Performing preimplantation genetic screening for aneuploidy detection is believed to improve implantation rates in RIF. Trophectoderm biopsy is preferred as the risk of mosaicism is lower. Blastocyst analysis was associated with high pregnancy rates. Hence, the application of comprehensive chromosome screening is likely to assist a subset of patients with RIF (those capable of producing blastocysts) in achieving pregnancies
- Role of endometrial receptivity array: The altered window of implantation (WOI) is one of the proposed causes of RIF. ERA is the tool designed to find out this displaced WOI by studying the expression of genes of the proteins in the endometrium. There is insufficient evidence to support the routine use of currently available ERA testing in ART. A recent 5-year multicenter RCT comparing personalized embryo transfer (pET) after ERA test to fresh and frozen ET without the test showed comparable outcomes per transfer
- Role of immunotherapy: There are several immunological factors responsible for RIF. However, the results of immunotherapy are contradictory in RIF. The subcutaneous injection of granulocyte colony stimulating factor (G-CSF) can improve the outcomes of patients with recurrent miscarriage and the intrauterine infusion of G-CSF in women with a thin endometrium increases the thickness of the endometrium and pregnancy rate. A thin endometrium is detrimental to ET and may cause RIF. The IVF success rate after the administration of intravenous immunoglobulin (IVIG) increases in women with previous IVF failure, a high natural killer cell number, and/or an elevated Th1/Th2 ratio. The optimal protocol for the administration of IVIG is undefined and the overall benefits of IVIG remain controversial. In 2006, Japanese scientists first reported that the administration of autologous peripheral blood mononuclear cells (PBMCs) could significantly promote clinical pregnancy rate, implantation rate, and live birth rate in patients with repeated failure of IVF–ET. Then, Okitsu et al., demonstrated that only in patients who had three or more implantation failures, the clinical pregnancy rate, and the implantation rate in the PBMC-treated group were significantly higher than those in the nontreated group. It is better to recommend immunotherapy after two or more implantation failures with euploid embryos. However, further research is required to design the exact protocol of immunotherapy in the patient selection for RIF
- Role of intrauterine platelet-rich plasma (PRP) instillation: Two randomized controlled trials investigated whether administration of intrauterine PRP could improve IVF outcomes in women with RIF. Pooling of results showed a significantly increased chance of clinical pregnancy in treated women. In patients with RIF with good endometrium, the role of intrauterine PRP is controversial. After PGT and ERA, the cases of implantation failures can have some beneficial effects of intrauterine PRP instillation, but further research is required to prove its exact role in idiopathic RIF
- Role of HLA-C compatibility: Owing to their genetic variability and ability to bind to specific HLA class I allotypes, KIRs on uNK cells have been considered good candidates for balancing maternal leukocyte tolerance towards the embryo. It has been postulated that an adequate interaction between maternal KIRs and their ligands, the HLA class I molecules, expressed by the extravillous trophoblast cells, is crucial for sustained implantation
- Role of microbiome profiling: There is emerging evidence suggesting association between dysbiotic microbiota and RIF. A recent meta-analysis of six cohort studies

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including 1,095 women and several other studies have reported association between impaired reproductive outcomes and dysbiotic microbiota

- Lifestyle modification: They play a crucial role in optimization of ART outcome. Cigarette smoking, alcohol consumption, high BMI, stress, deficiency of vitamin D are some of factors associated with lower ART success
- Associated factors: Other factors to be considered are:
  - Karyotyping of female and male partner
  - Assessment of uterine cavity by 3D USG offers a non-invasive approach over invasive ones
  - Investigation of chronic endometritis
  - Optimization of metabolic and endocrinologic factors
  - Optimization of male factor.

SURROGACY

Factors responsible for RIF have important implications regarding treatment; however, in many couples, a definitive cause cannot be found. In those couples in whom no etiology is found after investigation for RIF and in whom empirical therapy was not effective, surrogacy is the only option. The role of intrauterine and intra-arterial stem cell therapy remains experimental and further research is required in this field. However, it is always advisable to give the option of stem cell therapy for thin endometrium before going for surrogacy. Then it should be left to the patient to decide depending on their financial and psychological status.

LABORATORY PERSPECTIVES TO IMPROVE THE RATE OF QUALITATIVE BLASTOCYST

At the laboratory level, the factors that play an important role in the failure of implantation are chromosomal abnormalities, damage to sperm DNA, zona hardening, and inadequate culture conditions. Newer techniques such as time-lapse imaging, artificial intelligence (AI) software, and metabolomics help us to select an embryo with good implantation potential. AI software gives us two scores—viability score and genetic score. Based on the combination of these two scores, we can select the most appropriate embryo for transfer. If zona hardening is the problem, assisted hatching is the solution. The technique of intracytoplasmic sperm injection and taking a biopsy for PGT also are very important factors in the formation of the embryo.

CONCLUSION

Recurrent implantation failure with unknown cause significantly hampers IVF success. It can be considered as an evolving field with a significant need for well-defined research. In the current generation of ART recipients and practitioners, the temptation to intervene after two or more failed embryo transfers is significant. The main goals in the case of women presenting with RIF are getting a good quality genetically normal embryo and understanding uterine receptivity. Empirical treatments should be offered only after aneuploidy cause of the embryo has been ruled out and they should be evidence based. Counseling plays an important role in these cases, which should be stressed on the possibility of multiple ovum pick-ups, embryo arrest, PGT-A, and the role of ERA and other empirical treatments if all of these fail.

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SUGGESTED READINGS

1. Casper RF. It's time to pay attention to the endometrium. Fertil Steril. 2011;96(3):519-21.
2. Churchill SJ, Bavan B, Lathi RB. The prognostic value of endometrial receptivity array in recurrent implantation failure. Fertil Steril. 2017;107(3):E7-E8.
3. Cutting R, Morroll D, Roberts SA, et al. Elective single embryo transfer: Guidelines for practice British Fertility Society and Association of Clinical Embryologists. Hum Fertil (Camb) 2008;11(3):131-46.
4. Das M, Holzer HE. Recurrent implantation failure: gamete and embryo factors. Fertil Steril. 2012;97(5):1021-7.
5. Fragoului E, Goodall N, KatzJaffe M, et al. The role of aneuploidy in repeated implantation failure: implications for patient counseling and preimplantation genetic screening. Fertil Steril. 2008;90:S88.
6. Maesawa Y, Yamada H, Deguchi M, et al. History of biochemical pregnancy was associated with the subsequent reproductive failure among women with recurrent spontaneous abortion. Gynecol Endocrinol. 2015;31(4):306-8.
7. Nastaran A, Maryam E, Behroz A, et al. Surrogacy as a good option for treatment of repeated implantation failure: a case series. Iran J Reprod Med. 2013;11(1):77-80.
8. Nazari L, Salehpour S, Hosseini MS, et al. The effects of autologous platelet-rich plasma in repeated implantation failure: a randomized controlled trial. Hum Fertil (Camb). 2020;23(3):209-13.
9. Okitsu O, Kiyokawa M, Oda T, et al. Intrauterine administration of autologous peripheral blood mononuclear cells increases clinical pregnancy rates in frozen/thawed embryo transfer cycles of patients with repeated implantation failure. J Reprod Immunol. 2011;92(1-2):82-7.
10. Scarpellini F, Sbracia M. Use of granulocyte colony-stimulating factor for the treatment of unexplained recurrent miscarriage: A randomized controlled trial. Hum Reprod 2009;24(11):2703-8.
11. Shaulov T, Sierra S, Sylvestre C. Recurrent implantation failure in IVF: A Canadian Fertility and Andrology Society Clinical Practice Guideline. Reprod Biomed Online. 2020;41(5):819-33.
12. Winger EE, Reed JL, Ashoush S, et al. Elevated preconception CD56+ 16+ and/or Th1:Th2 levels predict benefit from IVIG therapy in subfertile women undergoing IVF. Am J Reprod Immunol 2011;66(5):394-403.
13. Yanaihara A, Iwasaki S, Okai T. Causes and treatment of implantation failure. Taiwan J Obstet Gynecol. 2005;44(1):26-30.
14. Yoshioka S, Fujiwara H, Nakayama T, et al. Intrauterine administration of autologous peripheral blood mononuclear cells promotes implantation rates in patients with repeated failure of IVF-embryo transfer. Hum Reprod. 2006;21(12):3290-4.
15. Zamaniyan M, Peyvandi S, Heidaryan Gorji H, et al. Effect of platelet-rich plasma on pregnancy outcomes in infertile women with recurrent implantation failure: a randomized controlled trial. Gynecol Endocrinol. 2021;37(2):141-5.
16. Zhang X, Gao Y, Liu W, et al. Frozen blastocyst embryo transfer vs. frozen cleavagestage embryo transfer in couples with recurrent implantation failure: a cohort study. Hum Fertil (Camb). 2021;24(4):284-9.

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- Separate chapters address third-party reproduction such as egg donation, embryo donation, and surrogacy, along with emerging issues in ART
- Authored by experts, it serves as a valuable resource for gynecologists, reproductive specialists, and healthcare professionals involved in infertility management and ART

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