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Editorial

Health Problems and Financial Burdens in Mislabeling IVF Failures as RIF

As an embryologist dealing with infertility problems, every day I witness many infertile couples are referred by gynecologists and infertility specialists or sometimes based on their direct request for advice on the cause of their previous IVF failures and decision on the future treatment plan. The common feature of these couples is that in cases with two or more failures and even in cases with a single cycle failure, regardless of the quality of the transferred embryos and characteristics of endometrium, repeated implantation failure (RIF) is the common diagnosis for them. Therefore, specialists and frequently the couples themselves make a request to take advantage of advanced techniques or other add-on interventions so that their next cycle would be successful without repeating the failure. Therefore, unsuccessful IVF treatment is a main problem for infertile couples and healthcare providers; in fact, there are fewer surgical and medical interventions with a failure rate of more than 50% through application of advanced treatments. The reason for certain number of unsuccessful IVF treatments can be attributed to low efficiency of human reproduction and impaired fecundity in some cases, and the explanation for the rest is associated with lack of knowledge regarding this complex process, which has become more obvious during the last half century with extensive advances in science and technology (1). Now one of the main undiscovered issues for embryologists is determining the exact difference between IVF cycle failures and repeated implantation failure of embryos. Does replacing one term with another cause problems in the treatment procedures of infertile couples?

In studies on RIF, the first attempt should be determining whether the cause of RIF is related to embryo or endometrium. Moreover, establishing the number and conditions of failed cycles is of secondary importance. Despite enormous data and discussion on this subject, RIF remains a mystery in ART. As a phenomenon without an agreed definition, there are roughly 76 different definitions of RIF in literature reviews (2). Possible causes of RIF include unhealthy habits (such as smoking and obesity), poor gamete quality, thrombophilia, and uterine abnormalities (such as congenital uterine anomalies, polyps, fibroids, intrauterine pathology, and hydrosalpinx). However, many unknown causes require further research on RIF (3). The most important criterion in defining RIF is the number of embryos transferred in previous failed cycles. Initially, RIF was defined as failure of IVF cycles following transfer of at least 10 embryos. More recent definitions consider RIF as lack of conception after transfer of at least four top quality embryos. However, based on some definitions, the number of embryos and cycles may be adjusted by taking into account the embryo euploidy and women age. Today, most specialists declare RIF after at least four failed cycles with good quality embryos (2). The exact label of RIF is when there are three or four consecutive cycles of euploid embryo transfer with good preparation of a normal endometrium, though the occurrence of such condition is very rare (<5%). Even if we accept controversies and concur with multiple viewpoints and definitions of RIF, the next question is what additional and potentially ineffective treatments will be imposed on couples if the RIF is incorrectly applied instead of failed IVF cycles. Currently, there are various therapies and interventions for RIF which fall into the following five general categories (3):

1. Uterine interventions such as endometrial scratching, diagnostic and operative hysteroscopy, fertiloscopy and laparoscopy, endometrial biopsy for histological and microbiological evaluation and endometritis treatment, laser irradiation pretreatment of endometrium, and copper IUD insertion.
2. Embryological interventions and treatment add-ons including sequential embryo transfer (at the cleavage and blastocyst stage), co-culture of embryos with autologous cumulus cells, using intracytoplasmic morphologically selected sperm injection (IMSI), enrichment of embryo transfer medium with hyaluronic acid (Embryo Glue), extending embryo culture to the blastocyst stage, zygote intrafallopian transfer (ZIFT), assisted hatching (AH), preimplantation genetic testing for aneuploidy (PGT-A), and embryo selection using time-lapse microscopy (TLM).
3. Immune-modulating interventions including prescription of intravenous immunoglobulin (IVIG), intrauterine administration of peripheral blood mononuclear cells (PBMCs), intrauterine injection of pretreated menstrual blood stem cells, prescribing immunosuppressive drugs, administration of subcutaneous or intrauterine granulocyte colony stimulating factor (G-CSF), intrauterine injection of autologous platelet-rich plasma (PRP), intrauterine injection of human chorionic gonadotropin (hCG), administration of low molecular weight heparin (LMWH), aspirin, prednisolone, and intravenous intralipid.

4. Enhancing endometrial receptivity using human growth hormone (GH), vaginal sildenafil, or technologies aimed at identifying the window of implantation (WOI) such as the endometrial receptivity array (ERA).
5. A group of partially approved therapeutic interventions of alternative medicine, including traditional Chinese medicine (TCM) and acupuncture.

As it can be seen, a wide range of expensive interventions for the success of IVF and ongoing pregnancy are prescribed by healthcare providers for RIF patients, and therefore, misdiagnosing a couple with RIF inflicts a heavy financial burden on the individuals, wastes their golden time to receive proper treatment, and even in some cases, irreparable physical injury would be the final outcome. On the other hand, even if couples are properly selected and each of these interventions is prescribed accurately, many of them have questionable efficacy or the studies provide weak supporting evidences for their use which ultimately implies uncertainty in their application (4).

Unfortunately, these interventions are now in common use around the world. Their popularity is not limited to one country, one region or a few selected clinics. For example, IVF clinics in the UK prescribed one or more of these add-ons to 74% of their patients in 2018. Like IVIG, it is an expensive treatment, costing between 2,000-14,000$ per IVF cycle, and the UK Department of Health and Social Care does not recommend IVIG for the treatment of RIF (4). PGT-A can cost anywhere from 4,000-10,000$ depending on the fertility clinic and the number of tested embryos; PGT-A has been red rated by Human Fertilisation and Embryology Authority (HFEA) due to poor evidence from RCTs to show its effectiveness in improving the chances of pregnancy in RIF. However, limited studies have reported that PGT-A can significantly increase live birth rates when applied at blastocyst-stage embryos of women older than 35 years (5).

Successful pregnancy, in addition to a top quality blastocyst, requires a receptive endometrium. According to available data, suboptimal endometrial receptivity is the main cause of 2/3 of implantation failures. A report on the relationship between age and implantation rate has shown that with increasing female age, the degree of asynchrony between the embryo and the endometrium increases. Based on these findings, 50% of embryo transfers in women under 35 years were asynchronous, while this rate is 68.1% in women over 35 years (2). In a large retrospective study on 4429 patients who achieved three consecutive euploid single embryo transfers, the results demonstrated that the true prevalence of RIF is <5%. In patients who performed three euploid single blastocyst transfers, clinical pregnancy was achieved in 95.2% of cases. Such results in women with normal uterus cast doubt on the etiology of RIF due to endometrial disorders. It again emphasizes the need for comprehensive clinical trials on the causes and etiology of RIF and also RCTs for each of these already routinely used IVF add-ons (6). Therefore, before labeling couples with RIF, a careful investigation should be carried out to find the reasons for the failure of previous cycles, and the selection of any add-ons for increasing success rate in future cycles should be based on obtained evidence of previous cycles. In addition, consultation of the treatment team, including gynecologists, andrologists, embryologists, and other specialists is necessary for selection of the best treatment plan for every RIF patient.

References

1. Lubinsky M. Evolutionary justifications for human reproductive limitations. J Assist Reprod Genet. 2018;35(12):2133-9.
2. Pirtea P, de Ziegler D, Ayoubi JM. Recurrent implantation failure-is it the egg or the chicken? Life (Basel). 2021;12 (1):39.
3. Busnelli A, Somigliana E, Cirillo F, Baggiani A, Levi-Setti PE. Efficacy of therapies and interventions for repeated embryo implantation failure: a systematic review and meta-analysis. Sci Rep. 2021;11(1):1747.
4. Lensen S, Shreeve N, Barnhart KT, Gibreel A, Ng EH, Moffett A. In vitro fertilization add-ons for the endometrium: it doesn't add-up. Fertil Steril. 2019;112(6):987-93.
5. Simopoulou M, Sfakianoudis K, Maziotis E, Tsioulou P, Grigoriadis S, Rapani A, et al. PGT-A: who and when? a systematic review and network meta-analysis of RCTs. J Assist Reprod Genet. 2021;38(8):1939-57.
6. Pirtea P, De Ziegler D, Tao X, Sun L, Zhan Y, Ayoubi JM, et al. Rate of true recurrent implantation failure is low: Results of three successive frozen euploid single embryo transfers. Fertil Steril. 2021;115(1):45-53.

Mohammad Reza Sadeghi
Editor-in-chief