Present and Prospective Diagnostic and Therapeutic Options for Repeated IVF Failures

Recent evidence shows that through best standard operating procedures, chances of successful pregnancy and live birth delivery rates are less than 50%. Repeated Implantation Failure (RIF) following transfer of one or more numbers of cleavage or blastocyst stage embryos is the main cause of low pregnancy rate in IVF cycles; therefore, finding the causes and modifying treatment protocols to increase IVF success rates are currently hot topics for research. RIF is defined as a failed pregnancy following transfer of ten or more high quality embryos through at least three cycles of fresh embryo transfer (1).

A successful pregnancy following embryo transfer depends on the three sides of implantation triangle: a receptive endometrium, a good quality embryo at the blastocyst stage and synchronization between endometrium and embryo through appropriate molecular dialogues. Uterine and ovarian disorders such as endometriosis, endometrial polyps, adhesions, uterine septa, submucosal and intramural fibroids, endometritis, adenomyosis, hydrosalpinx, leiomyoma and polycystic ovarian syndrome (PCOS) are associated with repeated implantation failure. Different studies have shown that resection of submucosal fibroids and intrauterine septum, hysterescopic polypectomy, salpingectomy, endometriosis surgery and myomectomy improve implantation and clinical pregnancy rates through molecular changes in endometrial steroid receptors, and changes in gene expression such as integrins, LIF, EMX2, HOXA-10 and IGFBP-1. (2).Therefore, gynecological surgery to provide a receptive endometrium is suggested as the first line of intervention in RIF due to the aforesaid uterine anomalies. Regarding the physiological role of endometrium in reproduction, due attention needs to be given to discovery of novel biomarkers for establishing the implantation window and monitoring endometrial thickness and receptivity. The aforesaid measures will change the outcome of ART cycles, especially RIF cycles.

Another side of the implantation triangle and the most determinant factor in the failure of IVF cycles is embryo quality. According to cytogenetic studies, more than 60% of *in vitro* derived embryos have at least one aneuploid blastomere at cleavage stage, even though chromosomal anomalies can be found in embryos with normal morphology. Mosaicism and aneuploidy of embryo interfere with its subsequent development, implantation and ongoing pregnancy. Therefore, selection of embryos with higher rates of implantation and development is an effective option to reduce RIF. In most IVF clinics, selection of embryo is based on a prolonged culture and blastocyst transfer, but blastocyst transfer is not always possible due to poor culture or the low number of cleavage embryos (3). In addition, recent development in *"omics"* technology, such as proteomics and metabolomics, analysis of conditioned culture medium or genomics and transcriptional analysis of embryo biopsies have provided more accurate selection of the best embryos and they will be available as routine tests in IVF clinics in the near future.

The third side of this triangle is the correct timing of embryo transfer for appropriate molecular dialogue between embryo and endometrium. Despite excellent status of one side of implantation triangle, the defect of one side will lead to three-side insufficiency followed by repeated implantation failure. A variable that can affect all the three sides of implantation triangle is ovarian stimulation protocols. Recent data have shown that long protocol stimulation with high doses of gonadotropins produce large numbers of oocytes and embryos with frequent chromosomal defects, poor quality of endometrium and low implantation and pregnancy rates of the derived embryos. However, although mild stimulation regimens provide limited numbers of oocytes and embryos with lower rates of aneuploidy but higher implantation and pregnancy rates are expected (4).

In conclusion, decision on treatment plan for couples with repeated implantation failure should be based on the simultaneous optimization and correction of all the three sides of implantation triangle. Neglect to optimize and correct one side of the triangle will lead to repeated IVF cycle failures.

References

1. 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.

2. Cakmak H, Taylor HS. Implantation failure: molecular mechanisms and clinical treatment. Hum Reprod Update. 2011;17(2):242-53.
3. Assou S, Boumela I, Haouzi D, Anahory T, Dechaud H, De Vos J, et al. Dynamic changes in gene expression during human early embryo development: from fundamental aspects to clinical applications. Hum Reprod Update. 2011; 17(2):272-90.
4. Santos MA, Kuijk EW, Macklon NS. The impact of ovarian stimulation for IVF on the developing embryo. Reproduction. 2010;139(1):23-34.

Mohammad Reza Sadeghi
Editor-in-chief