Recurrent Implantation Failures

Abstract
Repeated implantation failure is a major cause of infertility. Many new modalities are now available which can be used in selected cases.

Keywords: Endometrial receptivity array, Endometrial thickness, Intracytoplasmic sperm injection, Repeated implantation failure.


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Introduction
Pregnancy rate (PR) following one cycle of in vitro fertilization (IVF) and endometrial thickness (ET) can be as high as 60%. But even in the very successful units, some couples fail repeatedly. Repeated implantation failure (RIF) is an unaddressed major cause of infertility in otherwise healthy women and one that has remained poorly characterized.1,2 Although various definitions of RIF exist,3 the clinical community agrees that after the failure of three IVF cycles in which one or two morphologically high-grade embryos are transferred, special protocols must be enforced. The causes for RIF may be because of reduced endometrial receptivity, embryonic defects, or multifactorial causes. After three failures, a try of blastocyst transfer is highly recommended.

Case History
The case, a 33-year-old female, married for 8 years presented to the fertility clinic with inability to conceive. She and her husband were on treatment for last 5 years.

Obstetric History
She was P0A1, it was an IVF pregnancy in 2011, but she had missed abortion.

Menstrual History
Her menstrual cycles were regular at an interval of 28 days with average flow.

Past Medical History
She was a known case of hypothyroidism but had poor compliance with medications.

Chronological Treatment History
The patient after giving a thorough history and going through initial workup was posted for hysteroscopy in 2011, which revealed no abnormality. In April 2011, she was given controlled ovarian stimulation with agonist protocol using recombinant follicle-stimulating hormone. On the day of pickup, 10 M2 oocytes were retrieved. An IVF was done with husband’s sperms retrieved through testicular sperm aspiration. Four embryos (four-celled grades I–II) were transferred on day 3 but the patient did not conceive.

In July 2011, she was initiated with antagonist protocol for ovarian stimulation; after pickup, 17 M2 oocytes were retrieved and embryo transfer was done for her, but no pregnancy resulted.

In September 2011, again she was given ovarian stimulation with antagonist protocol. Donor sperms were used for IVF; three embryos were transferred: One was her own (two-celled grade I), and another was four-celled grade I which was transferred but it did not result in pregnancy.

In November 2011, long protocol of ovarian stimulation and donor IVF were done and it resulted in pregnancy but underwent missed abortion.

In November 2012, for the fifth time she was tried with embryo donation in which 2 4-celled grade I embryos were transferred but even this did not result in pregnancy.

For the sixth time she was counseled for endometrial receptivity array (ERA) which was receptive and planned...
for embryo donation. She received progynova 2 mg TDS followed by Inj Gestone 100 mg for 3 days and Tab Sildenafil 2.5 mg thrice a day for 5 days. After confirming optimal endometrial preparation, embryo transfer was done and two blastocysts of grade IVAA were transferred. Estrogen and progesterone supplements were continued as luteal support. In this cycle, Tab Wysolone was given. Fifteen days postembryo transfer, beta human chorionic gonadotropin levels were 342 µIU/mL and 30 days post-embryo transfer ultrasound scan revealed presence of gestational sac with fetal pole.

Antenatal course, patient continued with the pregnancy and delivered a male child of 1.3 kg (preterm) by cesarean section done around 30 weeks in view of premature rupture of membrane. The baby was shifted to the neonatal intensive care unit in view of preterm and respiratory distress.

**LAB INVESTIGATIONS**

**Wife**
- Luteinizing hormone 1.1
- Thyroid-stimulating hormone 3.72
- Prolactin 17.79.

**Husband**
- Husband semen analysis
- Azoospermia
- Fine needle aspiration cytology revealed few Sertoli cells
- Degenerated spermatogenic cells with mature sperms.

**DISCUSSION**

Failure to achieve a pregnancy following 2 to 6 IVF cycles, in which more than 10 high-grade embryos were transferred to the uterus, was defined by various clinicians as RIF. Today with the tendency of transferring only one or two embryos, the definition of RIF is not apparent. Nevertheless, we suggest that after failure of three cycles in which reasonably good embryos were transferred, further investigation should be initiated. Embryonic loss, which occurs repeatedly after assisted reproduction, may be attributed to many factors. These can be grouped into three categories: Decreased endometrial receptivity, embryonic defects, and factors with combined effect.

**Assumed Causes of RIF**
- Decreased endometrial receptivity
- Uterine cavity abnormalities
- Thin endometrium
- Altered expression of adhesive molecules
- Immunological factors
- Thrombophilies
- Defective embryonic development
- Genetic abnormalities (male/female/gametes/embryos)
- Zona hardening
- Suboptimal culture conditions
- Multifactorial effectors endometriosis
- Hydrosalpinges.

**Suggested Methods for the Treatment of RIF**
- Improving endometrial receptivity
- Hysteroscopic correction of cavity pathology
- Myomectomy
- Treatment of thin endometrium
- Endometrial stimulation (biopsy)
- Immunotherapy (intravenous immunoglobulin, steroids, aspirin and heparin)
- Treatment of the embryos
- Preimplantation genetic screening
- Assisted hatching (AH) zygote
- Intrafallopian transfer co-culture
- Blastocyst transfer cytoplasmic transfer
- Improving ET technique.

**Suggested Methods for Improving RIF**

**Antagonist Protocol**

**Immunotherapy**
Combined treatment of glucocorticosteroids and aspirin has been reported to improve PR in autoantibody seropositive patients who have RIF.

**Assisted Hatching**
Failure of the embryonic zona pellucida to rupture following blastocyst expansion has been suggested as a possible cause for RIF. To help the release of the embryos from their zona, different types of AH have been developed. These involve the creations of an opening in the zona pellucida either mechanically (partial zona dissection) or chemically (zona drilling with acid tyrode) or by laser “damage” of the zona pellucida, before ET.

**Blastocyst Transfer**
Transfer of embryos at the blastocyst stage is a more physiological approach. Improved embryo selection and uterine receptivity may explain the benefit of embryo transfer at the blastocyst stage for couples with RIF.
Use of Heparin

Although several studies have identified possible causative factors for implantation failure following ART, only few of them have indicated effective therapeutic solutions. A recent review by Nelson and Greer7 (Human Reproduction Update, 2008) suggested that heparin has the potential to improve ART outcomes as it is a structural analog of sulfates, which play an important role in conception and early pregnancy events. Heparin administration in ART could enhance the success rate by:
- Changing the hemostatic response to controlled ovarian stimulation and altering thrombosis risk and
- Modulating the fundamental physiological processes needed for blastocyst apposition.

Prednisolone in RIF

Some studies say use of prednisolone does not have any effect on implantation rates. But, a meta-analysis was conducted that did show some benefit in cases of unexplained recurrent implantation failure. Meta-analysis revealed a nonsignificant effect of prednisolone on pregnancy outcome during ICSI cycles [PR: relative risk (RR) 1.02, 95% confidence interval (CI) 0.84–1.24; clinical PR: RR 1.01, 95% CI 0.82–1.24; implantation rate: RR 1.04, 95% CI 0.85–1.28]. Prednisolone administration may improve pregnancy outcomes in women with idiopathic RM; its efficacy in women undergoing ICSI is not significant.8

Role of Sildenafil

Sildenafil citrate is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type V that prevents the breakdown of cGMP and potentiates the effect of nitric oxide on vascular smooth muscles. Sildenafil citrate could lead to an improvement in uterine blood flow and, in conjunction with estrogen, lead to the estrogen-induced proliferation of the endometrial lining. Sildenafil citrate may increase ET and affect the outcome of frozen–thawed embryo transfer cycles.9

Importance of ERA

The ERA consists of a customized array containing 238 genes expressed at the different stages of the endometrial cycle and is coupled to a computational predictor, i.e., able to identify the receptivity status of an endometrial sample and diagnose the personalized window of implantation of a given patient regardless of the sample’s histologic appearance.10 The accuracy of the ERA test is superior to endometrial histology, and results were reproducible;10 the accuracy of the diagnostic tool ERA has been demonstrated to be superior to endometrial histology and results are completely reproducible 29 to 40 months later. Compelling evidence indicates the existence of an endometrial receptivity alteration in patients with RIF.

Criteria

- ≥3 implantation failures in previous IVF/ICSI cycles with transfer of at least two good-quality embryos in each cycle
- Inclusion
- ET ≥ 6 mm
- Trilaminar pattern after proper progesterone priming.

CONCLUSION

There are many known and unknown reasons for RIF, and we do not have the tools to diagnose in each case the exact cause for the repeated failure. However, we think that after failure of three transfers of good-quality embryos in a unit with a PR of at least 30%, one should take some special measures. There are no hard data from randomized controlled trials that any of the treatments has a significant value, but on the contrary, everyone agrees that taking a different approach achieves a pregnancy in many cases that failed repeatedly. After three failures, repeated hysteroscopy and a try of blastocyst transfer are highly recommended.1 A change in the stimulation protocol has a place. AH, pre implantation genetic screening, and coculture are probably beneficial in experienced hands. Long-term use of danazol or GnRH agonists probably has a place in repeated failures with endometriosis. Steroids might have a place in patients with any sign of autoimmunity, and zygote intrafallopian transfer has a place in cases of difficult embryo transfers.

REFERENCES