CASE REPORT

Successful fertility outcome in a couple with recurrent implantation failure and testicular cancer survivor: A case report

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Abstract

A couple of Indo-American descent, presented to our clinic with a history of primary infertility and repeated IVF implantation failure. Male was a testicular cancer survivor who had erectile dysfunction and azoospermia. Female partner had polycystic ovarian syndrome (PCOD). She had three unsuccessful attempts of embryo transfer at another fertility clinic. At our clinic, she underwent controlled ovarian stimulation, COH started from day two period with rFSH (follicle stimulating hormone) followed by HMG (human menopausal gondadotropin) with antagonist protocol followed by preimplantation genetic screening of embryos. Subsequently, she began HRT (hormone replacement Therapy) protocol for ERA cycle from day 2, where she also underwent hysteroscopy on day 7. After five days of progesterone supplementation, she underwent endometrial biopsy for ERA (endometrial receptivity assay). Frozen embryo transfer cycle was started with the same HRT protocol used in her previous ERA cycle. Post embryo transfer, immunotherapy with steroids and fortnightly intralipids was given. Pregnancy test was positive with a BHCG value of 290 mIU/mL. and she delivered naturally after 39 completed weeks of gestation. A stepwise personalized treatment approach maximizes the chances of a successful outcome in presence of both male and female factors. Frozen or fresh sperms for ICSI with PGS along with hysteroscopy, ERA and under cover of immune modulation yielded positive results. *(Afr J Reprod Health 2021; 25[3]: 130-134).*

Keywords: Recurrent implantation failure, Preimplantation genetic screening (PGS), Endometrial receptive assay (ERA), Hysteroscopy, TESA

Résumé

Un couple d'origine indo-américaine, présenté à notre clinique avec des antécédents d'infertilité primaire et des échecs répétés d'implantation de FIV. L'homme était un survivant du cancer des testicules qui souffrait de dysfonction érectile et d'azoospermie. La partenaire féminine avait un syndrome des ovaires polykystiques (SOPK). Elle a eu trois tentatives infructueuses de transfert d'embryons dans une autre clinique de fertilité. Dans notre clinique, elle a subi une stimulation ovarienne contrôlée, la COH a commencé à partir du deuxième jour avec la rFSH (hormone folliculostimulante) suivie de l'HMG (gondadotrophine ménopausique humaine) avec protocole antagoniste suivi d'un dépistage génétique préimplantatoire des embryons. Par la suite, elle a commencé le protocole HRT (hormonothérapie substitutive) pour le cycle ERA à partir du jour 2, où elle a également subi une hystéroscopie le jour 7. Après cinq jours de supplémentation en progestérone, elle a subi une biopsie de l'endomètre pour ERA (test de réceptivité de l'endomètre). Le cycle de transfert d'embryons congelés a commencé avec le même protocole HRT utilisé dans son précédent cycle ERA. Après le transfert d'embryon, une immunothérapie avec des stéroïdes et des intralipides bimensuels a été administrée. Le test de grossesse était positif avec une valeur de BHCG de 290 mUI/mL. et elle a accouché naturellement après 39 semaines complètes de gestation. Une approche de traitement personnalisé par étapes maximise les chances de succès en présence de facteurs masculins et féminins. Les spermatozoïdes congelés ou frais pour ICSI avec PGS avec hystéroscopie, ERA et sous couvert de modulation immunitaire ont donné des résultats positifs. *(Afr J Reprod Health 2021; 25[3]: 130-134).*

Mots-clés: Échec d'implantation récurrent, Dépistage génétique préimplantatoire (PGS), Test de réception endométriale (ERA), Hystéroscopie, TESA

Introduction

As per Simon and Laufer, RIF is an implantation failure when three consecutive transfers were done with at least 1-2 high-grade embryos[1]. Implantation failure is a commonly encountered phenomenon primarily due to embryo quality, embryo genetics, lesions inside the uterine cavity and also the unseen immune dysfunction[2]. Male factors also contribute to the embryo quality. Poor quality sperms, reduced sperm count and altered morphology can affect the fertilization rates and the embryo quality. One such

cause of poor sperm quality is testicular cancer. Testicular cancer, TC is the most common cancer in young men, the global burden had shown a 1.8 fold increase between 1990 and 2016[3]. Testicular cancer patients have reported impaired semen quality resulting in hypospermia, oligozoospermia, asthenozoospermia[4]. Treatment procedures like chemotherapy and radiation therapy have further affected spermatogenesis, leading to decreased sperm concentration, count, motility and altered morphology[5]. In a systematic review done by Nazareth I *et al*. reported a significantly lowered erectile and ejaculatory dysfunction after the cancer treatment[6]. Sperm banking or cryopreservation of sperm has become a viable option for men with testicular cancer. Intracytoplasmic sperm injection (ICSI) of cryopreserved semen has proved to be highly effective in cases of severe oligoasthenoteratozoospermia[7]. Ping *et al*. have reported a successful pregnancy outcome in testicular cancer patients by cryopreserving their sperm samples at human sperm banks[8].

Despite recent advancements, the management of couples presenting with RIF following testicular cancer in male partner poses a significant challenge... But, meticulous evaluation and personalised treatment can result in successful outcomes. So, here we present a case report of successful pregnancy outcome achieved in a couple with RIF by ICSI using TESA method from a man with prior treated testicular cancer.

Case report

A 29 year old Indo- American origin female and 31 year male of American origin couple presented to our clinic in March 2019. The couple were married for four years and had presented with history of primary infertility and three cycles of intracytoplasmic sperm injection- preimplantation genetic screening (ICSI-PGS) implantation failure. In 2004, at age 18, the male partner was diagnosed with stage 3 non-seminomatous germ cell tumor with teratoma of the upper pole of left testis with left side retroperitoneal metastasis. Four cycles of systemic chemotherapy: platinum, etoposide phosphate, and bleomycin sulfate (PEB) regime were administered, which resulted in a decline of the tumour markers. One month post-chemotherapy, primary tumor and the metastatic sites had increased in size. He underwent retroperitoneal lymph node mass dissection, left radical orchiectomy and left supraclavicular nodes removal. He was declared cured of testicular cancer at his final follow-up in 2011. The treatment resulted in erectile dysfunction with the inability to have intercourse or ejaculation. The patient nor the family was counselled about future reproductive planning or given options for sperm freezing before cancer therapy.

Female partner was diagnosed with the polycystic ovarian syndrome (PCOD). Because of PCO and male factor, they opted for Assisted Reproductive technology- Intra cytoplasmic sperm injection (ART-ICSI). The couple underwent three cycles of IVF in India without success. During the 3rd cycle of IVF, third party reproduction in the form of donor eggs and sperms were used to understand repeated implantation failure. Donor eggs were fertilized with husband's sperm, and donor sperms were injected in wife's eggs as an option to analyse implantation failure, but the results were inconclusive.

On initial evaluation at our fertility centre, thorough counselling was done. Detailed fertility plan with stepwise, personalized treatment in the form of ICSI and pre-implantation genetic screening (PGS) followed by endometrial receptive assay (ERA), hysteroscopy and immunomodulation during frozen cycle replacement was advised.

In June 2019, male partner underwent testicular mapping with the andrologist. He was treated with oral clomiphene citrate 25 mg for one month along with antioxidants and lifestyle modifications. An adequate semen sample was obtained by testicular sperm extraction (TESA) and was cryopreserved.

In the same month, the female partner underwent controlled ovarian stimulation after downregulating with birth control pills. Controlled ovarian hyperstimulation (COH) started from day two period with rFSH followed by HMG with antagonist protocol. We could retrieve 13 oocytes and ICSI was done with frozen sperms resulted in fertilization of 10 eggs. Six blastocysts were formed and underwent biopsy for PGS followed by freezing of embryos. PGS results showed two euploid normal blastocysts.

2004	• Male 18 years non seminomatous germ cell tumour - teratoma of testis - subjected to chemotherapy and surgery.
2011	• Complete remission and cure
2016	• Marriage
2016-2018	• 3 cycles of IVF
March 2019	• First consultation at the research site
May to june 2019	• Clomiphene citrate for male partner
June 2019	• Testicular sperm retrival and sperms frozen
June 2019	• Controlled ovarian stimualtion and ICSI with husband sperm + PGS • Embryos at 2 euploid blastocyst stage frozen
July 2019	• Mock HRT cycle for ERA testing + hysterscopy + immune testing
August 2019	• Frozen embryo transfer + immune therapy
May 2020	• Healthy male baby of 3.7kg delivered.

Figure 1: Timeline of key intervention points

In July 2019, female partner started with HRT protocol from cycle day 2. Office hysteroscopy was done, which revealed multiple small cervical polyps in the cervical canal. Cauterization was done, and the histopathology report showed benign glandular cervical polyp. Progesterone was started with the appearance of triple line at 9mm. After five days of progesterone supplementation, endometrial biopsy

was done for ERA (endometrial receptive assay) to personalize the embryo transfer. In the same cycle, she was treated with probiotics. The blood sample was tested for NK cells activity and was positive for CD19, CD19+cells, and CD5+. These are cytotoxic cells that in high concentration can cause immune rejection of pregnancy and can cause implantation failure. The patient was treated with steroids and intralipid infusion.

In August 2019, a frozen embryo transfer cycle was started with the same HRT protocol used in her previous ERA cycle. Personalized embryo transfer was done with Elective single embryo transfer(eSET), elective single blastocyst transfer (Grade AA) under ultrasound guidance. She was advised progesterone vaginal pessaries, progesterone injections and low molecular weight heparin injections daily. Post embryo transfer, she underwent immunotherapy with steroids and fortnightly intralipids.

The pregnancy test was positive after 12 days of transfer with a Beta-hCG value of 290 mIU/mL. She had an uneventful pregnancy, and at 39 completed weeks of gestation, she delivered a healthy male baby. The couple has one surplus euploid embryo and adequate sperms frozen for future use. (Figure 1).

Discussion

This report documents the successful pregnancy outcome in recurrent implantation failure case using a frozen-thawed self-semen sample in a testicular cancer survivor patient. This was an unusual case of recurrent implantation failure despite transferring the chromosomally healthy embryo. Husband had side effects of extensive surgery and chemotherapy, resulting in erectile dysfunction. In this case, TESA was done to aspirate the sperm from the male who had history of testicular cancer managed by chemotherapy and surgery. The self-semen of the patient was used in ICSI. This novel approach of TESA followed by ICSI resulted in successful fertility outcome.

The presence of profuse cervical polyps could have hindered implantation either by creating a low-grade inflammatory response or by inhibiting embryo transfer procedure by an excessive mucous discharge which could have entangled the embryo in the catheter. AI-Turki Haifia reported hysteroscopy as a valuable, gold-standard technique in the management of infertility[9]. Pabuccu *et al*., have published a significantly higher pregnancy rate (39.4%) in patients who were treated by a hysteroscopy for a detected uterine abnormality[10]. El-Toukhy *et al*. in their meta-analysis highlighted a significant improvement in the outcome of pregnancy rates and live births among hysteroscopy patients compared to controls (RR=1.63, 95% CI 1.35–1.98, p<0.001)[11].

ERA biopsy in the same cycle as hysteroscopy might have activated the endometrial growth and maturation. Mahajan *et al*. demonstrated that ERA as an important, accurate test to diagnose endometrial receptivity and reported a pregnancy rate of 66.7% in ERA treated patients. It helps in personalizing the embryo transfer and also aids in growth and activation of the endometrial lining before definitive transfer[12].

In the current report, the administration of probiotics might have helped in maximizing the chance of implantation. Ideally, the general probiotic health status should be maintained in cases of RIF. Moreno *et al*. reported l*actobacillus*-dominated microbiota in a receptive endometrium had a significant increase in implantation [60.7%], and pregnancy rate [70.6%]. Addition of probiotics is a novel microbiological dimension to the IVF reproductive process[13].

Immune modulation in the form of steroids and intralipid might have helped to salvage implantation and pregnancy in the current case. It should be explicitly offered to women with a history of multiple cycles of implantation failure. Pregnancy is unique as maternal tolerance towards growing fetus is immunomodulated by specific immune cells called TREG cells[14]. Every case of implantation failure has to be analysed discretely, and a fertility treatment plan should be discussed with the couple making them aware of success as well as its limitations. Pregnancy loss or implantation failure is a significant loss for the family in terms of emotions, stress and financial burden. The critical limiting factor is the financial burden of the treatment, which many couples are not able to comply. Clinicians need to be prudent to personalize the IVF treatment with detailed couple counselling.

Conclusion

Based on this case report, we conclude that TESA with ICSI can act as an effective management modality in patients with previous testicular cancer or testicular chemotherapy or surgery. Finally, in the presence of both male and female elements, frozen or fresh sperms for ICSI with PGS along with hysteroscopy, ERA and under cover of immune modulation yields positive results in a majority of women with RIF. In cases of gonadotoxic treatment, patients and family should be counselled and educated and offered gamete cryopreservation for future fertility use.

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Conflict of interest

The authors declare no conflicts of interest.

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