10.5005/jp-journals-10016-1030
CASE REPORT

Fertility Preservation: A Case Series

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ABSTRACT

Improvement in survival rates of cancer patients has lead to a shift in focus toward fertility issues, especially in young survivors. Male fertility preservation is well established. Embryo cryopreservation remains most successful female fertility preservation option. Other female fertility preservation procedures like oocyte/ovarian tissue cryopreservation either have limited efficacy or in experimental stages. We have highlighted not uncommon clinical scenarios where the fertility preservation option was exercised. There is an urgent need to spread awareness among clinicians and patients regarding the various available fertility preservation measures. Timely referral will help in improving the quality of life of cancer survivors.

Keywords: Fertility, Cryopreservation, Semen, Embryo.

INTRODUCTION

Advances in medical oncology have resulted in an improvement in the 5-year survival rates for cancer patients. In addition, the long-term survival rates for childhood cancers have also improved.[1] With improvement in survival rates there is a greater than before focus on the quality of life. Fertility issues have gained importance especially for the young male and female cancer survivors.

Both chemotherapy and radiotherapy can affect fertility due to their detrimental effect on gonadal function. Extent of gonadal damage though depends mainly upon the ionizing radiation dose, chemotherapeutics agent used and patients age.[2,3] Recent advances in fertility preservation options have opened up a variety of choices. Unfortunately most cancer patients are not aware of the opportunities available as most often fertility issues are not discussed with the patient, the spotlight being on the primary disease. Other reasons for nonusage are a lack of awareness on the part of the treating physician, monetary constraints, uncertainty over the success of such procedures and an urgency to get treatment underway.

Male fertility preservation is relatively easier to handle for the treating oncologists/reproductive medicine specialists. Semen cryopreservation is a well-established procedure and is being offered in most fertility clinics.[4] Fertility preservation in the prepubertal male is a more complex matter.

Date of Received: 16-09-11
Date of Acceptance: 19-09-11
Date of Publication: September 2011

Female fertility preservation is complicated with few clinically established choices. Most options are still novel, unfamiliar and at an experimental stage.[5]

We have been offering semen cryostorage for men since the last 15 years. We have also recently started offering female fertility preservation options like embryo and oocyte cryopreservation, GnRH suppression and oophoropexy. In this series, we report four cases highlighting the clinical scenarios in which fertility preservation procedures were offered.

CASE REPORTS

Case 1

A 28-year-old male, diagnosed to have acute myeloid leukemia was referred to our unit for semen cryopreservation prior to starting treatment. He was scheduled to undergo bone marrow transplant as part of the treatment and was accompanied by his spouse aged 21 years. His semen analysis was reported as very severe oligoasthenoteratozoospermia and after appropriate counseling, two semen samples were frozen.

The couple returned 4 months later keen on fertility treatment and a repeat semen analysis now showed azoospermia. A decision to use the frozen semen sample was taken with the intention of carrying out an IVF/ICSI cycle. Routine pre-IVF screening included blood tests such as a viral screen and rubella antibody titer as well as a transvaginal ultrasound. An antagonist protocol was planned and controlled ovarian hyperstimulation was carried out using recombinant gonadotrophins. Of the 13 oocytes that were retrieved and injected (ICSI) with the sperms from the cryopreserved semen sample, eight fertilized. On day 3, 2 grade 1 embryo's were transferred, while the remaining

supernumerary were cultured till day 6 and two good quality blastocysts were vitrified and cryopreserved.

Unfortunately this cycle was not successful and the couple was counseled regarding frozen embryo transfer, which was carried out 2 months later. The endometrium was prepared using estradiol valerate and progesterone. Both the vitrifed blastocysts survived warming and were transferred. A serum beta hCG done 12 days later was found to be positive (412 μ/ml). An ultrasound scan 2 weeks later showed a single live intrauterine fetus with good cardiac activity. Hormonal support was continued till 12 weeks of gestation. She had an uneventful antenatal period and underwent a cesarean section at term, delivering a healthy baby girl weighing 3 kg.

Case 2

A 29-year-old woman, married for a year, was seen in the gynecology outpatient and was diagnosed by ultrasound to have a right solid ovarian mass, 6 to 7 cm in size. The left ovary and uterus appeared normal with no free fluid in the peritoneal cavity. As surgery was planned, detailed counseling regarding all the treatment options including radical surgery and fertility preservation were discussed. At laparotomy right salpingo-oophorectomy was done and an intraoperative frozen section revealed an atypical round cell infiltrate of probable hematopoetic/lymphoid origin. The left ovary, tube and uterus were conserved. Histopathology revealed a diagnosis of a diffuse large B cell lymphoma for which adjuvant chemotherapy was planned. Prior to chemotherapy the patient was referred to the reproductive medicine unit for exploring fertility preservation options. Her husband's semen analysis was normal. In the available limited time period, the patient was offered embryo cryopreservation and subsequent GnRH analog therapy for ovarian protection during chemotherapy.

She underwent an IVF cycle using the antagonist protocol. At transvaginal oocyte retrieval a total of eight oocytes were retrieved from the left ovary of which seven were in metaphase II stage. Intracytoplasmic sperm injection was performed. On day 3, six good quality embryos obtained. At this point, the options were to freeze all the 6 cleavage stage embryos or to allow them to be cultured till day 5, since we have a very successful blastocyst vitrification program. Acknowledging the possibility of losing embryos by waiting till day 5, we decided to vitrify three of the good quality embryos on day 3, allowing the remaining embryos to proceed to the blastocyst stage. Two additional blastocysts were available for vitrification on day 6. A total of five embryos were cryopreserved. The patient was then put on long acting depot GnRH analog prior to chemotherapy in order to protect the ovaries from the gonadotoxicity of the chemotherapeutic agents. The patient is being followed up in the hematology department and is currently disease-free.

Case 3

A 35-year-old unmarried woman, diagnosed to have a right sided breast carcinoma was referred to our unit prior to neoadjuvant chemotherapy for fertility preservation. The option of oocyte cryopreservation was proposed. Detailed counseling regarding the experimental nature of the procedure and the risks due to delay in chemotherapy and exposure to a hyperestrogenic environment was done. Since she was keen on oocyte cryopreservation, controlled ovarian hyperstimulation (COH) with an antagonist protocol was started from the second day of the period. In a bid to reduce serum estrogen levels an aromatase inhibitor (Tab letrozole 2.5 mg) was also started along with the COH. A total of 22 oocytes were retrieved (16 metaphase II and 6 metaphase I). The mature oocytes were vitrified while the 6 metaphase I oocytes were cultured *in vitro* to metaphase II and then vitrified. A total of 22 oocytes were frozen. The patient was then put on long acting GnRH analogs prior to chemotherapy. Presently the patient has completed chemotherapy and is scheduled to undergo surgery.

Case 4

A 27-year-old woman married for 7 years was seen in reproductive medicine unit. She had been diagnosed with Hodgkin's lymphoma 3 years ago and had received chemotherapy as a part of the treatment. Subsequently, she developed idiopathic thrombocytopenic purpura (ITP) for which she underwent a therapeutic splenectomy. She was seen in our outpatient along with her husband. A transvaginal ultrasound was normal as was her husband's semen analysis. However, her day 2 FSH was 9.22 μ/ml, suggesting a compromised ovarian reserve. In view of the risk of premature ovarian failure (POF) due to prior chemotherapy, early treatment was recommended. As the tubes were found to be patent on evaluation by hysterosalpingogram, one cycle of controlled ovarian stimulation and intrauterine insemination was unsuccessfully carried out. The patient was advised IVF as the next treatment option.

Controlled ovarian hyperstimulation using the short protocol was planned and at oocyte retrieval 11 mature oocytes were obtained. Nine fertilized (by ICSI) and on day 3, good quality cleavage stage embryos were transferred underultrasound guidance. Serum beta hCG done 12 days later was positive (868 μ/ml). However, a transvaginal ultrasound 2 weeks later showed an irregular sac without a fetal pole suggestive of a nonviable pregnancy. Subsequently, the patient had a spontaneous abortion.

Patient underwent one more IVF cycle and conceived. At 12 weeks period of gestation, ultrasound revealed singleton pregnancy with good cardiac activity, adequate fetal growth and normal nuchal thickness. However, patient had a relapse of idiopathic thrombocytopenic purpura for which she was managed with steroids under hematology. Presently, patient has completed 24 weeks period of gestation and hematological parameters are within normal limits.

DISCUSSION

Advances in reproductive medicine have resulted in the availability of many more options for fertility preservation.

Percolation of this knowledge to the young cancer patient about to undergo treatment is dependent upon the awareness of the treating physician who may be a general surgeon, a radiotherapist or a medical oncologist. Improved outcomes following cancer therapy have resulted in a shift from a life and death issue to quality of life after treatment. Fertility potential thus becomes an important concern.

Patridge et al looking at awareness issues, found that only 51% women survivors were counseled regarding fertility preservation measures prior to treatment.[6] The level of awareness is likely to be much lower in most centers.

Male fertility issues are easier to address. Cryopreservation of semen is an established and successful technique.[4] However, sexual maturity is essential and most often the young male is able to provide a semen sample for analysis and preservation.[7] However, the prepubertal male and some ailing young adolescents may not be able to produce an ejaculate. Post-masturbation urine samples can be evaluated in cases of ejaculation failure. The options of penile stimulation and sperm retrieval though available are rarely offered. Very often the sample obtained is of poor quality and fertility treatment at a later stage may entail assisted reproductive technology.[8] The patient needs to be aware of the prognosis and expenses of such treatment schedules. Cryopreservation should be considered even for poor quality semen samples as the likelihood of permanent gonadal damage and subsequent sterility is a possibility following chemoradiotherapy.

The first case illustrates the importance of referring the patient for semen cryopreservation at the right time. The patient who had a severe oligoasthenoteratozoospermia prior to therapy became azoospermic following chemotherapy. ART using the cryopreserved sample was successful and helped the couple achieve parenthood.

Female fertility preservation is more complex with fewer clinically established procedures on offer. While most options are still at an experimental stage, embryo cryopreservation is a well-established procedure, has good results and is usually the procedure of choice when appropriate.

An important factor that needs to be taken into account is the time from planning to oocyte retrieval, which could be anywhere between 2 and 5 weeks.[5] For many patients, choosing to delay life-saving treatment in favor of fertility preservation is a difficult decision. Guidance from the primary treating physician who takes into account the overall picture including factors like the cancer type and stage of the disease will help in decision-making. However, ultimately the final decision needs to be made by the patient. The uncertainty of treatment outcomes makes the decision even more difficult. The ethical and legal issues of demise resulting in single partners or unclaimed embryos are difficult to explain at this stage. Nevertheless the hard facts need to be clearly understood and appropriate informed consent obtained, in order to stave off legal ambiguity at a later date. The anguish and often anger that cancer survivors suffer after learning that they were denied fertility preservation options due to lack of communication cannot be envisaged.

The other major concern is the hyperestrogenic environment generated by ovarian stimulation using gonadotrophins, especially so in estrogen sensitive cancers like breast cancers. Although use of antiestrogens like tamoxifen or aromatase inhibitors like letrozole does reduce estrogen levels during ovarian stimulation, the risk of exacerbations and long-term recurrence cannot be ruled out.[9]

In the second case, the patient underwent an IVF cycle in the interval between surgery and start of chemotherapy. Concerns regarding high estrogen levels were not an issue here since the cancer wasn't estrogen sensitive. Subsequently, the patient was put on GnRH analogs for ovarian safeguard during chemotherapy. A recent meta-analysis has shown that GnRH analogs are protective against gonadal toxicity due to chemotherapy and this option is worth considering even after measures like embryo and oocyte cryopreservation have been resorted to.[10]

Although still considered experimental oocyte cryopreservation is gaining popularity and can be offered to women without a male partner. However, it also carries concerns similar to embryo cryopreservation, i.e. a delay in oncology treatment and exposure to a high estrogenic milieu. Technically, oocyte cryopreservation is more demanding than embryo cryopreservation as oocytes are sensitive to temperature changes and the process of freezing/thawing can damage the meiotic spindles and lead to chromosomal abnormalities. Oocytes can be preserved either at the metaphase II or the germinal vesicle stage. Since it is a relatively new procedure, long-term safety data of children born through cryopreserved oocytes is still awaited. Since the pregnancy rates are lower and inconsistent, and long-term safety issues still need to be addressed, this option should be offered after careful deliberation and counseling.[11] The experimental nature of the technology should be emphasized before embarking on this treatment.

In case 3, the disease at the time of diagnosis was fairly advanced. As the patient was very keen on fertility preservation, oocyte cryopreservation was offered after explaining the various nuances of the issues involved, a difficult decision for both the treating clinician and the patient.

In case 4, the woman had been referred after completing chemotherapy. The case highlights the deleterious effect of toxic chemotherapy agents on gonadal function. Ovarian reserve was diminished as suggested by the borderline high serum FSH level although the total antral count was adequate. In view of the risk of imminent failure of the ovaries, a conservative approach could result in losing precious time on less effective treatment options. ART treatment can be considered in these scenarios after careful counseling. Even though the patient was disease-free for 3 years before undergoing ART treatment, need for constant surveillance and interdepartmental coordination is important in order to ensure that recurrences are picked up early.

Another relatively less demanding fertility preservation measure in women undergoing pelvic radiotherapy is laparoscopic oophropexy. Loss of gonadal function is more likely once the radiation dose crosses 300 cGy.[12] Since pelvic

irradiation therapies involve doses of more than 1000 cGy, premature ovarian failure rates are high following such treatment. A laparoscopic approach is simple, safe and doesn't delay starting radiotherapy.

Other options, like ovarian tissue cryopreservation and transplant, are mainly offered in a research setting. There have been a few reported pregnancies worldwide following ovarian tissue transplant but the technology is still at an early stage.[13]

CONCLUSION

There is an urgent need for increasing awareness among medical service providers regarding various fertility preservations options. Familiarity with the various available options leads to timely referral to the reproductive medicine specialist. The cases highlighted in this article illustrate several clinical scenarios in which fertility preservation options were exercised. The couples were referred appropriately giving time for counseling and allowing the patient take an informed decision, thus maximizing their chances of preserving fertility potential.

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