GUWAHATI OBSTETRIC AND GYNAECOLOGICAL SOCIETY

BULLETIN

SEPTEMBER, 2021

A Case Report

FERTILITY PRESERVATION IN A PATIENT WITH SYNOVIAL SARCOMA

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Cancer is not uncommon and it is no longer considered an incurable disease. Over the past three decades, there has been a remarkable improvement in the survival rates of cancer patients due to the progress in diagnosing certain cancers at an earlier stage and improvements in treatment. Five-year survival rates with testicular cancer, hematologic malignancies, breast cancer, and other cancers that occurs in young people may be 90% or greater. Annual number of patients who develop cancer are estimated to rise from about 9.79 lakhs in 2010 to 11.4 lakhs in 2020 and more than 140,000 cancer patients are diagnosed in their reproductive years (up to age of 45 years). The incidence of breast cancer in females below 45 yrs is as high as 45%, haematologic malignancies 34%, lymphomas 20%, cervix 9% and ovaries 5%. From 2002 to 2012, 83% of women less than 45 years suffering from cancer survived. This increase in the number of patients surviving cancer has shifted our attention on the delayed effects of cancer treatments on the quality of future life of the survivor and also on their future fertility potential.

Many forms of cancer are associated with impaired semen quality or impaired ovarian function at the time of cancer diagnosis. Moreover, the treatment in most of the cancer types in reproductive-age women involves either removal of the reproductive organs or cytotoxic treatment (chemotherapy and/or radiotherapy) that may partially or definitively affect reproductive function. Gonadal failure resulting from these treatments may affect different aspects of reproductive health, including pubertal development, hormone production, and sexual function in adults. The ovary is particularly sensitive to these adverse effects because of the set number of follicles present in the postnatal ovary. Reproductive lifespan is determined by the follicle pool, and therefore, cancer treatments that cause follicular depletion accelerate the onset of menopause. The irreversible gonadotoxic effects of some of the chemotherapeutic agents particularly for alkylating agents (e.g. cyclophosphamide, busulfan, and ifosfamide) is well documented. These agents are common components of chemotherapy for breast cancer, lymphomas, leukaemia and sarcomas. Pelvic radiation therapy is known to cause follicular destruction and exposure to 5-10 Gy pelvic radiation is toxic to oocytes, resulting in premature ovarian insufficiency in many women. Radiotherapy may also affect the uterus, leading to reduced vascularity, myometrium damage (fibrosis) and hormone- dependent insufficiency. Fertility may also be impaired by surgical removal or damage to reproductive organs. Ovarian damage is drug and dose dependent and is related to age at the time of treatment, with progressively smaller doses producing ovarian failure as the patient's age increases. Likewise, total body, abdominal, or pelvic irradiation causes ovarian and uterine damage, depending on radiation dose, fractionation schedule, and age at the time of treatment. Early loss of ovarian function not only puts the patients at risk for menopause related complications at a very young age, but is also associated with loss of fertility.

Multiple ways have been developed to preserve fertility in women with different types of malignancies. These include embryo and oocyte cryopreservation, cortical and whole ovary cryopreservation, ovarian

transplantation, ovarian transposition, and GnRH agonist protection. Mature oocyte cryopreservation and embryo preservation following in vitro fertilization (IVF) are the two techniques that have been endorsed by the American Society of Reproductive Medicine while others are still considered experimental.

Here we present a case of controlled ovarian stimulation and embryo cryopreservation in a patient suffering from synovial sarcoma of left hip joint who had underwent left hip disarticulation and was awaiting chemotherapy. The patient was supposed to receive ifosfamide, an alkylating agent structurally related to cyclophosphamide and doxorubicin. Both the drugs are known to cause ovarian toxicity, decreased ovarian reserve and gonadal dysfunction.

Case Report

A 28 year old female, nurse by profession presented in our clinic in May 2019 with the sole purpose of fertility preservation. The patient was a diagnosed case of synovial sarcoma of left hip and had undergone left hip disarticulation on 1stapril, 2019 in CMC ,Vellore. The patient was planned for chemotherapy. She was married for a year and had no history of any previous pregnancy. She had a regular menstrual history with cycle duration of 28-30 days. Her last menstrual date was 1stmay, 2019. On initial examination, her vitals were normal and her BMI was 19. Pelvic findings showed anteverted, normal size and mobile uterus with no adnexal masses. The routine investigations were done for the couple. The routine blood tests were normal and her AMH was 1.46ng/ml. Her transvaginal sonography (TVS) on11/5/19 (11th day of cycle) showed a normal uterus which measured 6.6 X 3.2X 4.0 cms. The endometrium was 6.3 mm. The right ovary measured 2.8 X 1.5 X 1.9 cms (volume- 4.15cc) and showed 5 follicles of size 2-7mm. The left ovary measured 2.7 X 1.8 X 1.9 cms(volume- 4.8cc). There were 4 small follicles in left ovary measuring 3,4,4,9 mm respectively and one dominant follicle measuring 14mm. The husband's semen analysis showed teratozoospermia. After discussion with her oncologist we came to know that she had two weeks time for the fertility preservation and had to start her chemotherapy thereafter. Since there was a follicle of 14mm the patient was given 75 IU of urinary hMG on 11/5/19 and 12/5/19 . TVS was repeated on 13/5/19 which showed a 18mm follicle following which trigger was given with hCG. Ovulation was confirmed on 15/5/19 by TVS. Stimulation was started with 300IU of urinary hMG from 17/5/19. The patient was reviewed on 21/5/19 and TVS was done. There was presence of 5 dominant follicles in right ovary and 2 dominant follicles in left ovary. The lead follicle measured 14mm so GnRH antagonist was added. 3 days later, on 24/5/19 there were 4 follicles measuring more than 18mm and another 5 measuring more than 14mm. Trigger was given to the patient on 24/5/19 at 10.30pm and OPU was done on 26/5/19 at 9.30am. 9 metaphase II oocytes were achieved and ultimately 2 grade A blastocysts and 2 grade B blastocysts were cryopreserved. The patient thereafter underwent six cycles of chemotherapy with ifosfamide, doxorubicin and mesna and she is presently doing well.

Discussion

Controlled ovarian stimulation (COS) and embryo or mature oocyte cryopreservation is the most preferred method for fertility preservation in cancer patients, due to its higher success rates compared with the other technologies. Therefore, It should be recommended to all patients if their medical condition allows performing COS or oocyte retrieval and if the patient has adequate time to undergo stimulation. Prompt consultation should be done with a reproductive endocrinologist as soon as diagnosis is made to facilitate initiation of ovarian stimulation and to avoid unnecessary delay. The choice of protocol for COS is determined based on the policy of preferences in each IVF center, the time available until the initiation of radio/chemotherapy and estrogen sensitivity of the tumour. Conventionally, COS is initiated at the beginning of the follicular phase and this requires 2-6 weeks time depending on the women's menstrual cycle phase at the time of presentation. This may lead to a significant delay in cancer treatment thus increasing the psychological stress of the patient as well as the oncologist leading to the patient's forgoing fertility preservation. As there is an urgent need to start cancer treatment in

most of the patients, new protocols to facilitate the start of the ovarian stimulation and oocyte/embryo cryopreservation process have been proposed. The recent theory of **multiple follicular waves** in a cycle resulted in the prospect of new approaches to ovarian stimulation and, in particular, the **random-start ovarian stimulation protocol**, namely the administration of exogenous gonadotrophins randomly on any day of the menstrual cycle. This is particularly useful in the cancer patients as they may present in mid-cycle or in the luteal phase. Moreover, in these patients there is no need to achieve synchrony between ovaries and endometrium, as there is no fresh embryo transfer thus making the random start stimulation protocol more acceptable. Cakmak H et al in his study demonstrated that the number of total and mature oocytes retrieved, oocyte maturity rate (number of MII oocytes/number of total oocytes), and fertilization rates were similar in early follicular and random-start protocols. Random-start ovarian stimulation thus provides a significant advantage by decreasing total time for the IVF cycle without compromising the IVF outcomes.

Fertility preservation (FP) is a fundamental issue for individuals of reproductive age and also for prepubescent boys and girls whose future fertility may be compromised. Most of the reviews have been focused on FP in cancer patients. However, there is often a need for FP in other pathologic situations too either due to the disease itself or due to the gonadotoxic treatment (Table 1). FP in non-medical indications like in women wishing to postpone maternity is also on the rise.

Both embryo and oocyte cryopreservation are first-line FP methods. Embryo cryopreservation is a well-established technology and it has a high pregnancy success rates. Dolman et al and Oktay et al in their studies have demonstrated a similar live birth rate (LBR) per patient among women with cancer undergoing IVF and embryo cryopreservation and in non-cancer patients undergoing IVF with fresh embryo transfer.

Oocyte cryopreservation (OC) can be offered to post pubertal females who lack a male partner, who do not wish to use donor sperm and to those who object to embryo cryopreservation. The first human birth from a previously frozen oocyte occurred in 1986. The use of vitrification, an ultra-rapid cooling technique, has led to a mark improvement in the efficacy of oocyte cryopreservation. In 2012, the ASRM Practice Committee removed the experimental label from oocyte cryopreservation and this is now an established and successful procedure. Cobo et al in his study reported a LBR per patient of 50% among women aged <35 years and of 22.9% among those aged >36 years after the transfer of embryos obtained from vitrified oocytes. Rienzi L et al and sole M et al, also demonstrated comparable success rates between vitrified and fresh oocytes. Moreover, short-term studies of health of offspring from OC reveals no increase in congenital anomalies when compared with other IVF offspring.

In prepubertal girls where oocyte or embryo freezing can not be done, ovarian tissue freezing is becoming a viable option. It can also be offered to women who cannot delay treatment and in whom the hormonal treatments are contraindicated. Reimplantation of this tissue is done either in the pelvic cavity (orthotopic) or elsewhere (heterotopic) and this has the potential of restoring fertility and ovarian hormone secretion. This method is still considered experimental by the ASRM Practice Committee, but over 87 live births have been reported worldwide. Other methods for FP in women undergoing radiation includes reducing the radiation dose to the ovary by shielding or surgically moving the ovaries from the field of radiation (i.e. oophoropexy). Suppression of folliculogenesis with GnRHa for fertility preservation is still controversial and until definitive proof of efficacy is established, other fertility preservation options should be offered in addition to considering GnRH-a treatment.

In addition to the female patients, fertility preservation is also desired in males who have to undergo gonadotoxic treatment and in some other non-medical conditions like in sportspersons and in army personnels. Sperm cryopreservation is the only established FP method in adult and adolescent males. Assisted ejaculation methods such as penile vibratory stimulation or electroejaculation can be done when procurement

of semen sample by masturbation is not possible. Alternatively, sperm can be retrieved by epididymal aspiration or testicular biopsy in sexually mature men. In pre-pubertal boys testicular tissue cryopreservation may be offered but only in a research setting as fertility restoration strategies by autotransplantation of cryopreserved testicular tissue have not yet been tested for safe clinical use in humans.

Conclusion

As the number of cancer survivors is increasing, attention should be paid on their quality of life and the physical, psychological, social, and spiritual issues that they confront. A high quality of life for younger survivors includes the ability to have and raise a family. So, with such great improvements in survival rates for younger patients, oncologists should also pay attention to the impact of treatment on fertility and ways to preserve it. Physicians treating younger patients for cancer and noncancerous conditions must be aware of the adverse effects of treatment on fertility and how to minimize those effects and counsel the patients accordingly. If the gonadal toxicity is unavoidable, physicians should educate the patient regarding this and give them options of fertility preservation. The patient should be referred to a fertility specialist so that the fertility preservation can be started promptly without further delay.

Table 1

Indication	Disease
Autoimmune diseases	Systemic lupus erythematosus (SLE)
	Behcet's disease
	Churg-Strauss syndrome (eosinophilic granulomatosis)
	Steroid resistant glomerulonephritis
	Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)
	Inflammatory bowel diseases
	Rheumatoid arthritis Pemphigus vulgaris
	Autoimmune diseases unresponsive to immunosuppressive therapy
Hematopoietic	Haematological diseases (sickle cell anaemia, thalassaemia major, aplastic anaemia)
Medical conditions causing Primary Ovarian Insufficiency	Altered hypothalamic-pituitary-gonadal axis
	Ovarian oophoritis
	Benign ovarian tumours
	Mosaic Turner's syndrome
	Fragile X Mental Retardation
	Galactosaemia
	Beta-thalassaemia
	Endometriosis
	Klinefelter's syndrome
Male genetic disorders	
Testicular damage	
Gender reassignment procedures	
Severe body trauma requiring surgical intervention	

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Suggested Readings

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