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REVIEW ARTICLE

Oncofertility: Revisited

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ABSTRACT

As the survival rate of children, Adolescents and young adults improve following cancer therapy, it also creates an urgent demand in studying and progressing in the field of oncofertility. Options for fertility preservation include : medical treatment, surgical treatment, oocyte or embryo cryopreservation and expectant management. Treatment is individualised based on age, ovarian reserve, partner status, number of future children desired and time to cancer treatment. It is important to understand that oncofertility includes preservation of fertility as well as endocrine functions, helping them to have a better quality of life, post cancer therapy.

KEYWORDS

Oncofertility • Cryopreservation • Ovarian Transposition • Radiotherapy

INTRODUCTION

As the survival rate of children, Adolescents and young adults improve following cancer therapy, it also creates an urgent demand in studying and progressing in the field of oncofertility. Equal importance should be given to the quality of life following cancer therapy which includes providing information as we well as options available for these young individuals regarding fertility. The preservation on fertility depends on various factors including the age of the patient, location of cancer, type of treatment received, strength and location of

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Radiation and the drugs used.

CAUSE OF INFERTILITY DUE TO CANCER

The human ovary has a fixed number of primordial follicles that reach their maximum at 5 months of gestation.These follicles consist of the secondary oocytes that by normal physiological mechanism deplete around the age of 50 years. Oncological treatment usually requires extensive chemotherapy and/or radiotherapy, which are indicated to be distinctively ovotoxic, resulting in premature ovarian insufficiency (POI) and consequent infertility.[1]

In males, cancer treatment may affect spermatogenesis or the production of LH/FSH in the pituitary or testosterone by the Leydig cells in the testes; all hormones essential for pubertal development and sexual function.[2]

Another major cause that has seen to cause infertility is the imbalance of the Hypothalamic pituitary gonadal Axis (H-P-G axis) which can be either due to any intra cranial space occupying lesion or total body or intra cranial irradiation.

GONADOTOXIC RISK

There are various methods to calculate the gonadotoxic risks - fertility calculators, risk tables, AAD's (alkylating agent dosing), CED's (cyclophosphamide equivalent dose calculators) etc.

This risk calculation should be done ideally pre and post treatment so as to provide complete information to the patient.

The pre treatment calculation includes factors such as

- Familial history of infertility.
- Any previous history of Sexually transmitted disorders.
- Reproductive or obstetric history.
- Underlying medical/surgical treatments/ ailments.

Most of the clinicians fail to document these factors in the pre treatment phase making it difficult to predict the risk accurately in post treatment stage.

The gonadotoxic risk is divided into 4 zones

- No risk.
- Low risk (less than 20%).
- Intermediate risk (21–80%).
- High risk (greater than 80%)[3].

CHEMOTHERAPEUTIC AGENTS AND THEIR RISK FACTOR

Alkylating agents carry a moderate to significant risk of inducing infertility, which can be linked to the total dosage administered.

Platinum agents, anthracyclines, and taxanes present a moderate risk of infertility.

And 6 mercapturine, methotrexate, 5 fluorouracil, vincristine, bleomycin, and actinomycin present a low or negligible risk. High-dose chemotherapy linked to hematopoietic stem cell transplantation often leads to significant and frequently lasting infertility in the majority of cases.[4]

RADIATION AND REPRODUCTIVE HEALTH

The human oocyte is highly susceptible to radiation, and a radiation dose of just under 2 Gy for pelvic treatment can eliminate 50% of primary follicles. The suggested process of follicle depletion involves ionizing DNA damage caused by radiation. This change also triggers the activation of the TAp63 protein, resulting in the elimination of PFs. Regarding late effects, damage to blood vessels and stromal fibrosis after tissue hypoxia may represent another mechanism. This may lead to ovarian deterioration and later tissue impairment.

Radiation exposure to the entire abdomen and pelvis in females (> 15Gy in prepubertal girls, > 10 Gy in postpubertal girls, and > 6 Gy in adults) is linked to a significant risk of infertility.

The testis is very susceptible to radiation; a dose as low as 0.15 Gy leads to decreased sperm production, while doses of 0.5 Gy or higher may result in azoospermia. Partial restoration from azoospermia caused by irradiation can happen; nonetheless, the recovery period is related to the testicular dose.

METHODS OF FERTILITY PRESERVATION

Options for fertility preservation include:

- Medical treatment.
- surgical treatment.
- Oocyte or embryo cryopreservation expectant management.

It is an individualised planned treatment depending on the age, ovarian reserve, partner status, number of future children decided and time

to cancer treatment.[6]

EMBRYO AND OOCYTE PRESERVTION

Both these methods are the oldest, most approved and well established methods in the field of fertility preservation. Both include a common step that is ovarian stimulation . In recent studies GnRH antagonist protocol has shown better results in comparison to GnRH agonist method in terms of faster results, better pregnancy outcomes. Other recent advances in the methodology have contributed to the increase in the success rate which includes- vitrification of the oocyte/embryo prior to the cryopreservation, Doustim protocol (repetition of two ovarian stimulations within the same menstrual cycle protocol), increasing the number of ova retrieved during one cycle and inducing fast cycles.[7]

While most of the patients fit into this criteria, this method may not be a suitable for candidates who are in urgent need to begin oncological therapy, or pre pubertal individuals due to the non maturity of gonads. For these individuals options such as OCT can be considered.[8]

OVARIAN TISSUE CRYOPRESERVATION

Ovarian tissue removal and the cryopreservation of cortical fragments are components of ovarian tissue cryopreservation (OTC), which are subsequently transplanted back to restore ovarian endocrine and fertility functions. This procedure is primarily indicated for prepubescent girls, as it aids in preserving both fertility and the endocrine functions of the gonads. The reported recovery rate for these patients following the transplantation of ovarian tissue is 70% among survivors.

IN VITRO ACTIVATION OF PRIMARY FOLLICLES

Ovarian transfer Cryopreservation is a distinctive and effective technique; however, it may not be as effective in older age groups due to reduced ovarian reserve, thus making the lifespan of ovarian tissue grafts even shorter. In these instances, a combination of in vitro follicle activation (IVA) of primordial follicles and OTC was created to enhance the likelihood of successful pregnancy. In this process, the collected ovarian tissue is cut into cubes measuring 1 × 1 × 1 mm, and subsequently cultured with Akt stimulatory agents to stimulate the PI3K/Akt/FOXO3a and inhibit the Hippo signaling pathways. According to reports, primary follicles in patients with POI rarely activate on their own, so this procedure is recommended to stimulate the remaining PFs and encourage follicle growth in those with POI or diminished ovarian reserve.

OVARIAN TRANSPOSITION WITH RADIATION

In instances of pelvic radiation, ovarian transposition is recommended to safeguard the ovaries during the treatment. This procedure involves mobilizing the ovaries along with their vascular pedicle and relocating them to a different site, which is marked with radio-opaque clips for future identification. This approach is typically indicated for patients undergoing pelvic radiotherapy due to cervical cancer, as well as cancers of the vagina, rectum, or anus, pelvic lymphoma, or Ewing's sarcoma.

EFFECT OF UTERUS DUE TO RADIOTHERAPY

The existing literature on the impact of radiotherapy and chemotherapy on the uterus is limited; however, it is essential to investigate whether radiation exposure can induce DNA damage and alter the hormonal functions of the gonads. Such alterations may have a compounded effect on the hormone-dependent endometrium, which is vital for maintaining female fertility. At the tissue level, the responses to chemotherapy may vary between the endometrium and the myometrium. The endometrium is more readily accessible for examination through endometrial biopsies, as demonstrated by Garg *et al.* In contrast, the myometrium poses challenges for scientific investigation; nevertheless, it is imperative to evaluate the effects of chemotherapy on this layer, given its significant role in supporting pregnancy and childbirth. Endometrial biopsies can facilitate the comparison of molecular, histological, or proteomic alterations. A clinical case study conducted by Errol R. Norwitz et al. details a 23-year-old primigravida with a medical history of whole-body radiation treatment received at the age of five due to leukemia. This patient experienced a uterine rupture at 17 weeks of gestation. Histopathological analysis of the uterus revealed a percreta in the postero-fundal region, with myometrial thickness measuring between 1 and 6 mm.[10]

CONCLUSION

It is very important that oncofertility care is thought of as a regular practice rather than a special

consideration . It is also important to understand that oncofertility is an umbrella term and it includes preserving fertility as well as the endocrine functions and normal sexual functions of the individuals helping them to have a better quality of life, post cancer therapy. Established fertility preservation methods for reproductive-aged female cancer and infertility patients currently comprise oocyte and embryo freezing. Additionally, recent progress in reproductive science and medicine has enabled exploratory fertility preservation opportunities for both pediatric and reproductive-age individuals, such as ovarian tissue cryopreservation, in vitro oocyte maturation, ovarian transposition, ovarian suppression, and adjunctive therapy. It is very important that oncofertility care is thought of as a discipline rather than a special consideration.

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