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ISSN 2348-0416
USA CODEN: JASRHB

Journal of Applied Science And Research, 2019, 7 (1):90-95

(*http://www.scientiaresearchlibrary.com/arhcive.php*)

FERTILITY PRESERVATION

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ABSTRACT

Fertility preservation is becoming increasingly important to improve the quality of life in cancer survivors. Despite guidelines suggesting that discussion of fertility preservation should be done prior to starting cancer therapies, there is a lack of implementation in this area. A number of techniques are available for fertility preservation, and they can be used individually or together in the same patient to maximize efficiency. Oocyte and embryo cryopreservation are now established techniques but have their limitations. Ovarian tissue cryopreservation though considered experimental at present, has a wider clinical application and the advantage of keeping the fertility window open for a longer time. Both chemotherapy and radiotherapy have a major impact on reproductive potential and fertility preservation procedures should be carried out prior to these treatments. The need for fertility preservation has to be weighed against morbidity and mortality associated with cancer. There is thus a need for a multidisciplinary collaboration between oncologists and reproductive specialists to improve awareness and availability.

Keywords : Cancer, counselling, cryopreservation, fertility preservation

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INTRODUCTION

DEFINITION

Preserving your fertility involves freezing your eggs, sperm, embryos or reproductive tissue so that you can hopefully have a biological family in the future.Fertility preservation is the effort to help cancer patients retain their fertility, or ability to procreate.

INCIDENCE

The National Cancer Registry of India suggests that the annual number of patients who develop cancer in India is set to rise from about 9.79 lakhs in 2010 to 11.4 lakhs in 2020. More than 140,000 cancer patients are diagnosed in their reproductive years that is, up to age of 45 years and childhood cancer too seems to be increasing. It is believed that in 2010, every 250th adult will be a survivor of childhood cancer. Approximately, 40-80% of females face possible infertility as a result of their cancer treatments that is, chemotherapy, radiation, and surgery.

CAUSES

In many cases, the exact cause of the infertility

Remains unknown or unexplained—a situation called idiopathic infertility

POSSIBLE CAUSES OF FEMALE INFERTILITY

The most common overall cause of female infertility is the failure to ovulate, which occurs in 40% of women with infertility issues. Not ovulating can result from several causes, such as:

- Ovarian or gynecological conditions, such as primary ovarian insufficiency (POI) or polycystic ovary syndrome (PCOS)
- Aging, including "diminished ovarian reserve," which refers to a low number of eggs in a woman's ovaries due to normal aging
- Endocrine disorders, such as thyroid disease or problems with the hypothalamus, which affect the hormones produced by the body so that there might be too much or too little of a hormone or group of hormones
- Lifestyle and environmental factors
- **Problems with the menstrual cycle.**

FERTILITY PRESERVATION TECHNIQUES IN FEMALES

- Embryo cryopreservation
- Oocyte cryopreservation
- Ovarian tissue cryopreservation (OTC)
- *In vitro* maturation (IVM).

Embryo cryopreservation

This requires the patient to go through IVF. Since a sperm sample is required for oocyte fertilization, the woman must be married or should have a partner. Embryo cryopreservation is an established technology that provides a good success rate depending on the number and quality of embryos stored. Data on pregnancy and live birth rates in cancer patients after frozen embryo transfer are limited. A live birth rate of 38.7% per embryo transfer is reported for frozen embryo transfer in nononcological patients <35 years of age and 34.8% for oocyte donor cyclesCardozo*et al*. in a retrospective analysis compared PR in cancer patients who had a frozen embryo transfer with patients of tubal factor infertility undergoing IVF. Cumulative PR per transfer for cancer patients compared to controls was similar, 37 versus 43% respectively (P = 0.49) and cumulative live birth rate per transfer too did not show a difference 30 versus 32% respectively (P = 0.85). Cancer patients had a higher likelihood of live birth resulting in twins (44 vs. 14%; P = 0.035) possibly because there was no underlying infertility factor in these patients.

Limitations of the procedure:

- Controlled ovarian stimulation (COS) takes approximately 2 weeks from the 2nd day of the period, and this may delay cancer treatment
- High estradiol levels during stimulation may have a negative effect on estrogen-sensitive tumors
- Partner's or donor sperm required which limits reproductive autonomy in the future and increases stress levels
- Ethical, legal and religious implications regarding disposal of embryos in case patient dies before she can use the embryos or there is a separation of the partners

- Cannot be used in prepubertal patients.

Mature oocyte cryopreservation

When a woman is unmarried or does not have a partner mature oocyte cryopreservation is carried out. In fact, it has been suggested that oocyte preservation is a better option for all women to maintain reproductive autonomy. Oocyte cryopreservation also requires the patient to go through ovarian stimulation and OR. Data on pregnancy and live birth rates from oocyte cryopreservation in cancer patients are scarce, so success rates extrapolated from other populations, such as young oocyte donors, have to be used for patient counseling.

Due to improved freezing and thawing techniques PRs with oocyte cryopreservation have improved considerably. Cobo*et al*. in 2008 and in 2010, reported an implantation rate (IR) of 40% and clinical PR of 55% with vitrified oocytes which was similar to that with fresh oocytes. In the study by Rienzi 2010 on self-oocytes, the IR was 20% versus 21% and PR was 38% versus 45% vitrified versus fresh oocytes.

Both embryo and oocyte cryopreservation cannot be performed on prepubertal girls. Another disadvantage is that only a limited number of oocytes/embryos can be collected/generated in one attempt, which in turn restricts the number of attempts for pregnancy.

Ovarian stimulation for embryo or mature oocyte cryopreservation

This procedure should be recommended only if the patient's medical condition allows the COS and OR to be carried out safely and if there is a fair chance of a good ovarian response. Time is also a constraint since ovarian stimulation has to be started from day 2 of the menstrual cycle. The implications of delaying cancer therapy to complete the IVF procedure have to be taken into account. To avoid delay in treatment, random start of COS has been suggested. Oocyte recovery rates are not compromised prior to cancer therapy, but ovarian reserve may be compromised in women who have undergone prior gonadotoxic therapy

Ovarian stimulation regimes

Gonadotropin-releasing hormone antagonist protocols afford more flexibility and are favored because of lower estradiol rise and lower gonadotropin usage. Dose of gonadotropins can be decided based on ante-mullerian hormone (AMH) levels, antral follicle count (AFC), age and body mass index to get an appropriate response.

To overcome time constraints, luteal phase stimulation and random start protocols have been proposed. In the luteal phase protocol, GnRH antagonist is given for 3–4 days to achieve a quick down-regulation and COS is started subsequently with or without the onset of a menstrual bleed. Cakmak*et al*. 2013 proposed the random start protocol where COS is started irrespective of the phase of the cycle in which the patient presents. GnRH antagonist is started when the follicles secondary to the lead follicle reaches a size of 12 mm. Normal follicular growth and development is observed despite the increased progesterone levels seen in the luteal phase or a spontaneous luteinizing hormone surge, which may occur when the initial lead follicle reaches maturity. The authors concluded that the number of total OR, oocyte maturity rate, mature oocyte yield, and fertilization rates were similar in random-(n = 35) and conventional-start (n = 93) cycles. No superiority was noted when comparing COS started in late follicular (n = 13) or luteal phase (n = 22). Duration of stimulation was increased in both phases compared to conventional start of COS on day 2 of the cycle.

Anti-estrogensletrozole and tamoxifen have been added to OS regimes to lower the peak estradiol

levels in patients with estrogen-sensitive tumors. Oktay*et al*. showed substantially reduced peak estradiol levels after stimulation with tamoxifen, letrozole, or tamoxifen and low-dose gonadotropins (peak estradiol level: 419 pg/mL, 380 pg/mL, and 1182 pg/mL respectively) than with traditional COS with gonadotropins. In a follow-up of 5-48 months there was no increase in the rate of cancer recurrence for the treated women compared with untreated controls. Letrozole in a dose of 2.5-5 mg is started from cycle day 2 and given up to the day of human chorionic gonadotropin trigger. The addition of letrozole did not adversely affect oocyte maturity and competence in either random or conventional-start protocols however it has been reported to reduce total oocyte numbers available for cryopreservation. Tamoxifen, a selective estrogen receptor (ER) modulator binds with ER in target tissue, e.g. breast tissue and prevents proper binding of estrogen and subsequent transcription of DNA to mRNA. It is used as adjuvant therapy in breast cancer patients, and its use in OS protocols in breast cancer patients is seen as protective.

Complications

Since there is generally only a single attempt possible for IVF there is a temptation to go for heavy stimulation to recover the maximum number of oocytes. Such decisions should be taken with extreme caution as ovarian hyperstimulation syndrome (OHSS) in these women can pose a real danger apart from delaying cancer treatment. Antagonist regimes with GnRH agonist trigger should be the method of choice in patients at risk of OHSS. Other risks include delay of cancer therapy, theoretic stimulation of estrogen-sensitive cancers, a risk of thromboembolic phenomena.

***In vitro* maturation**

Involves aspiration of immature oocytes after minimal or no stimulation followed by IVM and cryopreservation of mature oocytes or embryos generated after fertilization. Immature oocytes can also be collected in the luteal phase and from antral follicles in the ovarian tissue removed for cryopreservation. This technique has been performed experimentally and with good success in girls as young as 5 years. So far, this technique has mainly been used in polycystic ovary syndrome patients, and data on efficacy and safety of IVM in cancer patients are not available. IR's with IVM are low being between 10% and 15%.

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation involves obtaining ovarian cortical tissue that is rich in primordial follicles, prior to ovarian failure by laparoscopy or laparotomy. Ovarian tissue is dissected into small fragments, and cryopreserved by slow-cooling technique or vitrification. The tissue is transplanted after completion of cancer therapy into the pelvis (orthoptic transplant) or outside the pelvis-abdominal wall, and fore-arm have been used (heterotopic transplant). Spontaneous pregnancies can occur after orthotopic pelvic transplant but IVF is necessary when a heterotropic transplant is carried out. Orthotopic transplantation has been more successful in humans, and many successful pregnancies have been reported. The first ongoing pregnancy from a heterotopic implantation of ovarian tissue has been reported recently by Stern *et al*. from Melbourne, in a patient who had both ovaries removed because of ovarian cancer. The tissue was transplanted into the abdominal wall, two oocytes were recovered after mild stimulation and embryos implanted into the uterus. No live births have been reported so far in females who cryopreserved tissue before puberty.

Low follicular survival rate after ovarian transplantation, precludes its use in women over 40 years. In younger patients, the amount of ovarian tissue cryopreserved theoretically should be proportional to the risk of age-related diminished follicular reserve. Based on the current evidence, removal of both ovaries for cryopreservation is not justified at this time unless the chemotherapy regimen has

an extremely high likelihood of inducing complete ovarian failure.

This technique has many advantages over oocyte and embryo cryopreservation. It does not delay the start of cancer therapy and avoids the risk of ovarian stimulation. There is no need for partner or donor sperm. It preserves a larger pool of follicles and allows for the resumption of ovarian function. Ovarian function generally resumes between 60 and 240 days posttransplant and lasts for up to 7 years. It is the only technique available for preserving fertility in prepubertal girls. Although no transplantations of tissue harvested from prepubertal girls have yet been reported in humans, the procedure is well-tolerated and holds great promise for the future.

Reseeding tumor cells following ovarian tissue transplantation is a major concern especially for malignancies like leukemias that are systemic in nature autologous transplantation is contraindicated in situations where cancer cells may be present in the cryopreserved ovarian tissue. It is unclear whether screening with histologic evaluation or with tumor markers is reliable and reduces the risk of reseeding tumor cells.Patients harboring the BRCA1 or BRCA2 gene may also be at risk. A temporary heterotopic transplantation followed by removal of the tissue after childbearing can be an option for at-risk specimens.

Currently, OTC is considered experimental though more than 30 live births have been reported so far. It can be recommended in carefully selected patients and should be offered only by centers with the necessary laboratory and surgical expertise.

FERTILITY PRESERVATION SERVICES

The practice committee of ASRM recommendations for fertility preservation services are summarized below.

Programmatic requirements for a fertility preservation program

Rapid access

It should be available as there is a shortage of time.

Interdisciplinary medical team

Interdisciplinary medical team is required which should include oncologists, reproductive endocrinologists and urologists, and reproductive surgeons trained in Fertility preservation techniques.

Laboratory requirements

Fertility preservation programs should be associated with an experienced ART program capable of providing a full complement of Fertility preservation techniques all the year round. Ideally, programs also should be able to counsel prepubertal patients and provide access to procedures (under Institutional Review Board-approved protocols) such as ovarian and testicular tissue cryopreservation, both of which are still considered experimental.

Counselors

- Mental health professionals: To counsel patients and help them in the decision-making process
- Genetic counselors: Some diseases are heritable so a genetic counselor should be available to discuss any potential risks of transmission of the disease to the resulting offspring and available genetic testing

- Financial counselors.

Interdisciplinary collaboration

Collaboration between medical and surgical oncologists, reproductive endocrinologists, and urologists is important. Oncologists have the initial responsibility to discuss the reproductive risks of intended cancer therapies. An experienced reproductive endocrinologist or urologist should discuss in detail the appropriate Fertility preservation techniques. Ideally all adolescents and individuals of reproductive age should be referred.

Medical considerations

Patients in need of fertility preservation should be given all the options available for preservation of their gametes, as well as alternatives such as the use of donor gametes, donor embryos, surrogacy, and adoption. The potential safety of future pregnancy after cancer should be addressed, taking into account the type of cancer and proposed treatment. Consent forms should include options for gamete disposition in the event of demise of the patient.

CONCLUSION

In "oncomedicine" disease-free state is becoming a reality in a significant number of young men and women. These patients would look at the prospects of reproduction once they achieve disease free status. If appropriate action is not taken in time to preserve their fertility, the toxic effects of chemo and radiation therapy may render them sterile. A number of techniques are available for fertility preservation and they can be used individually or together in the same patient to maximize efficiency for e.g. IVM and OTC, ovarian transposition and OTC or OTC followed by ovarian stimulation and oocyte preservation. Oocyte and embryo cryopreservation are now established techniques but have their limitations. OTC has a wider application and the advantage of keeping the fertility window open for a longer time. The need for fertility preservation has to be weighed against morbidity and mortality associated with cancer. There is thus a need for a multidisciplinary collaboration between oncologists and reproductive specialists to improve awareness and availability.

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