Fertility and Pregnancy in Breast Cancer Survivors

Bhagyashree.T
Pharmacy Practice, Krupanidhi College of Pharmacy, Bangalore- 560087

Abstract-Breast cancer is the most common cancer in the world and the leading cause of cancer death. While women develop breast cancer in approximately 99% of cases, men develop breast cancer in only 0.5% to 1% of cases. The chance of getting cancer is one in eight. According to available data, breast cancer is by far the leading cause of cancer related deaths in women under 45 years of age.

Younger patients usually have more aggressive tumors (more mitotically active and higher grade) and negative cells (triple negative or basal-like) are more common. Thanks to advances in modern medicine and the worldwide push to delay childbearing, young women are being diagnosed with and treated for breast cancer before they give birth.

Pregnancy planning has become more common among young women with a history of breast cancer. In this difficult situation, many issues should be discussed with the patient, such as cancer risk, birth control, chemotherapy for premature ovarian failure, the possibility of cancer and subsequent pregnancy. Discussion of obstetric issues with the patient and her partner, the long-term teratogenicity of contraceptives and breastfeeding are other important factors.

Keywords: cancer recurrence, fertility preservation method, premature ovarian failure after chemotherapy, long-term teratogenicity.

INTRODUCTION

Breast tumors grow uncontrollably to form tumors. It may start in one breast or both breasts. Cancer cells can affect breast tissue. The resulting tumor causes thickening or bumps. Metastasis is the process of cancer cells moving to nearby cancer cells or other organs. Metastasis can be fatal and fatal.

Symptoms of breast cancer may include:

- A lump or mass in the breast, which is usually painless;
- A change in the size, shape, or appearance of the breast
- Abnormalities or bleeding in the breast
- Darkening of the skin, redness, dimpling, or other abnormalities;

Treatment: -

Treatment for breast cancer depends on the specific disease and whether it has spread to the lymph nodes (stage II or III) or elsewhere.

To reduce the risk of the cancer recurring, doctors may offer a combination of treatments.

These include:

1. Surgery to remove the breast cancer
2. Radiation therapy can reduce the risk of the disease recurring in the breast and surrounding tissue
3. Medications such as hormone therapy, chemotherapy, or biological therapy can destroy cancer cells and stop them from spreading. Lymph nodes may also be surgically removed to evaluate the possibility of cancer.

Radiation therapy reduces the chance of cancer returning to the chest wall and treats cancer cells that are still in the breast tissue and/or lymph nodes.

FERTILITY AND PREGNANCY ISSUES FOLLOWING BREAST CANCER

Adjuvant chemotherapy regimens often used to treat breast cancer may cause early ovarian cancer due to their cytotoxic effects on ovarian cancer.

Recommended treatments for premenopausal women with breast cancer include surgery, radiation therapy, or ovarian cancer medications), antiestrogens, or a combination of these drugs. Although the use of cytotoxic drugs as adjunctive therapy may reduce mortality, there are concerns about long-term damage such as premature aging and reduced fertility. One of the problems that patients may encounter after breast cancer treatment is infertility. Although people who become pregnant after completing chemotherapy do not have adverse or adverse effects on their babies, the

importance of miscarriage (29%) and low birth weight (40%) emerges from time to time (2).
Adolescent survivors may have reduced fertility due to gonadotoxic drug use, and many of them are seeking strategies to control pregnancy.

EFFECT OF CHEMOTHERAPY ON FERTILITY

The type of cancer being treated, the patient's age at the time of treatment, the type of treatment, dose, and duration of treatment may affect fertility. With a history of infertility treatment, the risk assessment will also include age and type of treatment received.
Chemotherapy can cause periods of amenorrhea or oligomenorrhea, which can lead to symptoms of menopause when the follicles are destroyed. Menopause (more than 12 months without menstruation) and irreversible ovarian failure are caused by a decrease in the minimum number of primordial follicles required to complete the ovarian cycle. This may occur after several years of oligomenorrhea, during or after chemotherapy. Chemotherapy can damage DNA in oocytes because its antitumor mechanisms include causing DNA double-strand breaks, intra- and interstrand crosslinking, intercalation, and alkylation of base pairs. This can activate pathways involved in autophagy and/or apoptosis. In addition, chemotherapy can cause oxidative stress or damage the ovarian microvasculature, causing indirect DNA damage. Fertility research is necessary and there is a need to understand this process.
Chemotherapy drugs are classified as cell cycle nonspecific or phase-specific based on their anticancer effects. Pterin and 5fluorouracil act by inhibiting DNA synthesis during the S phase (DNA replication phase) of the cell cycle. Phase-nonspecific chemotherapy will damage cells at any stage of the cell cycle, even in the quiescent G0 phase.
Many cytostatics cause the proliferation of granulosa cells during follicular development, causing amenorrhea. If drug treatment is specific, the ovaries of the root system containing immature oocytes (quiescent cells) should not be affected.
a) High risk: alkylating agents (cyclophosphamide, oxoamide, busulfan, chlorambucil, melphalan, procarbazine, and cyclophosphamide).
b) Intermediate risk: platinum salts (cisplatin and carboplatin), anthracyclines (doxorubicin), taxanes (paclitaxel and docetaxel).
c) Low risk: vinca alkaloids (vincristine and vinblastine), antitumor antibiotics (bleomycin), antimetabolites (methotrexate and 5-fluoruracil)[18].

SUGGESTIONS FOR SOLVING FERTILITY PROBLEMS

Premenopausal women who want to have children face serious problems when they get breast cancer at an early stage. Chronic use of cytotoxic chemotherapy can lead to ovarian failure and infertility, while chronic use of hormonal therapy can lead to infertility. Early promise has been drawn from various strategies for preserving fertility after adjuvant chemotherapy.
Success Fertility is more likely to be preserved when patients are referred to a specialist at an early age. The only known method of preserving fertility is cryopreservation of embryos and mature oocytes. However, these surgeries require ovarian stimulation (OS), which delays the start of treatment by at least two weeks. The likelihood of BC recurrence did not increase with OS control. Although OS is not necessary, other fertility preservation methods such as cryopreservation of ovarian tissue, cryopreservation of immature oocytes, and ovarian gonadotropin-releasing hormone agonists are still in clinical trials (1).
1.EMBRYO PRESERVATIONFor breast cancer patients with a male partner or using donor sperm, the best method of fertility preservation is embryo cryopreservation. Techniques include in vitro fertilization (IVF), ovarian stimulation (OS), and oocyte retrieval. The age of the patient and the number of eggs or embryos retrieved are related to the success of this method. Retrieving more than 1 oocyte per cycle requires the use of gonadotropins for OS, which is important for successful IVF, especially for BC patients who usually only have a short time to follow the IVF protocol before starting gonadotoxic therapy. It was hypothesized that there was no association between fertility-preserving OS and higher risk of BC. It is not recommended for individuals who cannot postpone BC treatment because cryopreservation of the embryo may cause a delay of two to five weeks in oncology treatment.
2. OOCYTE CRYOPRESERVATION

For single women or those who refuse to use donor sperm, and in countries where embryo cryopreservation is illegal, oocyte cryopreservation is an option for embryo cryopreservation. This method has the same disadvantage as embryo cryopreservation in that it requires control of the operating system and oocyte collection.

3. CRYOPRESERVATION OF IMMATURE OOCYTES

Cryopreservation of immature or in vitro matured oocytes is a promising experimental fertility preservation strategy for BC patients. This method is independent of menstruation and does not require OS, but a short OS of three to five days is possible, which will shorten the time to cancer diagnosis and start cancer treatment. Immature oocytes can be kept in an immature state and grown in vitro after thawing, or they can be removed and stored after in vitro maturation. In vitro maturation (IVM) before cryopreservation is said to be better because it increases survival and growth compared to after thaw maturation.

4. CRYOPRESERVATION OF OVARIAN TISSUE

An experimental fertility preservation procedure called ovarian tissue cryopreservation (OTC) involves surgical removal of the ovarian cortex (which houses a large number of primordial follicles) and subsequent cryopreservation. After successful tumor treatment, patients can undergo ovarian transplantation from orthotopic (intra-abdominal cavity; atrophic ovary, pelvic peritoneal cavity) or ectopic (extra-abdominal; subcutaneous site such as forearm, abdominal wall). It has many benefits, including being able to be used at any time during the menstrual cycle, not requiring an operating system, being able to salvage many primordial follicles, restoring endocrine function, and being able to begin treating tumors awaiting a male partner or sperm. bar. OTC is an option for BC patients with OS who require immediate initiation of gonadotoxic therapy and who do not have enough time for embryo or oocyte cryopreservation. Most patients can regain ovarian function within 4-5 months after surgery, and more than 90% of patients have a recovery period of 4-5 years after surgery.

Ovarian survival can be affected by several factors, including advanced age at OTC, previous chemotherapy, graft development and cryopreservation methods, reversal of ovarian roots, and postoperative graft ischemia. Age is an important consideration, as the effectiveness of over-the-counter (OTC) contraceptives is largely dependent on the ovaries decreasing with age.

5. OVARIAN SUPPRESSION WITH GONADOTROPIN-RELEASING HORMONE AGONISTS

GnRHa administration is ideal for BC patients who want to preserve fertility because it is noninvasive, easy to perform, there is no need to use nursing equipment, and the start of chemotherapy should be delayed. GnRHa should be given at least one week before chemotherapy due to temporary side effects that occur in the first few days of treatment. The idea that gonadal inactivity during chemotherapy might reduce chemotherapy-induced damage led to the idea of using GnRHa.

GnRHa use may protect the ovaries through various mechanisms, such as reducing ovarian perfusion and drug delivery to the ovaries, preventing recruitment of primordial follicles from the ovaries, from increased follicle-stimulating hormone (FSH) concentration and increased cell apoptosis. Regulation of the intrinsic anti-apoptotic pathway and protection of ovarian cancer. The development of primordial and primary follicles results from growth factors secreted by more developed follicles that respond to gonadotropins and secrete TGF-β, BMP, and activin. According to the exhaustion theory, the gonadotoxic effects of chemotherapy lead to follicle death, decreased estrogen and inhibin, and therefore increased FSH.

Since GnRHa reduces FSH levels, it may reduce the number of primordial follicles recruited. However, GnRHa cannot act directly on the ovaries because there are no gonadotropin receptors in the follicles.

The use of GnRH agonists for fertility preservation is still considered experimental (1).

Fertility preservation method	Advantages	Disadvantages

Embryo cryopreservation	• Well-established technique • Possibility of PGD	• Need for OS • 2-5 week delay of oncologic treatment • Requires male partner/sperm donor • Expensive • Ethically questionable and legal issues
Cryopreservation of mature oocytes	• Well-established technique • No need for a male partner/sperm donor • Possibility of PGD	• Need for OS • 2–5-week delay of oncological treatment • Expensive
Cryopreservation of ovarian tissue	• No need for OS • Menstrual cycle independent method • No need for delay in oncologic treatment • Restoration of endocrine function • Fertility preservation method for young women who already started gonadotoxic chemotherapy • Combination with *in vitro* maturation • No need for male partner/ sperm donor	• Experimental method • Potential reintroduction of malignant cells within ovarian tissue • Expensive • Need for surgery • Success is highly dependent on ovarian reserve, it is not recommended for patients older than 35 years • Available only in highly specialized centers
Cryopreservation of immature oocytes	• No need for OS or short OS lasting for 3-5 days • Menstrual cycle independent method • Shortened period to initiation of cancer treatment compared to standard cryopreservation methods • No need for a male partner/sperm donor	• Experimental method • Expensive • Technically demanding • Implantation and pregnancy rates significantly lower than with standard cryopreservation methods
GnRHa	• Simple administration • Non-invasive • No need for assisted reproductive technologies • No need to delay the start of chemotherapy • No need for a male partner/sperm donor	• Experimental method • Conflicting efficacy data • Slightly more grade 2 adverse events (hot flushes, headache)

PGD = preimplantation genetic diagnosis; OS = ovarian stimulation; .

CONCLUSION

BC recurrence is not increased with pregnancy after BC treatment. Unfortunately, the issue of fertility preservation is rarely addressed by young BC patients. But it is a discussion that all women of childbearing age diagnosed with early BC and those who like it should have.

A new study suggests that pregnancy after cancer treatment is safe for the fetus and provides long-term health benefits for patients. Fertility and fertility management should be prioritized in the multidisciplinary care of young women with breast cancer. This requires a multidisciplinary approach that includes collaboration between oncologists and medical specialists.

ACKNOWLEDGEMENT

I would like to thank the organization for its support.

Conflicts of interest:- None

REFERENCE

[1] Vuković P. Fertility Preservation in Young Women with Early-Stage Breast Cancer. Acta Clinica Croatica. 2019;

[2] Miro Kasum, Michael von Wolff, Franulić D, Ermin Čehić, Tajana Klepac-Pulanić, Slavko Orešković, et al. Fertility preservation options in breast cancer patients. PubMed. 2015 Jan 1;31(11):846–51.

[3] Hachem HE, Atallah D, Grynberg M. Fertility preservation in breast cancer patients. Future Oncology. 2014 Aug;10(10):1767–77.

[4] World Health Organization. Breast cancer [Internet]. World Health Organization. 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/breast-cancer

[5] Lambertini M, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, et al. Pregnancy After Breast Cancer: A Systematic Review and Meta-Analysis. Journal of Clinical Oncology. 2021 Oct 10;39(29):3293–305.

[6] Razeti MG, Soldato D, Arecco L, Levaggi A, Puglisi S, Solinas C, et al. Approaches to Fertility Preservation for Young Women With Breast Cancer. Clinical Breast Cancer [Internet]. 2023 Apr 1 [cited 2023 Apr 3];23(3):241–8. Available from: https://www.sciencedirect.com/science/article/pii/S152682092300006X

[7] Christinat A, Pagani O. Fertility after breast cancer. Maturitas. 2012 Nov;73(3):191–6.

[8] Rodgers RJ. Fertility preservation in breast cancer patients. Minerva Ginecologica. 2019 May;71(3).

[9] Sonigo C, Grynberg M, Bringer S, Sermondade N. Oncofertilité et cancer du sein. Bulletin du Cancer. 2019 Dec;106(12):S43–52.

[10] Decanter C, Robin G. Stratégies de préservation de la fertilité chez la femme jeune atteinte de cancer du sein ou d'hémopathie maligne. Gynécologie Obstétrique & Fertilité. 2013 Oct;41(10):597–600.

[11] Comtet M, Sonigo C, Valdelièvre C, Sermondade N, Christophe Sifer, Michaël Grynberg. Préservation de la fertilité dans le cancer du sein : où en est-on en 2014 ? Bulletin du cancer. 2015 May 1;102(5):443–53.

[12] Rousset-Jablonski C, Chevillon F, Dhedin N, Poirot C. [Fertility preservation in adolescents and young adults with cancer]. Bulletin du cancer [Internet]. 2016 Dec 1 [cited 2022 Dec 9];103(12):1019–34. Available from: https://europepmc.org/article/med/27817861

[13] Perachino M, Poggio F, Luca Arecco, Blondeaux E, Stefano Spinaci, Marrocco C, et al. Update on Pregnancy Following Breast Cancer Diagnosis and Treatment. The cancer journal. 2022 May 1;28(3):176–82.

[14] Lambertini M, Goldrat O, Clatot F, Demeestere I, Awada A. Controversies about fertility and pregnancy issues in young breast cancer patients: current state of the art. Current Opinion in Oncology. 2017 Jul;29(4):243–52.

[15] Pascale This. [Breast cancer and fertility: critical review, considerations and perspectives]. PubMed. 2008 Jan 1;95(1):17–25.

[16] Dunn L, Fox KR. Techniques for fertility preservation in patients with breast cancer. Current Opinion in Obstetrics & Gynecology. 2009 Feb;21(1):68–73.

[17] PARK M, DAVIDSON R, FOX K. Preservation of Fertility and the Impact of Subsequent Pregnancy in Patients With Premenopausal Breast Cancer. Seminars in Oncology. 2006 Dec;33(6):664–71.

[18] Castillo C, Camejo N. Impact of breast cancer treatments on fertility and the importance of timing for a fertility preservation intervention. Revista de Senología y Patología Mamaria. 2022 Oct;35(4):305–11.

[19] Charlotta Dabrosin. An overview of pregnancy and fertility issues in breast cancer patients. Annals of Medicine. 2015 Nov 5;47(8):673–8.

[20] Sellami I, Beau I, Sonigo C. Chemotherapy and female fertility. Annales d'Endocrinologie [Internet]. 2023 May 1 [cited 2024 Feb 21];84(3):382–7. Available from: https://www.sciencedirect.com/science/article/pii/S000342662300063X?via%3Dihub#bib0305.

[21] Spears N, Lopes F, Stefansdottir A, Rossi V, De Felici M, Anderson RA, et al. Ovarian damage from chemotherapy and current approaches to its protection. Human Reproduction Update. 2019 Oct 10;25(6):673–93.

[22] Chen YY, Wu KJ. Status and clinical response of fertility preservation in young patients with breast cancer. Chung-Hua Wai K'o Tsa Chih. 2021 Feb 1;59(2):104–8.

[23] Shah NM, Scott DM, Kandagatla P, Moravek MB, Cobain EF, Burness ML, et al. Young Women with Breast Cancer: Fertility Preservation Options and Management of Pregnancy-Associated Breast Cancer. Annals of Surgical Oncology. 2019 Jan 24;26(5):1214–24.

[24] Christian N, Gemignani ML. Issues with Fertility in Young Women with Breast Cancer. Current Oncology Reports. 2019 May 16;21(7).

[25] Tomasi-Cont N, Lambertini M, Hulsbosch S, Peccatori AF, Amant F. Strategies for fertility preservation in young early breast cancer patients. The Breast. 2014 Oct;23(5):503–10.

[26] Marhhom E, Cohen I. Fertility Preservation Options for Women With Malignancies. Obstetrical & Gynecological Survey. 2007 Jan;62(1):58–72.