



FERTILITY PRESERVATION IN BREAST CANCER PATIENTS

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KEYWORDS :

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women worldwide, with its incidence steadily increasing, particularly in developing nations like India. While breast cancer in Western countries primarily affects older women, India has been witnessing a concerning trend: a higher number of cases in younger women, specifically those under 50 years of age. This pattern raises important questions about the actual scale of the problem, as it not only affects the health and well-being of the individuals but also places significant socio-economic burdens on families and society.

The median age of breast cancer diagnosis in India is notably younger than in Western countries—49 years in India compared to 62 years in the West. However, this comparison must be made in the context of India's much younger population, with around 75% of the country's population being under 50 years old. Despite this demographic factor, the higher incidence of breast cancer in younger women is a cause for concern and deserves further attention, as it presents distinct challenges for healthcare systems and for the individuals affected.

Impact of Early Diagnosis on Young Women

The implications of a breast cancer diagnosis at a young age are far-reaching. Unlike older women, many young women diagnosed with breast cancer are still in the prime of their lives—managing young families, careers, and household responsibilities. A diagnosis of breast cancer during this stage of life can cause significant disruption to their personal, professional, and social lives.

1. Psychological and Emotional Consequences

A cancer diagnosis can be particularly traumatic for younger women, leading to feelings of shock, fear, and anxiety about the future. The emotional impact of undergoing treatment, including the potential loss of hair, mastectomy, and other physical changes, can severely affect self-esteem and body image. Additionally, concerns about fertility loss due to treatments such as chemotherapy further exacerbate emotional distress.

2. Fertility

Given the concern about fertility loss due to cancer treatment, fertility preservation options should be offered to young women. These options, such as egg freezing or ovarian tissue preservation, can give women the possibility of having children in the future, post-treatment.

3. Impact on Family and Social Roles

Breast cancer affects not just the individual but also her family. Younger women are often primary caregivers for children and elderly parents. A diagnosis of breast cancer creates a void in these caregiving roles, putting pressure on families both emotionally and financially. For women with young children, the thought of being diagnosed with a potentially life-threatening illness is particularly distressing, as they worry about the future well-being of their children.

4. Financial Strain

The financial burden of treating breast cancer is another significant challenge, especially for younger women. In India, where private healthcare is more common and the cost of cancer treatment is high, many patients struggle with out-of-pocket expenses. Despite some insurance schemes being available, the financial burden remains heavy for many, impacting families' financial stability for years. The inability to work during treatment only adds to this financial strain.

5. Career Disruption

Many women diagnosed with breast cancer are at a critical stage in their careers, which they may need to put on hold or abandon due to the demands of cancer treatments. Chemotherapy, radiation, and surgery often require extended time off, and some women may be unable to return to work due to the physical or emotional toll of the disease. This disruption can have long-term professional consequences, particularly in a country like India, where women already face challenges related to gender inequality in the workplace.

Given the growing number of young women diagnosed with breast cancer, early detection is key to improving outcomes. Early-stage breast cancer is much easier to treat and has a higher survival rate compared to more advanced stages. However, many young women in India do not seek medical attention for early signs of breast cancer, either due to a lack of awareness or underestimating the risk.

In India, there is a common misconception that breast cancer primarily affects older women, leading younger women to ignore symptoms such as lumps or changes in breast tissue. Additionally, there is a lack of widespread awareness about self-breast examination and other screening techniques like mammograms. As a result, many women only seek help once the cancer has advanced, making treatment more challenging and reducing the chances of a successful outcome.

To address this, public health initiatives should focus on educating women about the importance of early detection, including the benefits of regular breast self-exams and awareness of screening options like mammography and ultrasound. Such efforts should specifically target younger women and emphasize that breast cancer can affect anyone, regardless of age. Additionally, expanding access to these diagnostic tools can help improve early detection and reduce breast cancer mortality rates.

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Breast cancer is the most commonly diagnosed cancer among women globally, with over 2 million new cases annually. While advancements in early detection, treatment options, and survival rates are improving, the impact of cancer treatment on reproductive health has become a growing concern. Many women diagnosed with breast cancer are in their prime reproductive years and, consequently, may face the prospect of infertility due to the aggressive treatments commonly used in cancer care. Chemotherapy, radiotherapy, and certain hormonal therapies can significantly affect ovarian function,

leading to premature ovarian failure, infertility, or diminished ovarian reserve.

Fertility preservation (FP) has become an essential part of cancer care for women of reproductive age. This article explores the significance of fertility preservation in breast cancer patients, the options available, the challenges involved, and the current guidelines and recommendations to support patients in making informed decisions about their reproductive health.

The Impact of Breast Cancer Treatment on Fertility

Breast cancer treatments, particularly chemotherapy, are known to have detrimental effects on fertility. The ovaries, which are responsible for producing eggs and regulating hormonal cycles, are highly sensitive to the effects of chemotherapy and radiation. The impact on fertility can vary depending on several factors, including the patient's age, type of chemotherapy, and the cumulative dose received.

Chemotherapy: Chemotherapeutic agents, especially alkylating agents such as cyclophosphamide, are toxic to ovarian follicles. These drugs can reduce the ovarian reserve, accelerate follicular depletion, and impair ovarian function. The likelihood of fertility loss increases with the intensity of chemotherapy regimens, and older patients tend to have a lower chance of fertility preservation. For women over 35 years of age, the risk of infertility following chemotherapy is higher, as ovarian reserve naturally declines with age.

Radiation therapy: For patients who require radiation therapy, particularly those undergoing chest irradiation (as part of a treatment for breast cancer), the ovaries may be exposed to radiation, leading to permanent damage. Radiation doses greater than 20 Gy to the ovaries significantly increase the risk of infertility. In cases where the radiation field includes the pelvic region, ovarian damage is more pronounced.

Hormonal therapies: Many breast cancers are estrogen receptor-positive, and treatment often includes hormonal therapies such as tamoxifen or aromatase inhibitors. While these medications do not directly affect ovarian function, they can delay the return of normal ovarian function after chemotherapy or radiation. Tamoxifen, for example, can increase the risk of ovarian cysts and interfere with fertility.

The cumulative effect of these treatments is not just physical but also psychological. The possibility of losing fertility can add an additional layer of distress for women who are already coping with the emotional and physical toll of cancer treatment.

Fertility Preservation Options for Breast Cancer Patients

Several fertility preservation options are available for women diagnosed with breast cancer. The choice of method depends on various factors, including the patient's age, the type of cancer, the planned treatment regimen, and how much time the patient has before beginning cancer treatment.

1. Oocyte Cryopreservation (Egg Freezing)

Oocyte cryopreservation is one of the most widely used fertility preservation techniques for women with breast cancer. It involves stimulating the ovaries to produce multiple eggs, which are then harvested and frozen for future use. The patient can later undergo in vitro fertilization (IVF) to use the frozen eggs when she is ready to conceive.

Process:

- **Ovarian Stimulation:** The process typically involves administering hormonal injections for about 10-14 days to stimulate the ovaries to produce multiple eggs.

- **Egg Retrieval:** Once the eggs are mature, they are retrieved via a minor surgical procedure under sedation.
- **Freezing:** The mature eggs are frozen and stored for future use.

Timing And Challenges:

- This process generally takes 2-3 weeks, which can be challenging for breast cancer patients who need to start treatment quickly. However, for those with sufficient time, egg retrieval is a viable option.
- The success of oocyte cryopreservation depends on the woman's age and ovarian reserve. Younger women (under 35) tend to have better outcomes with egg freezing due to higher egg quality and quantity.

2. Embryo Cryopreservation

For women in a stable relationship or those who are open to using sperm from a partner or donor, embryo cryopreservation is another effective fertility preservation method. In this process, eggs are harvested, fertilized with sperm in a laboratory, and the resulting embryos are frozen for future use.

Process:

- Similar to oocyte cryopreservation, the woman undergoes ovarian stimulation to produce eggs.
- After egg retrieval, the eggs are fertilized with sperm, and viable embryos are frozen.

Challenges:

- The main drawback of embryo cryopreservation is the need for a sperm donor or partner involvement. It may not be a feasible option for single women or those who are not ready to conceive at the time of their diagnosis.
- Success rates for embryo freezing are generally higher than for egg freezing, as embryos are often more robust than eggs after thawing.

3. Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation involves the removal and freezing of ovarian tissue, which can later be reimplanted to restore fertility. This option is typically used in cases where ovarian stimulation for egg retrieval is not possible or when there is limited time before cancer treatment begins.

Process:

- A small portion of ovarian tissue is surgically removed and frozen. This tissue contains immature eggs.
- In the future, the tissue can be reimplanted into the woman's ovary or outside the body to potentially restore fertility.

Challenges:

- Ovarian tissue cryopreservation is still considered experimental and is less widely practiced compared to oocyte or embryo cryopreservation. The reimplantation of ovarian tissue is not always successful and can be associated with the risk of reintroducing cancer cells into the body.
- However, it has the advantage of being a quicker procedure, often requiring only a few days.

4. Ovarian Suppression with GnRH Agonists

For some women, ovarian suppression during chemotherapy can help preserve ovarian function by temporarily halting ovarian activity. Gonadotropin-releasing hormone (GnRH) agonists, such as leuporelin, can be used to suppress ovarian function and reduce the likelihood of chemotherapy-induced ovarian damage.

Process:

- GnRH agonists are administered as injections before, during, and after chemotherapy treatment to prevent

ovarian function during this period.

Challenges:

- While ovarian suppression may help reduce the risk of ovarian failure, it does not guarantee fertility preservation. The effectiveness of GnRH agonists in preventing infertility is still debated, and success rates are lower than those of egg or embryo freezing.

5. Ovarian Transposition

For women undergoing pelvic radiation therapy, ovarian transposition involves surgically moving the ovaries outside the radiation field to reduce the risk of ovarian damage. This procedure is typically performed in conjunction with other fertility preservation methods.

Process:

- The ovaries are repositioned surgically, often through laparoscopy, to a site where they are less likely to be affected by radiation.

Challenges:

- While ovarian transposition can reduce radiation damage, it does not entirely eliminate the risk of infertility. The success of this procedure is also influenced by the extent of radiation and the individual patient's anatomy.

Psychological Considerations and Counseling

The decision to pursue fertility preservation is not an easy one. Breast cancer patients often face complex emotions regarding their diagnosis, treatment, and future fertility. For many, the idea of delaying cancer treatment to pursue fertility preservation can be stressful and overwhelming.

Psychological counseling plays a critical role in helping patients navigate these decisions. Healthcare providers should ensure that women are well-informed about the risks to fertility posed by cancer treatments and the various fertility preservation options available. Counseling should include discussions about the emotional impact of cancer and fertility loss, potential outcomes, and the logistics of fertility preservation procedures.

Patients should also be made aware of the financial and time-related aspects of fertility preservation, as not all options may be covered by insurance, and some procedures may require significant out-of-pocket costs. Furthermore, patients should be informed about the success rates and limitations of each fertility preservation method, as well as the possibility that some methods may not lead to successful pregnancy outcomes in the future.

Fertility Preservation in Breast Cancer Patients Undergoing Chemotherapy

Chemotherapy-induced amenorrhea is a well-known complication for premenopausal women undergoing chemotherapy, leading to the loss of ovarian function and, in turn, fertility. This issue is particularly crucial for younger women with breast cancer who either have not yet had children or wish to have more children after completing their treatment. Fertility preservation during chemotherapy is therefore essential for these patients, and several strategies have been developed to reduce the risk of premature ovarian failure (POF) and increase the likelihood of conception after cancer treatment.

The Role of Gonadotropin-Releasing Hormone Analogues (GnRHa) in Fertility Preservation

One of the most effective strategies for preserving ovarian function during chemotherapy is the use of gonadotropin-releasing hormone analogues (GnRHa). These medications work by temporarily suppressing ovarian function, potentially

shielding the ovaries from the toxic effects of chemotherapy. The benefits of combining GnRHa with chemotherapy have been explored in various clinical trials, yielding encouraging results.

The **Preservation of Ovarian Function Study (POEMS)**, a randomized trial involving 257 premenopausal women with early breast cancer, explored the use of the GnRHa goserelin alongside chemotherapy versus chemotherapy alone in women with hormone receptor-negative (HR-) breast cancer. The findings were promising, showing that women who received both chemotherapy and goserelin had significantly better outcomes related to ovarian function and fertility. Specifically, ovarian failure occurred in just 8% of women in the goserelin group, compared to 22% in the chemotherapy-only group (Odds Ratio [OR] 0.30; 95% CI 0.09–0.97; $p = 0.04$). Additionally, pregnancy rates were higher in the goserelin group (21% vs. 11%; $p = 0.03$).

Furthermore, the study also showed a **significant improvement in disease-free survival (DFS) and overall survival (OS)** among those who used goserelin in combination with chemotherapy. DFS showed a statistically significant benefit ($p = 0.04$), and OS also improved ($p = 0.05$). These results suggest that GnRHa not only helps preserve ovarian function but may also improve long-term cancer outcomes.

Pooled Analysis of Ovarian Suppression Trials

A more recent pooled analysis of five randomized trials further supports the use of GnRHa for fertility preservation in breast cancer patients. This analysis included data from 873 premenopausal women with early-stage breast cancer, including both HR-negative and some HR-positive cases. The results indicated that ovarian suppression with GnRHa during chemotherapy significantly reduced the risk of chemotherapy-induced premature ovarian insufficiency (POI). The incidence of POI was 14.1% in the GnRHa group, compared to 30.9% in the chemotherapy-alone group (OR 0.38, 95% CI 0.26–0.57, $p < 0.001$). The GnRHa group also had a higher rate of successful conception (10.3% vs. 5.5%, Incidence Rate Ratio [IRR] 1.83, 95% CI 1.06–3.15, $p = 0.03$).

Despite the positive effects on ovarian function and fertility, the pooled analysis found that GnRHa did not impact DFS or OS, suggesting that while GnRHa improves fertility outcomes, it does not appear to influence long-term cancer survival.

Fertility Preservation in Triple-Negative Breast Cancer (TNBC)

The type of breast cancer plays a crucial role in determining fertility preservation strategies. For women diagnosed with **triple-negative breast cancer (TNBC)**, a more aggressive form of the disease with a higher risk of early relapse, it is generally recommended to wait at least two years after completing adjuvant therapy before attempting pregnancy. This waiting period allows for the risk of early relapse, which is highest within the first two years, to decrease before pregnancy is considered.

Fertility Considerations in Hormone Receptor-Positive (HR+) Breast Cancer

For **hormone receptor-positive (HR+)** breast cancer, which generally carries a lower risk of recurrence and offers a better prognosis, fertility preservation and pregnancy planning can be more complex due to the hormonal therapies used to prevent cancer recurrence, such as **tamoxifen** or ovarian suppression. These treatments can interfere with the ability to conceive, making pregnancy during or immediately after treatment challenging.

In women with HR+ breast cancer, pregnancy is typically not

recommended while undergoing hormonal therapy, particularly when tamoxifen is used. Tamoxifen, a selective estrogen receptor modulator (SERM), can negatively impact fetal development, and pregnancy during tamoxifen treatment may increase the risk of cancer recurrence.

After chemotherapy and adjuvant hormonal treatment, the timing of pregnancy depends on the specifics of the therapy regimen:

- For women treated with **tamoxifen** and ovarian suppression for five years (as per the **SOFT** and **TEXT** trials), pregnancy is generally not advised during treatment. These trials demonstrated that ovarian suppression combined with tamoxifen reduced recurrence risk but complicated fertility.
- In cases where tamoxifen alone is used, the **ATLAS** trial suggests extending tamoxifen treatment to **10 years** for premenopausal women, which further complicates pregnancy planning during or immediately after treatment.

As such, pregnancy after treatment for HR+ breast cancer requires careful planning and may involve significant delays after treatment.

Investigating Tamoxifen's Effect on Fertility

The effect of **tamoxifen** on fertility preservation is still not fully understood and requires further research. Tamoxifen is a critical part of therapy for HR+ breast cancer, significantly reducing the risk of recurrence, but its impact on fertility has yet to be fully explored. The ongoing **POSITIVE** study, which is part of the **BIG (Breast International Group)** initiative, seeks to answer whether interrupting tamoxifen treatment for pregnancy—by allowing a three-month drug-free washout period—has any adverse effects on cancer outcomes. The study will help determine if it is safe to stop tamoxifen temporarily for pregnancy and whether such a break might negatively affect long-term survival outcomes. Since HR+ cancers generally have a better prognosis, any potential harm from discontinuing tamoxifen for pregnancy would be unacceptable in clinical practice.

CONCLUSION

Fertility preservation during chemotherapy is a key consideration for younger women undergoing breast cancer treatment who wish to have children in the future. The use of gonadotropin-releasing hormone analogues (GnRHa) alongside chemotherapy has proven effective in preserving ovarian function and improving fertility outcomes, with studies showing better pregnancy rates and a reduced risk of ovarian failure. While GnRHa improves fertility, it does not appear to affect long-term cancer survival.

For women with triple-negative breast cancer (TNBC), it is advised to wait two years after completing treatment before attempting conception to minimize the risk of cancer recurrence. In the case of hormone receptor-positive (HR+) breast cancer, the timing of pregnancy is more complex due to the use of hormonal therapies like tamoxifen. In these patients, pregnancy is generally not recommended during ongoing treatment, and the timing of conception may need to be delayed for several years after therapy.

Overall, fertility preservation strategies must be tailored to the individual's cancer type, treatment plan, and fertility goals, with a personalized approach being crucial for optimizing both cancer outcomes and reproductive health.