Breast cancer and fertility preservation modalities

Surekha Tayade

Department of Obstetrics and Gynecology, Mahatma Gandhi Institute of Medical Sciences, Sewagram, Wardha, Maharashtra, India

*Correspondence Info:
Dr. Surekha Tayade
Professor,
Department of Obstetrics and Gynecology,
Mahatma Gandhi Institute of Medical Sciences,
Sewagram, Wardha, Maharashtra, India
E-mail: surekhatayademgims@yahoo.co.in

Abstract
Carcinoma of the breast is on constant rise even in developing countries. Adjuvant chemotherapy specially with alkylating agents such as cyclophosphamide is gonadotoxic and markedly accelerates the rate of depletion of ovarian follicles. Even women who regain menses after cytotoxic chemotherapy ± antihormonal therapy are likely to have undergone significant follicle depletion and reproductive aging of 10 years or more. Although loss of fertility is an important issue for young cancer survivors, there is often little or no discussion about fertility preservation before initiation of adjuvant therapy. Infertility specialists should aim for greater familiarity with prognosis and effects of different types of adjuvant therapy for carcinoma breast. Fertility preservation options such cryopreservation of embryos, oocytes, and ovarian tissue on the part of oncologists should be discussed with the suffering woman. With reduction in mortality from breast cancer, fertility preservation has become a major issue for young women developing breast cancer. Every young woman who is likely to undergo gonadotoxic cancer treatment should be counselled about the effects of therapy and options available to her to increase the likelihood of childbearing after cancer treatment.

Keywords: Breast Cancer, Fertility Preservation

1. Introduction
Over past 25 years, breast cancer incidence has risen globally, with the highest rates reported in westernized countries. Reasons for this trend include change in reproductive patterns, increased screening facilities and dietary changes. In Asian and Pacific Islander women the incidence has continued to increase at 1.5% per year, they are still significantly lower than the rates in white women. In a recent study conducted at All India Institute of Medical Sciences (AIIMS) it has been found that nearly one in 10 women, who visited the hospital between 2000 and 2011 afflicted with the disease, was younger than 35 years.1 Reductions in death rates from breast cancer largely reflect the early detection with the use of screening mammography and more effective multiagent adjuvant chemotherapy regimens.2 Unfortunately, a considerable number of patients feel that their cancer physicians do not sufficiently inform them about the impact of the cancer therapy on fertility and the options to preserve it.3 It is important to provide the most up-to-date and accurate information on the adverse effects of cancer treatments on fertility to young cancer patients whose concerns about their future fertility may shape their treatments.

2. Effects of chemotherapy on ovarian functions
Any toxic insult that targets the primordial follicles will result in a diminishment or total exhaustion of the ovarian reserve. Gonadal toxicity associated with the use of chemotherapy agents varies depending on the age of the patient and the type and cumulative dose of the cancer drugs.4 Chemotherapy agents particularly of the alkylating category (e.g., cyclophosphamide) are more cytotoxic and appear to exert their gonadotoxic effects via follicular loss in the human ovary by activating apoptotic machinery in both oocyte and enclosing granulosa cells as revealed by a human ovarian xenograft model.5 Younger patients (<35 years of age) have higher primordial follicle counts in their ovaries, and therefore they are more likely to retain some residual ovarian function post exposure to toxic insult than do older patients (>35 years of age). Because alkylating agents are not cell cycle specific, they are able to damage cells at different stages of the cell cycle including resting primordial follicles, resulting in a more widespread effect. Resting primordial follicles appear to be more sensitive to cyclophosphamide-induced gonadotoxicity than growing follicles at the primary stage and beyond.6 By contrast, chemotherapy agents that act in a cell cycle–specific manner, such as 5-fluorouracil and methotrexate, are less harmful for primordial follicles. Most of the published clinical studies used amenorrhea as a surrogate marker of infertility occurring during and after chemotherapy administration.6 Anthracycline-based regimens are less toxic than combinations containing an alkylating agent; therefore they are associated with a lower risk of permanent ovarian failure.

3. Gonadotropin-Releasing Hormone agonists as an adjuvant hormonal therapy in breast cancer treatment
Hormonal manipulation has been used for over 100 years to treat breast cancer. Ovarian ablation suppression and tamoxifen are currently accepted adjuvant endocrine therapies for premenopausal breast cancer. Methods of permanently ablatting ovarian function include surgical oophorectomy and radiation-induced ovarian failure; medical castration with luteinizing hormone-releasing hormone analogues is a reversible approach. Adjuvant chemotherapy frequently results in permanent amenorrhea and thus represents an indirect form of ovarian ablation. These agents include LHRH agonists and antagonists, both of which decrease ovarian estradiol production indirectly by impinging on the hypothalamic-pituitary-ovarian axis which causes infertility by ovarian failure.7,8 Ultimately all these chemotherapy drugs impair ovarian function and which further impairs fertility.

4. Effect of radiotherapy on fertility
Ovarian follicles are sensitive to damage from ionizing radiation, which may result in atrophy of the organ and reduced primordial follicle reserve. Pelvic radiation also exerts an effect on the uterus, causing changes in both the musculature and blood flow, which can lead to endometrial damage and a higher rate of obstetrical complications.9,10
5. Fertility preservation options in breast cancer patients

The reduction in ovarian reserve in breast cancer patients with the use of adjuvant/neoadjuvant chemotherapy is compounded by the need to delay pregnancy while undergoing hormonal treatment (tamoxifen with or without GnRH agonists) for ≥5 years in ER-positive diseases. The 5-year survival in all stages of breast cancer has reached 89% in the United States.11 As a result of the high survival rates and the increased emphasis on the quality of the life of the survivor, fertility preservation is gaining importance. As stressed in the recent clinical guidelines by the American Society of Clinical Oncology, all cancer patients with interest in future fertility should be referred for consideration of fertility preservation.12 Current fertility preservation options vary from well-established to experimental ovarian tissue and oocyte cryopreservation. Embryo cryopreservation has been a proven method to preserve fertility. However, in nearly all cancers, with the possible exception of breast cancer, chemotherapy is initiated soon after diagnosis. Because preparation and stimulation for oocyte retrieval usually requires 2 to 3 weeks or longer, it is generally not feasible to freeze embryos from an adult female cancer patient for potential future use. Even in breast cancer patients, most would not be candidates for oocyte or embryo freezing due to concerns that high oestrogen levels might have detrimental effects on the primary tumour.

i) Embryo Freezing

IVF and embryo cryopreservation is the most established fertility preservation technique for patients with partners and a sufficient amount of time before cancer treatment. It is not technically challenging and has been used for nearly two decades to store unused embryos from IVF and embryo transfer cycles. Although isolated pregnancies from egg freezing have been reported for many years, it is only recently that egg freezing can be performed with reproducible success resulting in reasonable survival rates (50-70%), fertilization rates (50-60%) and pregnancy rates approaching those obtained with fresh eggs. Embryo freezing is a well established procedure in IVF laboratories, and generally results in reasonable success rates. The national average live birth rates for women under 38 years of age is 21% (ASRM/SART Report, 2000).

ii) Oocyte Freezing

Cryopreservation of oocytes is one of the emerging options suitable for young adolescents, women without partners, or women who do not wish to have their oocytes fertilized by sperm from a partner or anonymous donor. The first live birth after successful oocyte cryopreservation in a human was reported in 1986.13 Unfortunately, it is still associated with lower pregnancy rates in contrast with more encouraging results with IVF and embryo freezing due to some technical challenges encountered during the freeze-thaw process and the in vitro maturation of immature oocytes. Even though oocyte cryopreservation is still considered experimental, the technology is improving, and our recent meta-analysis showed that live-birth rates per oocyte thawed were 1.9% and 2.0% for slow freezing and vitrification, respectively, before June 2005. Live-birth rates per injected oocyte and ET, respectively, were 3.4% and 21.6% for slow freezing and were 6.6% and 60.4% for IVF with unfrozen oocytes. These success rates appear to be even higher with a more recent oocyte freezing technique, vitrification, but the data are limited on the latter live-birth rate for per injected oocyte is 3.4% for slow frozen oocytes.14 It is thought that mature oocytes are more susceptible to damage during the first meiotic division due to the volume ratio, low metabolic rate, and the absence of zona pellucida make primordial follicles less susceptible to damage from freezing15,16. One of the major concerns in transplanting ovarian tissue from cancer patients is the risk for reseeding cancer cells. Previous studies showed that most of the occult metastases belong to the infiltrating lobular histological subtype, which constitutes <15% of all breast cancers and more commonly occurs in postmenopausal women.17 It should also be remembered that patients with BRCA-1 and BRCA-2 genes are at a higher risk for harbouring occult ovarian cancer. To date no cancer recurrence in ovarian grafts has been reported in the medical literature.

6. Conclusion

Several options are available to preserve fertility in breast cancer patients undergoing chemotherapy. The most appropriate option should be determined considering several factors, including the patient's age, the type of adjuvant treatment, the time available before chemotherapy, and the length of delay to start fertility preservation. The most chemotherapy-sensitive oocyte cryopreservation is the method of choice with the highest success rate. Oocyte cryopreservation is considered in single women who do not wish to use donor sperm. Both approaches require 2 weeks of ovarian stimulation beginning with the onset of the patient's menstrual cycle. Recently developed ovarian stimulation protocol with aromatase inhibitor letrozole appears to provide a safe ovarian stimulation. When a breast cancer patient does not have sufficient time to undergo ovarian stimulation, ovarian cryopreservation can be offered as the last resort. The benefit of ovarian protection by GnRH agonist treatment is unproven.

References