Original Article

Practical consensus recommendations on fertility preservation in patients with breast cancer

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Abstract

Young women diagnosed with cancer today have a greater chance of long-term survival than ever before. Successful survivorship for this group of patients includes maintaining a high quality of life after a cancer diagnosis and treatment; however, lifesaving treatments such as chemotherapy, radiation, and surgery can impact survivors by impairing reproductive and endocrine health. Expert oncologists along with reproductive medicine specialists discuss fertility preservation options in this chapter since fertility preservation is becoming a priority for young women with breast cancer. This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at these practical consensus recommendations for the benefit of community oncologists.

Key words: Embryo cryopreservation, gonadotrophin ovarian tissue, letrozon, oocyte, ovarian function suppression

Introduction

Breast cancer is the most common cancer type in young women of reproductive age: approximately 7% of breast cancer cases are diagnosed in women ≤40 years and this corresponds to more than 40% of all malignancies diagnosed in this age group.[1]

The available anticancer treatments (surgery, radiotherapy, chemotherapy, endocrine therapy and biologic therapy) have improved both disease-free survival (DFS) and overall survival (OS) in young breast cancer patients but they can cause acute and chronic side effects, such as a negative impact on gonadal function that may lead to impaired fertility.[2] The fertility issues in these patients have acquired a growing importance in the last few years not only because of the improved prognosis of cancer patients but also due to the tendency of delaying child-bearing in India as well as in western countries, so that many women can be childlessor may want to enlarge their family at the time of breast cancer diagnosis.[3]

Expert group of oncologist and reproductive medicine specialists' met in the oncology update-X-2017 meet, to discuss on available strategies, standard and experimental, for fertility preservation in young breast cancer patients.

The update in oncology-X-2017 was organized by Sir Ganga Ram Hospital group to discuss and arrive at a consensus statement to provide community oncologists practical guidelines for challenging common case scenarios in Breast Cancer. This chapter discusses the consensus statements arrived at by the expert group. While the discussions takes the scenario as exists in India as a representative country with limited resources, the final manuscript is applicable globally.[4,5] The discussion was based on domain expertise of the National as well as international faculty, published evidence and practical experience in real life management of breast cancer patients. Opinion of the 250 oncologist including medical oncologist, radiation oncologist, surgical oncologist, molecular oncologist and radiologist present in the update in oncology-X-2017 was taken into consideration by the expert panel.

The expert group was chaired by Dr S. K. Verma and Dr Purvish Parikh whereas the discussions were moderated by Dr Abha Majumdar and Dr Jyoti Bajpai. The core expert group consisted of Dr. Ruma Satwik, Dr. Nitesh Rohtagi, Dr. Veena Jain, Dr. Mukesh Nagar, Dr. Deni Gupta, Dr. Rajeev Agarwal and Dr. Shweta Mittal. Consensus answers were used as the basis of formulating the consensus statement providing community oncologists with ready-to-use practical recommendations. The survey answers were used as the basis for formulating the consensus statement so that community oncologists have a ready-to-use Fertility Prevention Recommendations in Breast cancer patients.

As part of the background work, the best existing evidence was compiled and provided to the expert group panel members for review in preparation of the expert group meeting.[6-8] The national and international experts invited to this meeting were also provided the data on the voting by the audience delegates from the update in oncology-X-2017. Members of the panel were also allowed to share their personal experiences, make comments and record dissent while voting for the consensus statements. Total of four broad question categories were part of the expert group discussions [Table 1].

This manuscript is the outcome of the expert group consensus arrived at on Sunday, May 21st, 2017.

The main factors that should be considered for the choice between the available fertility preservation techniques for young women candidates for anticancer therapies are: patient's age and ovarian reserve, type of anticancer therapy planned, availability of a partner at the time of diagnosis, the time available before the initiation of anticancer treatments, and the possibility that

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Table 1: Question categories addressed by the update in oncology-X-2017

Broad question title
Case - A 25-year-old premenopausal lady diagnosed with infiltrating duct carcinoma left breast. She undergoes modified radical mastectomy. HPE results - T1N0M0. ER positive, PR positive, HER 2/neu negative. She needs adjuvant chemotherapy followed by hormonal therapy. She is desirous of second pregnancy
Question I - Will you go for controlled ovarian stimulation before chemotherapy?
Question II - What will you use for controlled ovarian stimulation?
Question III - What are the available options?
Update in oncology-X-2017

ER=Estrogen receptor, PR=Progesterone receptor, HER 2=Human epidermal growth factor receptor 2

cancer has metastasized to the ovaries.[9] Irrespective of the pros and cons of the different strategies, every young breast cancer patient who is candidate for anticancer therapies (particularly chemotherapy and endocrine therapy) should have access to fertility counseling to receive information about how to preserve fertility while on such treatments.[9] Fertility counseling should include discussion about available strategies to preserve fertility which are appropriate for that particular patient including points like techniques, timing, possible complications, success rates, costs and ethical implications.[10]

Effect of Radiation, Cytotoxic Chemotherapy, and Hormonal Therapy on Fertility

Radiation

Ovarian follicles are sensitive to damage from ionizing radiation, which may result inatrophy of the organ and reduced primordial follicle reserve.[11] While radiation therapy iscommonly a part of breast cancer treatment, the ovaries are typically spared significanttoxicity from this modality. The fertility threat caused by radiation is related to several factors including patient age, dose and trajectory of radiation, and use of concurrent chemotherapy.[12] The total dose of radiation to the pelvis needed to increase the risk of premature ovarian failure (POF) is estimated at 20 Gy, with failure occurring at lower doses in women35 years of age and older.[13,14] 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.[15] For patients receiving radiation treatment directed to the abdomen and pelvis, the risk of these complications is most pronounced when conception occurs in less than a year after radiation therapy has been completed.[16] Of the 50 Gy delivered to the breast during standard whole-breast radiotherapy, only2.1–7.6 cGy reaches the uterus through internal scatter, which is considerably less than the dose needed to induce POF or cause detrimental effects to the uterus.[17,18] Because of this small but detectable radiation dose to the pelvis, pregnancy or harvesting of eggs for *in vitro* fertilization (IVF) should not occur during radiotherapy for breast cancer, but should be possible after treatment is completed.

Cytotoxic chemotherapies

The impact of chemotherapy for breast cancer on fertility is significantly affected by the patient's baseline ovarian reserve. Patients should undergo an initial fertility work-up which should include an assessment of ovarian function through blood testing [basal follicle stimulating hormone (FSH), leutenizing hormone (LH), and estradiol]. Further, ultrasound guided estimation of ovarian volume and antral follicle count can be used to estimateovarian reserve.[19,20] Additionally, there is evidence that anti-Mullerian hormone (AMH) levels may correlate well with antral follicle count and may be more consistent markers of ovarian reserve.[21,22] Knowledge of the patient's baseline fertility status prior to treatment will enable counseling specific to the patient's treatment-related fertility threat and help to guide decision-making regarding the patient's candidacy for any fertility sparing options.

Patients requiring therapy with an alkylating agent, such as cyclophosphamide, if osfamide and platinum compounds have the highest risk of ovarian toxicity and menopause as a consequence of their treatment. In ananalysis of more than 2500 patients treated for breast cancer with multiple cycles of alkylating agents, such as cyclophosphamide/methotrexate/5-fluorouracil (CMF), the risk of a menorrhea was 40% for women ≤40 years of age, and 76% for women 41 years of age and older.[23] Treatment with an anthracycline-based regimen, such as doxorubicin/cyclophosphamide (AC), utilizes an anthracycline along with a lower dose of the alkylatingagent, and thus is associated with a lower risk of POF.[24] The risk associated with the addition of a taxane (T) is less well defined. In a study by Tham *et al*., the incidence of permanent amenorrhea with AC followed by T vs AC alone was increased in women over 40 years of age. Younger women often resumed menstruation several months after treatment had completed, which suggests that it is age of exposure rather than cumulative dose which is the strongest predictors of chemotherapy induced amenorrhea.[19,25] The effects of trastuzumab and bevacizumab, or newer epothilone agents such as ixabepilone, on fertility have not yet been rigorously evaluated.

Hormonal therapies

The selective estrogen receptor modulator (SERM)' tamoxifen, has not typically been associated with cessation of ovulation. Furthermore, at higher doses, tamoxifen can act like the related compound clomiphene, a fertility drug, to stimulate ovulation. Despite this, tamoxifen may cause irregular or absent menses in some patients when given after gonadotoxic chemotherapy or when used alone. While there is a 15% decrease in the odds of continuing menstrual cycles after the first 1–2 years of therapy, tamoxifen-induced amenorrhea is thought to be reversible and temporary.[26,27]

Tamoxifen use during pregnancy or while attempting to conceive is discouraged, as it has been associated with abnormalities in the development and function of the fetal reproductive tract and an increased risk of mammary tumors in the offspring of animal models.[28,29]

There are sparse reports in literature regarding human pregnancy and tamoxifen, but the general opinion is that tamoxifen should not be taken during pregnancy or while attemptingto conceive.[30] Though there are no prospective studies or class 1 data, indirect evidence suggests that anti-estrogen therapy with tamoxifen can be delayed to allow for pregnancy after surgery and radiotherapy for breast cancer have been completed, without negatively influencing patient outcomes.[31,32]

Current Strategies for Fertility Preservation in the Breast Cancer Patient

Ovarian suppression during chemotherapy

For patients requiring chemotherapy, suppression of ovarian function (OFS) through manipulation of the hypothalamic–pituitary–gonadal axis concurrent with systemic therapy has been postulated for preservation of ovarian function.[33] Destruction of follicles engaged in the maturation pathway by chemotherapeutic agents causes an increase in FSH secretion through a loss of negative feedback. This increase in FSH causes additional follicles to enter the maturation pathway, exposing them to the effects of cytotoxic therapy. This cycle can theoretically be interrupted by the administration of a gonadotropin-releasing hormone (GnRH) agonist that achieves reversible arrest of follicle mobilization and maturation preventing an increase in FSH concentration.[34]

There is some concern regarding the impact of GnRH agonists on the efficacy of chemotherapy based on evidence that tamoxifen administered simultaneously with chemotherapy may decrease the effect of cytotoxic therapy.[35] This effect may be caused by a tamoxifen-mediated arrest of cancer cell proliferation which then decreases tumor cell sensitivity to chemotherapy. A similar effect may thus be seen with estrogen suppression viaGnRH agonists.[36]

For these reasons till now, the role of temporary OFS with GNRH analogs during chemotherapy as astrategy to preserve ovarian function and fertility in premenopausal early breast cancer patients remains highly controversial. This option is considered experimental by the ASCO and ESMO guidelines on fertility preservation in cancer patients. However, a pooled analysis which included individual patient data from 5 trials (PROMISE-GIM6, POEMS/SWOG S0230, Anglo Celtic Group OPTION, GBG-37 ZORO, Moffitt-led trial) in which premenopausal women with early breast cancer were randomized to receive (neo) adjuvant chemotherapy alone or with concurrent administration of GnRHa. A total of 873 patients from 5 randomized trials were included.

POI rate was 14.1% in the GnRHa group and 30.9% in the control group (adjusted OR 0.38; 95% CI 0.26-0.57; $P < 0.001$). The incidence of 1-year amenorrhea was 36.8% in the GnRHa group and 40.4% in the control group (adjusted OR 0.92; 95% CI0.66-1.28; $P = 0.623$). The incidence of 2-year amenorrhea was 18.2% in the GnRHa group and 30.0% in the control group (adjusted OR 0.51; 95% CI 0.31-0.85; $P = 0.009$). A total of 37 patients had at least one posttreatment pregnancy in the GnRHa group and 20 in the control group (IRR 1.83; 95% CI 1.06-3.15; $P = 0.030$). There were no significant differences in DFS (adjusted HR 1.01; 95% CI 0.72-1.42; $P = 0.999$) or OS (adjusted HR 0.67; 95% CI0.42-1.06; $P = 0.083$) between the GnRHa and control groups.

Subgroup analyses of both efficacy and safety endpoints according to age of the patients, hormone receptor status, type and duration of chemotherapy will be presented at the conference.

This study pro vides level 1A of evidence for the efficacy and safety of temporary ovarian suppression with GnRHa during chemotherapy in premenopausal early breast cancer patients. Given the findings of this pooled analysis, temporary ovarian suppression with GnRHa during chemotherapy should be considered as a new standard option to reduce the likelihood of chemotherapy-induced POF and possibly improve future fertility in premenopausal early breast cancer patients [Tables 2-4].[37]

Embryo cryopreservation

Embryo cryopreservation following *in vitro* fertilization (IVF) is the most widely available and well-established fertility preservation strategy today[38] According to the Society for Assisted Reproductive Technologies, data from 2010indicate that 38% of frozen–thawed embryo transfers resulted in live births to women younger than 35 years (average 1.9 embryos transferred).[39] Embryo cryopreservation is a common fertility preservation option for women with partner's or sperm donors who can contribute sperm for egg fertilization. However, the additional decision making required to select donor sperm may be an insurmountable barrier, emotionally and logistically, for some women in the immediate period after a cancer diagnosis.

The ovarian hyper stimulation required for *in vivo* follicle development prior to retrieval may require a slight delay of cancer treatment, from 2 to 4 weeks; this delay may not be possible for women with certain cancers. Furthermore, ovarian stimulation can only be used in postpubertal women. In addition, patients must to be physically evaluated and determined to be eligible to undergo ovarian stimulation.

Oocyte cryopreservation

For women who are not in a position to create embryos, particularly young women who do not have a partner or a source of donor sperm, the option to cryopreserve unfertilized oocytes provides an alternative for preserving future fertility. Patients undergo a cycle of hormone stimulation using the same regimens used in traditional IVF, and oocytes are retrieved and then cyropreserved for use at a later date. Though this technique has been available since 1986, initial results with oocyte cryopreservation and thawing were poor dueto problems with intracellular ice formation and the osmotic effect on the oocyte. Only 100live births resulting from this technique had been reported before 2004.[40] Since then, advances have been made in oocyte cryopreservation techniques. Preservation by the ultrafastfreezing method known as vitrification, avoids ice crystal formation, and modificationsin the freezing solution such as higher sucrose concentration and the addition of stabilizing

Table 2: Question 1 (I) - Will you recommend controlled ovarian stimulation before chemotherapy?

Options (%)	Yes	No
Percentage of polled oncologists	100	0

Expert group consensus: Controlled ovarian stimulation can be done before chemotherapyunder the age of 35–40 years

Table 3: Question 1 (II) - What will you use for controlled ovarian stimulation?

Options (%)	Gonadotropins alone	Letrozole with gonadotropin	Tamoxifen with gonadotropin	All of the above
Percentage of polled oncologists	71.4	28.6	0	0

Expert group consensus: Letrozole with gonadotropin is recommended for controlled ovarian stimulation because the estrogen levels is likely to be lower with this combination

Table 4: Question 1 (III) - What are the available options?

Options (%)	Oocyte preservation	Embryo preservation	Both
Percentage of polled oncologists	50	25	25

Expert group consensus: If partner is available embryo preservation is preferred. If partner is not available oocyte preservation is the recommended option

substances such as proteins and anti-oxidants, have improved oocyte survival and pregnancyrates.[41] Recently, a birth rate of 5–6% per thawed oocyte has been described, with over 500 babies reportedly born using these methods prior to 2010.[42] American society for reproductive medicine (ASRM) has removed the experimental tag associated with this technique in their guidelines issued in 2013.[43]

Ovarian tissue cryopreservation

A fertility preservation technique that does not require exposure to an elevated serum hormonal milieu is ovarian tissue retrieval.[44] Criteria used to identify women for this procedure are the same as for IVF. This technique may also be optimal for women who are not in a position to create embryos. Tissue from the ovarian cortex, which is rich in oocytes, is retrieved prior to the start of therapy. Once the ovarian tissue is removed, ovarian cortical tissue strips can be cryopreserved or individual follicles can be aspirated from the ovary and cryopreserved.[2]

Following the completion of cancer therapy, ovarian cortical tissue can be used for subsequent re-transplantation. There have been three reports of live births from ovarian tissue reimplantation for women with cancer.[15-47] However, the reintroduction of tissue into cancer patients is considered suboptimal as it carries a potential risk of also reintroducing cancer cells to the patient. Another option for utilizing cyropreserved ovarian tissue following cancer therapy is a still experimental procedure called in-vitro follicle maturation (IFM). Follicle development and oocyte maturation are highly dependent on the three-dimensional architecture of the follicle and its extracellular matrix.[48]

Conclusion

In conclusion fertility preservation is a priority for young women with breast cancer. The expert group of oncologist discussed on the options available to preserve fertility in breast cancer patients undergoing chemotherapy or hormonal therapy or radiotherapy. The decisions of whether to resort to fertility preservation and which method to be use depends on a number of factors, including the patient's age, the type of adjuvant treatment, the time available before chemotherapy, and the length of delay to childbearing postchemotherapy. The embryo cryopreservation is a good fertility preservation option for women with partners or sperm donors is present, who can contribute sperm for egg fertilization. Women that do not have a partner and do not wish to use donor sperm, Oocyte cryopreservation becomes the treatment of choice. Recent data suggested that OFS during chemotherapy has emerged as reasonable option.

In summary, despite many young breast cancer patients have concerns about fertility at the time of diagnosis, only a minority undergo one of the available fertility preservation strategies and little over one-sixth change their therapeutic strategy. More efforts are needed to ameliorate the communication on the fertility issues in all women of reproductive age diagnosed with cancer to improve their opportunities to participate in informed decisions regarding their treatment and future reproductive ability.

Take Home Message

1	Both embryo cryopreservation and oocyte cryopreservation require controlled ovarian stimulation (COS).
2	Letrozole + gonadotropincombination is recommended since it is likely to lead to lower rise in estrogen levels
3	The embryo cryopreservation is a good fertility preservation option for women with partners. For women who do not have a partner/ do not wish to use donor sperm, Oocyte cryopreservation is a reasonable option.
4	If partner is available embryo preservation is preferred. If partner is not available oocyte preservation is the recommended option.
5	Ovarian tissue cryopreservation is a new option for fertility preservation and remains an experimental method.
6	Ovarian function suppression (OFS) during chemotherapy has emerged as new promising and safe option for fertility preservation.

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Conflicts of interest

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