


Patient-Related Awareness of Impact of Cancer-Directed Therapy on Fertility in Young Women Diagnosed of Breast Cancer

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Abstract



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Chemotherapeutic agents used in the treatment of breast cancer (BC) adversely impact growing ovarian follicles and can induce permanent premature ovarian failure or reduce ovarian reserve in younger women. As treatments result in improved survival of BC patients, young survivors face quality of life (QOL) issues, including treatment-related infertility. We conducted a survey to evaluate awareness among patients regarding the impact of cancer-directed therapy on fertility and available options of fertility preservation (FP). We interviewed 350 women with BC under 40 years of age at the start of treatment, of which 321 (91.70%) were in varying stages of follow-up, 8 women (2.30%) were scheduled to start treatment, and 21 (6.00%) women were under treatment. All received chemotherapy or hormone therapy with or without ovarian suppression. Of the 350 women who responded to the survey, 321 (91.70%) women were on follow-up, 8 (2.30%) women were due to start treatment, and 21 (6%) women were on treatment. The median age at diagnosis was 35 years, with 12.9% of women aged less than 30 years, 15 (4.28%) were unmarried, 31 (8.85%) were nulliparous, and 98 (28%) had one child. Overall, 271 (77.42%) women were aware (at the start of treatment) of impact of therapy on fertility, but only 48/271 (17.71%) women were aware of the options of FP. In this cohort, 94/350 (26.85%) women felt FP was a priority, 64/350 (18.28%) women perceived their family as incomplete, and 17/64 (26.56%) women were willing to consider invasive reproductive assistance (IRA). Reasons for refusal for IRA included cost, risk of relapse, and delay of treatment. There was an association between being unmarried ($p = 0.00$), having an incomplete family (0.00),

Keywords

- ▶ breast cancer
- ▶ fertility preservation
- ▶ QOL

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considering more children ($p = 0.00$) and willingness to consider IRA. FP is a priority for women treated for BC and an important QOL domain that needs to be addressed at the start of treatment. We found a high level of awareness of impact of cancer-directed therapy to fertility in this cohort, but low awareness and acceptance for options for FP.

Introduction

Breast cancer is the most common cancer in women,¹ with a median age of presentation in India being 47 years in India.² On an average, woman under 35 years of age constitutes less than 10% of patients presenting with breast cancer in India.³ Diagnosis of breast cancer at young age is associated with greater frequency of adverse prognostic factor profiles, also independently associated with poor prognosis^{4,5} and most of these patients require chemotherapy. Additionally, selective estrogen receptor modulator tamoxifen with or without ovarian suppression is given to all hormone receptor-positive breast cancer patients in the premenopausal age group for the duration of at least 5 years as adjuvant endocrine therapy.⁶ Chemotherapeutic agents used in the treatment of breast cancer adversely impact the different stages of follicle growth, induce permanent premature ovarian failure in the older premenopausal women, and induce ovarian reserve damage in the younger women.⁷ Chemotherapy can affect this reserve by directly inducing damage to the ovary the magnitude of which is inversely related to age with younger women at lower risk compared to older women.⁸ Additionally though tamoxifen is not known to cause infertility, it may interfere with childbearing because of the duration of the treatment 5 to 10 years during which time women are advised not to get pregnant.⁹ However, more recent results from the positive trial may offer respite for women desirous of a pregnancy while on adjuvant hormone therapy.¹⁰ As the landscape of systemic therapy changes, we are seeing improvements in survival and quality of life among survivors has come to the forefront. Fertility-related concerns have a significant impact on quality of life and often impact treatment decisions among young women with breast cancer. As the field of oncofertility continues to develop around the globe, regular assessment of both international and regional barriers to quality care must continue to guide process improvements.¹¹ Fertility preservation in a woman with cancer largely refers to safeguarding the ability of the individual to conceive and carry a child to term, at a time they wish to do so and the term oncofertility was thus coined by Woodruff in 2006 for fertility preservation in cancer patients.¹² We conducted a survey to evaluate the awareness among patients regarding the adverse effects of cancer-directed therapy on fertility and available options of fertility preservation.

Methodology

Objective: The aim of this study was to evaluate the level of awareness regarding the adverse effect of cancer-directed

therapy on fertility and available options of fertility preservation among young women diagnosed with breast cancer. The study was approved by the institutional ethics board.

Method: We conducted a prospective observational study wherein, after obtaining informed consent, we interviewed 350 women with curative breast cancer from August 2017 to August 2018, who were under 40 years of age at the time of their treatment, all of whom have or will receive chemotherapy and/or hormone therapy with or without ovarian suppression using luteinizing hormone releasing hormone agonist (LHRHa) or gonadotropin-releasing hormone analogues, as part of their treatment. We excluded women over 40 years of age and those who had undergone a hysterectomy. All eligible women answered a predesigned questionnaire that was constructed by treating oncologists at our center which is a tertiary cancer center. The survey included questions curated by members of the breast cancer disease management group and gynecologists at our tertiary cancer center (Supplementary Material 1).

Statistical consideration: Assuming that 40%¹³ of the target population will have knowledge about the effects of cancer-directed therapy on fertility and methods of fertility preservation, a sample size of 350 was required to achieve a confidence interval of 95% with an alpha error of 0.05. The study endpoints are descriptive and reported as percentages. The association between patient factors and choices made was compared using chi-squared test.

End-point: The awareness among patients regarding effect of cancer-directed treatment on fertility and the options available for fertility preservation.

Results

Of the 350 women with nonmetastatic breast cancer who responded to the survey, 321 women (91.70%) were in varying stages of follow-up (and had not had a recurrence), 8 (2.30%) women were scheduled to start treatment, and 21 (6.00%) women were under treatment for breast cancer. The median age at diagnosis of respondents was 35 years (range: 22–40), with 12.9% under 30 years of age. At presentation, 209 women (59.71%) had early breast cancer and 141 (40.28%) had locally advanced cancer, and 269 women (76.85%) were homemakers (→ [Table 1](#)).

Patients were interviewed for details of reproductive factors and parity, wherein (→ [Table 2](#)), 15 (4.28%) women were unmarried and 335 (95.71%) were married. Majority of women (221; 63.14%) had two or more children, 31 (8.85%) were nulliparous, and 98 (28%) had one child. Among the 98 who had one living child, 9/98 women (9.18%) gave history of having

Table 1 Patient characteristics

Patient characteristics	No. of patients
Early breast cancer	209 (59.71%)
Locally advanced breast cancer	141 (40.28%)
On follow-up	321 (91.70%)
Under treatment	21 (6%)
On NACT	06
Post-surgery	06
On adjuvant chemotherapy	06
On adjuvant radiotherapy	03
Due to start treatment	8 (2.30%)
Homemakers	269 (76.85%)
Employed	66 (18.85%)
Self-employed	15 (4.28%)
Median age at diagnosis	35 years (mean 34.58 years, range 22-40)
≤ 25	14 (4%)
25–29	31 (8.90%)
30–35	138 (39.40%)
36–40	167 (47.70%)

Abbreviation: NACT, neoadjuvant chemotherapy.

Table 2 Marital status and parity

Factors that impact fertility needs (marital status and parity)	No. of patients
Unmarried	15 (4.28%)
Married	335 (95.71%)
Nulliparous	31 (8.85%)
1 child	98 (28%)
2 or more children	221 (63.14%)

Table 3 Awareness of adverse effects of cancer-directed therapy on fertility and options of fertility preservations

	No. of patients
Patients aware of adverse effects of cancer-directed therapy on fertility	271/350 (77.42%)
A) Source of information (could tick more than one option)	
Patients informed by the treating Physician	243/271 (89.66%)
Patients informed by the nurse	16/271 (5.90%)
Patients informed by family and friends	9/271 (3.32%)
Patients informed by media	6/271 (2.22%)
B) Patients aware of options of fertility preservations	48/271 (17.71%)
C) Awareness on type of fertility preservation (could tick more than one option)	
LHRHa use	13/271 (4.79%)
Embryo preservation	35/271 (9.22%)
Oocyte preservation	8/271 (2.95%)
Ovarian tissue preservation	3/271 (1.10%)
Success rates of fertility preservation	40/271 (14.76%)

lutinizing hormone releasing hormone agonist

required assisted reproductive methods in the past. When asked if the women perceived their family was complete at the start of treatment, 283 (80.85%) answered in the positive, while 64 (18.28%) wanted more children and 3 (0.85%) were not sure. Of those with incomplete families, 31 were nulliparous, 21 had one child, and 12 had two or more children.

At the start of treatment, 271 (77.42%) women were aware of adverse effect of cancer-directed therapy on fertility, 243 (89.66%) were informed by the treating physician, and the remaining women were informed by the nurse (5.90%), family and friends (3.32%), and media (2.22%). Overall, 48/271 (17.71%) women were aware of the options of fertility preservation, 13/271 (4.79%) were aware of LHRHa use, 35 (9.22%) were aware of embryo preservation, 8 (2.95%) were aware of oocyte preservation, 3 (1.10%) were aware of ovarian tissue preservation, and only 40 (14.76%) were aware of success rates of any fertility preservation technique. Assuming additional information was given only to those who had not completed their family, we evaluated the frequency of information given to those 64 women who reported their family is not complete, 52/64 (81.3%) were aware of adverse effect of cancer-directed therapy on fertility, and of the 52 women, 13 (25%) women were aware of the options of fertility preservation, 3 (5.8%) were aware of LHRH use, 11 (21.2%) of embryo preservation, 02 (3.8%) of oocyte preservation, 01 (1.9%) ovarian tissue preservation, and only 11(21.1%) were aware of success rates of any fertility preservation technique.

One-hundred and thirty-two women (37.3%) reported that the doctor took measures to preserve ovarian function and 46 (13.1%) women felt it was safe to have a child on treatment. Misconceptions related to intercourse were also apparent with 137/350 (39.14%) reporting they felt it was not acceptable to have intercourse while on treatment (→Table 3).

Of the 350, 65 (19%) women felt future pregnancies would affect their cancer relapse.

Table 4 Patients who wanted fertility preservation

	N/D (%)
Patients who had completed their family	283/350 (80.85%)
Patients who weren't sure about completeness of family	3/350 (0.85%)
Patients who wanted more children	64/350 (18.28%)
Nulliparous	31/64 (48.43%)
One child	21/64 (32.81%)
Two or more children	12/64 (18.75%)
Would consider invasive procedures for reproductive assistance	
Yes	17/64 (26.56%)
No	47/64 (73.43%)
Reasons for refusal (Could tick more than one option)	
Cost	32/64 (50%)
Fear of invasive procedures	32/64 (50%)
Risk of relapse or delay of treatment	32/64 (50%)
Lack of awareness of safety of procedures	35/64 (54.68%)

Of the 64 who felt they had not completed their family, 17 (26.56%) suggested they would consider an invasive procedure (embryo or oocyte or ovarian tissue preservation) for reproductive assistance. The reasons for refusal cited were cost by 32 (50%) women, fear of invasive procedure 32 (50%) women, risk of relapse or delay of treatment by 32 (50%) women, and lack of awareness of safety of procedures by 35 (54.68%) women ([Table 4](#)).

There was a significant association between being unmarried/nulliparous versus having a child ($p = 0.00$), considering family incomplete versus not (0.00), wanting more children versus not ($p = 0.00$) and the women's willingness to consider invasive procedures for reproductive assistance. We grouped the importance of fertility preservation as perceived by these as high, moderate, and low and found that 94/350 (26.85%) felt it was a high priority and 45/94 (47.87%) had not completed their family at the time of treatment for breast cancer ($p = 0.00$). Also 57 women suggested they considered having a child if cancer free for a few years, while 42 (73.3%) women considered fertility preservation a high priority ($p = 0.00$).

Discussion

The cross-sectional study presented here evaluated the knowledge and awareness of cancer-directed systemic therapy on fertility among women treated for breast cancer. Despite a median age at diagnosis of 35 years (range 22–40), with 12.9% under 30 years of age in this cohort, over 80% had completed their family; this is not unusual to the average Indian family unit, which is in stark comparison to reports from the west.¹⁴ Advances in treatment of breast cancer have resulted in higher survival rates and with 20% young survivors wanting to have children and many more facing symptoms associated with premature ovarian failure, fertility preservation at the start of treatment has been gaining focus.

The American Society of Clinical Oncology guidelines¹⁵ recommend that women in the reproductive age group should be given the opportunity to preserve their fertility with embryo cryopreservation, oocyte cryopreservation, ovarian tissue cryopreservation or LHRHa, requiring health-care providers to discuss the same with patients prior to starting treatment.

Majority (77.4%) of women in this cohort were aware of adverse effect of cancer-directed therapy on fertility, and at the start of treatment, almost 90% were informed by the treating physician. This may be a reflection of the survey having been conducted at a tertiary referral center. Other reports including a cross-sectional survey from a gynecology department in north India reported that only 32% of the patients were aware of the detrimental effect of cancer treatment future fertility and was related to the socioeconomic status of the woman and 32% received the information from their treating physician.¹³ A systematic review¹⁶ reported on factors that influence a physicians discussion on fertility preservation with young cancer patients and suggested the physicians knowledge, sense of comfort, patient factors, and availability of educational materials were the main barriers. With fertility preservation being incorporated in major guidelines, the attitude of oncologists has also improved as is seen in our survey with 90% women being informed by their treating oncologist.

However, only 25% of those who felt their family was not complete were aware of the options of fertility preservation and 17/64 (26.56%) women suggested they would consider an invasive procedure (embryo or oocyte or ovarian tissue preservation) for reproductive assistance.

Despite awareness of the toxicity of systemic therapy and desire to preserve fertility, there are many misconceptions and fear in the mind of the women. The reasons for refusal to consider future pregnancies with assisted reproduction methods cited in our study included cost, fear of invasive

procedure, risk of relapse or delay of treatment, and lack of awareness of safety of procedures. Studies have reported that patients who found out about fertility preservation from their healthcare providers were far more likely to use cryopreservation options than those who found out about it from other means.¹⁷

With changes in guidelines and practices over the years,¹⁸ awareness among treating oncologists may have improved, so we also reviewed our referral pattern for fertility preservation in the more recent years. Options for fertility preservation were offered to all eligible women and 22% chose the option of gonadotropin releasing hormone but less than 2% were willing for invasive procedures, and most refused the same due to cost or fear of recurrence. This suggested that despite more information for both oncologists and patients, use of invasive methods of assisted reproduction and fertility preservation is still not often discussed or chosen in our oncology practice.

A strength of this cohort is that we included over 91% women on follow-up without recurrence, assuming now that they can thus focus on quality-of-life concerns, we may get a more accurate view of how these women prioritize fertility. Limitations of this survey include a possible recall bias as women were interviewed on follow-up about discussion that has taken place at the start of their treatment. Additionally, we have not accessed the economic and educational level of this cohort that may influence these choices and decisions.

Conclusions

Despite a high level of awareness of impact of cancer-directed therapy on fertility in this cohort, we found low awareness and acceptance for options for fertility preservation. Fertility preservation must be discussed with women in the reproductive age group prior to starting treatment to benefit women for whom it is a high priority. Oncologists are the most common source for this information for the patient and can dismiss myths and fears related to cancer recurrence and fertility preservation.

Conflict of Interest

None declared.

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