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Fertility Preservation in the Young Breast Cancer Patient

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Abstract

Background—ASCO guidelines include incorporation of fertility preservation guidelines into the care of breast oncology patients. The purpose of our study is to examine the baseline knowledge of and preferences concerning fertility preservation among women of childbearing age with newly diagnosed breast cancer at time of initial visit to MSKCC.

Methods—A questionnaire on reproductive history, fertility knowledge and preservation options was administered to women ages 18–45 years with newly diagnosed breast cancer at MSKCC between May and September 2011.

Results—Sixty women met the inclusion criteria and were eligible for analysis with a median age of 40 years (range 20–45). We found 50% of women either desired children in the future or were unsure if they wanted children; 9% reported receiving information about fertility preservation options prior to their MSKCC visit. Women who had never been pregnant were more likely than those with prior pregnancies to consider having children in the future ($p=0.001$), and to contemplate fertility preservation options both before ($p=0.001$) and after ($p=0.0002$) cancer treatment.

Conclusion—Early referral allows patients to take advantage of fertility preservation options while preventing delay in the initiation of systemic therapy. Referral by the breast surgical

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oncologist at the time of initial visit has the potential to increase fertility knowledge, as it appears many women have not yet received fertility information at this early treatment stage.

Keywords

fertility; fertility preservation; breast cancer; reproductive health

INTRODUCTION

Breast cancer is the most common cancer in women in the United States (U.S) and worldwide.^{1,2} It has been estimated that the incidence of invasive breast cancer in the U.S. will be almost 232,000, and incidence of ductal carcinoma in situ will be >50,000 in 2015.^{3,4} Most of these women will be treated successfully, with an overall 5-year relative survival rate of 88.1% for breast cancer in women of all ages, and 5-year relative survival of 87.1% in women <45 years of age diagnosed with breast cancer.⁵ Thus, most women diagnosed with breast cancer will become long-term survivors, making survivorship and quality-of-life issues important.

Recently, a trend has emerged of more women delaying motherhood, for reasons⁶ including education, employment, financial stability, and possibly the advent of assisted reproductive technology allowing for successful pregnancies in older women.⁷ The increase in birth rates among women >40 years of age has bypassed those of women 40 years of age.⁸ The first-birth rate for women 35–39 years of age was 8.9/1000 in 2000, and rose to 11.0/1000 in 2012, a 24% increase. Over the same time period, first-birth rates in women 40–44 years of age rose from 1.7 to 2.3 per 1000, a 35% increase.⁸

Cancer treatments may adversely affect fertility. However, currently available information is insufficient to predict the likelihood and extent of ovarian damage suffered by an individual woman.⁹ Breast cancer treatment can include surgery, chemotherapy, endocrine therapy, and radiation therapy. Chemotherapy regimens have shown to be gonadotoxic¹⁰, with possible causation of temporary and/or permanent amenorrhea, premature menopause¹¹, and infertility. The POEMS study of premenopausal women 25–49 years of age (median 38 years) found 33% of patients treated with chemotherapy without ovarian suppression met criteria for ovarian dysfunction, while 14% of patients treated with chemotherapy with ovarian suppression met criteria for ovarian dysfunction at the 2-year endpoint.¹² Chemotherapy can also have long-term effects on the ovary; it is thought to decrease ovarian reserve.^{13,14}

Many women are concerned about the effects cancer treatment may have on their fertility.¹⁵ Younger age, non-White race, being nulliparous, and receiving chemotherapy are factors associated with greater concern about fertility in women with newly diagnosed breast cancer.¹⁶ Fertility concerns can influence a woman's treatment decisions.^{15,16} Many cancer survivors, especially those who do not already have children, want children in the future.¹⁷

Many women lack information about the impact of cancer treatment on their reproductive health.^{18,19} In a study of African American women with breast cancer, only 45.8% were aware of the potential for cancer treatment to compromise their future ability to have

children. Factors associated with greater awareness among women were younger age, nulliparity, and tubal ligation history.²⁰

Fertility preservation options available to women include egg and embryo freezing, and ovarian tissue freezing, which is experimental. These should be performed prior to initiation of adjuvant systemic therapy.²¹ Alternative family-building options for women infertile after chemotherapy include donor eggs or embryos, adoption, and, for women who cannot carry a pregnancy, surrogacy. Fertility discussions should ideally take place before treatment to provide the most potential fertility options.

Providing women with fertility preservation information can decrease stress, improve quality of life, and benefit psychological well-being.²²⁻²⁴ The American Society of Clinical Oncology has released recommendations regarding fertility preservation emphasizing importance of early, clear, and accurate counseling about treatment effects on fertility and fertility preservation options.²⁵ Despite these recommendations, many women still lack sufficient knowledge to make informed decisions about such options^{18,19}, and many feel their fertility needs and concerns are inadequately addressed.¹⁵ Another study found only about 50% of oncologists regularly refer patients with fertility questions to a specialist.²⁶

These ASCO guidelines emphasize incorporation of fertility preservation guidelines into the care of breast oncology patients, but questions remain on who should be referring patients. The purpose of our pilot study is to examine the baseline knowledge of and preferences concerning fertility preservation among women of childbearing age with newly diagnosed breast cancer who are being seen by a breast surgical oncologist soon after diagnosis. It also addresses whether early referral by a breast surgical oncologist may allow for intervention regarding fertility preservation options for patients.

METHODS

Between 05/2011–09/2011, women referred to the Breast Surgery Clinic at Memorial Sloan Kettering Cancer Center (MSKCC) were invited to participate in an institutional-review-board–approved, cross-sectional pilot study. Eligibility criteria included women between 18–45 years of age with a new diagnosis of breast cancer, and not previously treated. Patients were approached in the waiting room on the day of their first surgical visit to MSKCC, but before seeing the surgeon. Patients were surveyed anonymously, with questions on demographics, reproductive history, fertility knowledge and fertility preservation preferences, desire for childbearing, and adoption, allowing for assessment of patients' baseline fertility knowledge before seeing an MSKCC clinician.

Instrument

This survey was developed by MSKCC investigators with specific research interest and expertise in the field of cancer and fertility, and with input from outside expert reproductive endocrinologist consultants.

The survey comprised 33 questions (4 study eligibility, 5 demographics, 2 general and cancer health information, 9 reproductive status and history, 5 fertility history, and 8 fertility

preferences and knowledge questions). Most required simple binary responses (yes/no); some asked respondents to choose one answer from 3–6 options. Questions on age, years on birth control, and number of pregnancies/children allowed number specification. For questions regarding fertility options they would consider before and after treatment, participants were instructed to select all/any responses applicable.

Statistical Analysis

Statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, NC). Continuous variables were summarized using median and range. Categorical variables were summarized using frequency and percentage. Fisher's exact test was used to assess associations between prior pregnancy and the likelihood of being interested in having children in the future, considering fertility options, and receiving fertility information; p-values <0.05 were considered significant.

RESULTS

Patient Demographics

Sixty women met inclusion criteria and were eligible for analysis. Table 1 summarizes patient demographics. Median subject age was 40 years (range 20–45 years). 60% of women (n=36) were 40 years of age or older, while only 4 women were younger than 30 years of age. The majority of women were White/Caucasian (n=39, 65%). Patients were highly educated, with most having a college or postgraduate degree (n=47, 78%). Most were diagnosed with breast cancer within the previous 2 months (n=59, 98%).

Reproductive Health

Consistent with our sample's age distribution, patients were predominantly premenopausal (n=47/58, 81%). Forty-eight (80%) had been pregnant before, with a median of 3 pregnancies (range 1–6)(Table 2). Forty-five (94%) of these had children; 46 (77%) used oral contraceptives for a median of 5 years (range 0–22 years).

Fertility History

15% (n=9) of women reported a time of 12 months when they attempted to, but could not, get pregnant. Out of these 9 women, there were 4 cases where both the woman and the partner were evaluated, and 1 case where only the partner was evaluated for a fertility problem. In the remaining 4 cases, neither the woman nor her partner was evaluated. Four women went on to use either oral or injectable fertility medication. Two used 1 of the following assisted reproductive technology methods: artificial insemination, in-vitro fertilization, or embryo transfer.

Fertility Preferences/Knowledge

Thirty women (50%) were not interested in having children in the future, 15 (25%) were interested in having children in the future, and 15 (25%) were unsure. Table 3 summarizes responses related to future fertility preferences among those who indicated they were either interested or unsure about having children in the future. All patients were asked on whether

they would consider fertility interventions as well as egg donors, and adoption. Ten women stated they did not know enough about options available before treatment to answer; 10 stated they did not know enough about options available after treatment to answer. Overall, 12 women did not know enough to answer at least one of these questions.

Among those who reported being interested or unsure about future childbearing, the majority (25/28, 89%) believed that their cancer treatment will influence their ability to conceive or have children in the future (2 responses were missing).

Only 9% (n=5/57) of women reported receiving any information about their ability to have children and/or options for fertility preservation before their MSKCC visit. The most common source of this information was a fertility specialist (n=3), followed by a medical oncologist (n=2) and a gynecologist (n=1), with one woman reporting receiving information from >1 source. Women who were nulligravid were more likely to report having received fertility information (3/12=25% versus 2/45=4%, p=0.06).

Future Fertility Considerations

Women who had never been pregnant were significantly more likely to be interested in having children in the future (8/12=67% versus 7/48=15%, p=0.001) and to consider fertility preservation options before cancer treatment (6/12=50% versus 3/48=6%, p=0.001) and alternative family-building options after treatment (7/12=58% versus 3/48=6%, p=0.0002) than women who had prior pregnancies. We found no significant differences between Caucasian and non-Caucasian patients in their interest in future children (p=0.132). Among those who were interested in children in the future or unsure, there was no significant difference in the beliefs that breast cancer will affect fertility (p=0.188) (Table 4).

DISCUSSION

Our study population consisted of highly educated women in their late 30s and 40s, most of whom already had children. 50% of women surveyed considered having children in the future, consistent with previous findings demonstrating a significant number of women are still interested in having children following breast cancer diagnosis and treatment.^{17,27} Among women who considered having children in the future, 89% reported believing cancer treatment might impact their ability to conceive or have a child, in contrast to other studies reporting <50% of women believing cancer would impact their fertility.²⁰ However, a different study showed that women overestimated their risk of infertility from cancer treatment.¹⁵

Despite the high prevalence of women considering children in the future and being cognizant of potential cancer treatment effects on their fertility, only 9% of the women in our study reported having received information about fertility preservation before their first surgical consultation at MSKCC (the time of survey completion), with nulligravid women more likely to receive information than women who had been pregnant before. The majority of our patients (98%) were seen within 2 months of their diagnosis, thus they were unlikely to have had a reproductive endocrinologist consult regarding fertility preservation options unless they had a prior history of infertility evaluation. This low number may give insight

into our patients' lack of baseline knowledge about fertility preservation, since our survey was obtained during a first-time visit to the MSKCC breast surgery clinic and is consistent with similar low knowledge bases reported in other studies.¹⁹ Twelve of 30 (40%) women who were interested in having children felt they did not know enough to answer questions about fertility preservation. Studies also show that despite providers discussing fertility, many women do not feel their needs are adequately addressed.¹⁵ It is possible that even the few women who received prior fertility information were left unsatisfied.

Breast surgical oncologists are primarily the first physicians who women with breast cancer encounter to discuss treatment options. Surgery itself does not impair future fertility, but is often only part of the multidisciplinary treatment required. Women with breast cancer may also receive chemotherapy and/or endocrine therapy that can potentially impact their fertility. Early referral to a reproductive endocrinologist may offer women opportunities to discuss fertility preservation options without a delay in administration of subsequent adjuvant therapy should a fertility intervention be desired. Breast surgical oncologists are best positioned to initiate these discussions and provide early referrals to reproductive endocrinologists. Early referrals may allow for initiation of fertility preservation before the woman's first medical oncologist visit. Studies have shown that early referral allows women to undergo fertility preservation without significantly delaying their adjuvant treatment.²⁸ Additionally, early referral provides patients the option to undergo multiple cycles of preservation if needed to increase their success rate.²⁹ Our results show women who had never been pregnant were more likely to be interested in having children in the future and to consider fertility preservation—consistent with studies that describe the characteristics of women who are most likely to be affected by the possibility of infertility. Nulliparous women are more likely to desire children in the future and have fertility concerns.^{15,17,27} Our results also contribute to the evidence toward nulliparous women being more likely to pursue fertility preservation.²³ More research on the characteristics of women who pursue fertility preservation is needed.

In this study, more women reported they would consider freezing eggs and ovarian tissue versus freezing embryos. Previous studies found the most common methods utilized by cancer patients pretreatment were embryo cryopreservation and egg cryopreservation.^{16,23} This may indicate the relative change in rankings after adequate counseling about different fertility preservation options, with more women opting for proven methods of preservation after a specialist consultation.

One strength of this study is the relative homogeneity of its study population, which is representative of younger patients at our institution. This homogeneity allowed us to draw conclusions that inform fertility-related interventions. However, this study population characteristic may also be a limitation, as the generalizability of these results may be limited in other populations.

Our survey was given before any consultation with healthcare providers at our institution and therefore may be a good indicator of patient baseline knowledge before exposure to MSKCC healthcare providers, but does not allow us to comment on fertility knowledge and opinions later in treatment, or on which fertility options are ultimately pursued. Our survey

was given while waiting for a first consultation. Therefore, the women in our study were very close to time of diagnosis, which may have affected their stress, anxiety, and even depression levels. One study has reported depressive symptoms being highest soon after diagnosis, then decreasing over time.³⁰ Another study limitation is use of an instrument not yet validated. We developed this instrument for our pilot study, and it has not been previously used in a similar setting. Although most survey questions were straightforward, this may raise questions regarding instrument reliability and validity. Additionally, the number of study subjects was relatively limited; a larger study to validate our findings would be of benefit.

Conclusion

This study has led to beneficial changes at MSKCC. The study information gathered has enabled our institutional fertility program to help women learn more about cancer treatment effects on fertility, and to explain and guide women through their options to help mitigate possible consequences and undergo fertility preservation when desired. This cross-sectional pilot study has also informed a longitudinal study currently evaluating fertility knowledge and preferences over time.

This study highlights the lack of knowledge about fertility issues among young newly diagnosed women with breast cancer and the value of having breast surgical oncologists initiate discussion about fertility early in the treatment trajectory. Information from this study should help guide breast surgical and medical oncologists address patient fertility questions and concerns. Learning about the potential impact of future treatment on fertility, options for fertility preservation before treatment, and family building after treatment, can facilitate early referrals to reproductive specialists. Providing women with correct information about cancer treatment effects on their ability to have children may help ameliorate their treatment fears.

Our study results raise questions about the optimal time to inform patients about the risks of treatment on fertility, and at which point in treatment certain information should be given. Early referral allows patients time to weigh their options and make fully informed decisions, and to pursue egg or embryo freezing without delaying systemic therapy initiation. Thus, our study shows that referral by the breast surgical oncologist at the time of initial visit may potentially increase fertility knowledge and prevent delay initiating systemic therapy.

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Synopsis

Here we examine knowledge of and preferences concerning fertility preservation among women of childbearing age with newly diagnosed breast cancer. We find that referral by the breast surgical oncologist at time of initial visit can increase fertility knowledge.

Table 1

Patient demographics (n=60)

Characteristic	n (%) or median (range)
Age, years	40 (20–45)
20 – 34	11 (18.3%)
35 – 39	13 (21.7%)
40 – 45	36 (60.0%)
Ethnicity	
Hispanic/Latino	3 (5.0%)
African-American/Black	7 (11.7%)
Asian	9 (15.0%)
Caucasian/White	39 (65.0%)
Biracial/Multiracial	2 (3.3%)
Education	
Some high school, but no degree	1 (1.7%)
High school degree or GED	4 (6.7%)
Some college, but no degree	8 (13.3%)
College degree	28 (46.7%)
Postgraduate degree	19 (31.7%)
Married or committed relationship	
No	11 (18.3%)
Yes	49 (81.7%)
Time since diagnosis, months	
0 – 1	54 (90.0%)
1 – 2	5 (8.3%)
>2	1 (1.7%)

Table 2

Past reproductive health history (n=60)

Characteristic	n (%) or median (range)
Gravidity	
No	12 (20%)
Yes	48 (80%)
Number of pregnancies among gravidous women (n=48)	
	3 (1–6)
Parity	
No	15 (25%)
Yes	45 (75%)
Pregnancy history among parous women (n=45)	
Number of children	2 (1–4)
Age at first birth, years*	30 (16–44)
Age at last birth, years*	33 (24–44)

* n=44 for age at first birth and age at last birth due to missing data

Table 3

Questions on fertility preferences and preservation. (a) Interested in future children? (b) Would consider FP before cancer treatment? (n=30 women indicating Yes/Unsure for interest in future children) (c) Would consider alternative family building after cancer treatment? (n=30 women indicating Yes/Unsure for interest in future children)

Interested in future children? (n=60)	<u>n (%)</u>
Yes	15 (25%)
No	30 (50%)
Unsure	15 (25%)
Would consider FP before cancer treatment?	<u>n</u>
Freeze embryos with partner's sperm	3
Freeze embryos with donor sperm	1
Freeze eggs	8
Freeze ovarian tissue	3
Do not know enough to answer	10
Undecided	13
Would not consider any	4
Would consider alternative family building after cancer treatment?	<u>n</u>
Donor eggs	2
Donor embryos	1
Surrogacy	4
Adoption	9
Do not know enough to answer	10
Undecided	9
Would not consider any	6

FP, fertility preservation

Table 4

Fertility Interest and Beliefs by Race Type

Characteristic	Caucasian n (%)	Non-Caucasian n (%)	p-value
Interested in children in the future?			0.1324
No	23 (59%)	7 (35%)	
Unsure	7 (18%)	8 (40%)	
Yes	9 (23%)	5 (25%)	
Believe breast cancer treatment will affect fertility? (Among only patients who are interested or unsure)			0.1880
No	0 (0%)	2 (17%)	
Yes	14 (93%)	10 (83%)	
Don't know	1 (7%)	0 (0%)	