ORIGINAL ARTICLE: FERTILITY PRESERVATION

Which patients pursue fertility preservation treatments? A multicenter analysis of the predictors of fertility preservation in women with breast cancer

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Objective: To evaluate predictors of undergoing fertility preservation treatment (FPT) in women with breast cancer.
Design: Secondary analysis of a clinical database.
Setting: Three academic fertility preservation centers.
Patient(s): One hundred eight patients with breast cancer undergoing FPT and 77 patients with breast cancer not undergoing FPT from 2005 to 2010.
Intervention(s): None.
Main Outcome Measure(s): Patients' demographic and medical information.
Result(s): Women who had FPT were older, wealthier, and had lower cancer stage compared with women who did not have FPT. The rate of the administration of neoadjuvant chemotherapy (NAC) was significantly lower in women who underwent FPT. After adjusting for age, body mass index (BMI), income, cancer stage, and center, a negative correlation persisted between NAC and FPT (odds ratio 0.091, 95% confidence interval 0.009–0.904). When we stratified the women by center, women at center 1 had a significantly lower FPT rate, lower parity, higher BMI, more advanced cancer stage, and lower income compared with centers 2 and 3. The rates of NAC were significantly higher in center 1.
Conclusion(s): Although age, BMI, income, cancer stage, center, and NAC seem to be associated with undergoing FPT, NAC is the only modifiable variable. Because NAC restricts the time available for FPT, oncologists may consider offering adjuvant chemotherapy, except in cases in which NAC clearly improves survival, in women who are interested in FPT. (Fertil Steril® 2012;■:■–■. ©2012 by American Society for Reproductive Medicine.)
Key Words: Fertility preservation, predictors, breast cancer, neoadjuvant chemotherapy

Increasing survival rates after breast cancer have heightened the importance of quality of life issues, including fertility preservation treatment (FPT), defined as embryo or oocyte cryopreservation. Oncologists are increasingly aware of the importance of discussing reproductive issues with patients and referring appropriate patients to fertility preservation specialists. Because oncologists have the essential role of initiating the discussion about FPT, the American Society of Clinical Oncology and American Society of Reproductive Medicine have developed guidelines about this topic (1, 2). Specifically, the guidelines suggest that oncologists "should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists." Currently many academic institutions offer FPT, and oncologists collaborate with fertility preservation specialists for prompt referrals and treatments. As a result, an increasing number of patients are referred to fertility preservation specialists.

However, not all referred patients ultimately undergo FPT. For example, a recent study of 70 European infertility centers showed that only 7.6% of breast cancer patients referred to fertility specialists before chemotherapy initiation underwent FPT (3). Considering that patients who elect to have a fertility

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preservation consultation (FPC) are likely interested in their fertility after cancer treatment, it is notable that a minority of patients underwent FPT, despite initial consultation.

Many factors may influence a patient's decision to pursue FPT. Parity, educational background, income, and prior knowledge about fertility preservation options have been found to influence the decision to pursue FPT (3–6). Other factors, such as cancer treatment plans (adjuvant vs. neoadjuvant chemotherapy [NAC]), prognosis, and physician encouragement, could possibly influence a patient's choice about FPT (7, 8). Nonetheless, data on the characteristics of women with breast cancer who ultimately undergo FPT are limited. Understanding predictors of FPT may help identify system-wide patterns that affect likelihood of utilization of assisted reproductive techniques. Providers could potentially tailor their referral patterns for FPT according to these predictors and/or modify practice patterns to allow all interested women to participate in these opportunities. The aim of this study was to assess factors associated with FPT in patients with newly diagnosed breast cancer at three large academic hospitals.

MATERIALS AND METHODS

We performed a secondary analysis of a clinical database of women with breast cancer undergoing FPC before chemotherapy between January 2005 and December 2010 from three academic centers in three different states (center 1: University of North Carolina at Chapel Hill, North Carolina; center 2: Institute for Fertility Preservation, Valhalla, New York; center 3: University of Pennsylvania, Philadelphia, Pennsylvania). The inclusion criteria were as follows: age $\leq$42 years, availability of complete data about the date of the FPC and date of chemotherapy initiation, and cancer stage I–III.

Data regarding patients' demographic and medical information were abstracted from medical records. Estimated annual income was calculated through an income tax database by home ZIP code (9). Distance from the clinic was calculated as the distance between the patient's home ZIP code and the clinic ZIP code. Fertility preservation treatment utilization rate was calculated as the number of the patients who received FPT divided by the total number of patients included.

Analysis was performed with SPSS 17. Continuous data (presented as mean ± SD) was analyzed by ANOVA, *t* test or Mann–Whitney U test as appropriate. Categoric data were analyzed using χ^2 or Fisher's exact tests as appropriate. A two-tailed *P* value of $<.05$ was considered statistically significant. Multivariable logistic regression models were constructed to evaluate the association between pursuing FPT and clinical and treatment characteristics, including the administration of NAC.

RESULTS

The exact dates for FPC and initiation of chemotherapy were available for 236 patients. Of those, 51 were excluded (33 were older than 42 years, 11 were stage 0 (ductal carcinoma in situ), 2 were stage IV, and stage was not available in 5 women). One hundred eighty-five women met all inclusion criteria. Of those, 36 were from center 1, 116 were from center 2, and 33 were from center 3.

Of the 185 patients, 108 (58.4%) underwent FPT. In univariate analysis, the FPT group had a lower mean body mass index (BMI), was wealthier, and had lower cancer stage compared with the group that did not undergo FPT (Table 1). The rate of administration of NAC was significantly lower in women in the FPT group. Age, parity, *BRCA* mutation status, history of infertility, family history of breast/ovarian cancers, and hormone receptor status of cancer were not different between women who underwent FPT and those who did not. The likelihood of having

TABLE 1

Comparison of demographic and cancer characteristics of patients who underwent and did not undergo FPT.

Parameter	FPT group (n = 108)	No-FPT group (n = 77)	*P* value
Demographics			
Age (y), mean ± SD	36.1 ± 4.3	34.7 ± 5.2	.05
BMI (kg/m^2), mean ± SD	23.2 ± 4.1	25.5 ± 5.9	.02
Nulliparity (%)	83.8	71.4	.05
Income ($US/y), mean ± SD	150,323 ± 139,807	95,677 ± 93,290	.002
Distance to clinic (mi), mean ± SD	135.2 ± 415.5	96.6 ± 355.9	.52
Time from initial diagnosis to FPC (d), mean ± SD	50.8 ± 76.3	46.2 ± 71.9	.7
Having insurance coverage[a] (%)	61.5	69.8	.48
Having partner[a] (%)	86.2	75.6	.27
Cancer			
Stage (%)			
I–II	96.3	83.6	.01
III	3.7	16.4	
Size (cm), mean ± SD	1.9 ± 1.1	2.0 ± 1.1	.71
Hormone receptor positive[b] (%)	80.2	71.6	.20
Lymph node positive (%)	70.7	62.9	.34
NAC use (%)	2.7	31.0	$<.001$

[a] Data from center 1 (n = 36) and center 3 (n = 33) only.
[b] Estrogen receptor and/or progesterone receptor.

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TABLE 2

Baseline characteristics and outcomes of FPT of patients who underwent FPT by center.

Parameter	Center 1 (n = 10)	Center 2 (n = 82)	Center 3 (n = 16)
Age (y)	36.9 ± 4.5[a]	36.6 ± 3.8[b]	32.4 ± 4.9
Baseline FSH (IU/mL)	5.8 ± 3.5[c]	8.9 ± 4.1[d]	5.0 ± 2.6
No. (%) of patients stimulated with letrozole–gonadotropin	6 (66.6)[e]	82 (100)[e]	9 (52.9)[e]
Total gonadotropin used (IU)	3,403.1 ± 1,447.6[a,f]	1,987.8 ± 801.9	2,275.8 ± 1,022.6
No. of oocytes retrieved	10.7 ± 6.5	15.4 ± 9.4	15.6 ± 9.4
No. of oocytes fertilized	4.7 ± 4.7	7.6 ± 5.0	6.7 ± 5.2
Fertilization rate (%)	53.1 ± 25.6[c]	77.9 ± 18.1[b]	47.6 ± 25.5
No. of oocytes cryopreserved	N/A[g]	8.1 ± 10.8	6.8 ± 4.4
Mean no. of embryos cryopreserved	3.8 ± 3.2	7.6 ± 6.6	6.8 ± 5.2

Note: Values are mean ± SD unless otherwise noted.
[a] $P<.05$, center 1 vs. center 3.
[b] $P<.001$, center 2 vs. center 3.
[c] $P<.05$, center 1 vs. center 2.
[d] $P<.05$, center 2 vs. center 3.
[e] $P<.001$, comparing all centers.
[f] $P<.001$, center 1 vs. center 2.
[g] No patient underwent oocyte cryopreservation.

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insurance coverage or a partner was not different between the two groups.

Of the 108 patients who underwent FPT, 90 (83.3%) underwent embryo cryopreservation, 10 (9.3%) underwent oocyte cryopreservation, and 8 (7.4%) underwent both. Of those, 97 (89.8%) were stimulated with a letrozole–gonadotropin protocol, 7 (6.4%) with an antagonist protocol, and 4 (3.7%) with a luteal-phase long protocol. In centers 1 and 3, the letrozole–gonadotropin protocol was used principally in patients who had estrogen receptor–positive cancer; however, in center 2 the letrozole–gonadotropin protocol was used regardless of estrogen receptor status (Table 2).

Women in center 1, compared with centers 2 and 3, had significantly fewer nulliparous patients (50%, 87.1%, and 89.5%, respectively; $P=.009$) and a lower FPT utilization rate (27.8%, 70.7%, and 48.5%, respectively; $P<.001$). Compared with center 2, patients at centers 1 and 3 were significantly younger and had lower estimated income. The rates of lymph node involvement and administration of NAC were significantly higher in center 1 (Table 3). In vitro fertilization treatment outcomes, defined as number of oocytes or embryos cryopreserved, were not different among the three centers (Table 2).

Figure 1 illustrates that women who underwent NAC had only an average of 14 days (range, 6–26 days) between FPC and initiation of chemotherapy, as opposed to 55 days for women who had surgery first. Among the 19 patients who received NAC, only 1 patient from center 2 underwent FPT. In

TABLE 3

Patient demographics, cancer characteristics, and FPT utilization rate by center.

Parameter	Center 1 (n = 36)	Center 2 (n = 116)	Center 3 (n = 33)
Demographics			
Age (y)	33.7 ± 4.8[a]	37.1 ± 3.8[b]	32.2 ± 5.6
BMI (kg/m^2)	27.0 ± 5.7[a]	22.5 ± 4.3	24.6 ± 4.5
Nulliparity (%)	50.0[c]	87.1[c]	89.5[c]
Income ($US/y)	57,986 ± 25,724[a]	167,098 ± 143,318[b]	68,146 ± 38,774
Distance to clinic (mi)	63.4 ± 61.5	165.0 ± 489.5	22.6 ± 19.3
Time from initial diagnosis to FPC (d)	32.4 ± 34.9	58.1 ± 90.5	34.8 ± 19.1
Cancer			
Stage (%)			
I–II	82.6	95.1	87.5
III	17.4	4.9	12.5
Size of cancer (cm)	1.6 ± 0.7	2.0 ± 1.2	2.1 ± 1.1
Hormone receptor positive[d] (%)	68.6	80.2	75.0
Lymph node positive (%)	53.6[c]	26.0[c]	31.3[c]
NAC use (%)	48.4[e]	3.0[e]	6.1[e]
FPT utilization rate (%)	27.8[e]	70.7[e]	48.5[e]

Note: Values are mean ± SD unless otherwise noted.
[a] $P<.001$, center 1 vs. center 2.
[b] $P<.001$, center 2 vs. center 3.
[c] $P<.05$, comparing all centers.
[d] Either estrogen receptor and/or progesterone receptor.
[e] $P<.001$, comparing all centers.

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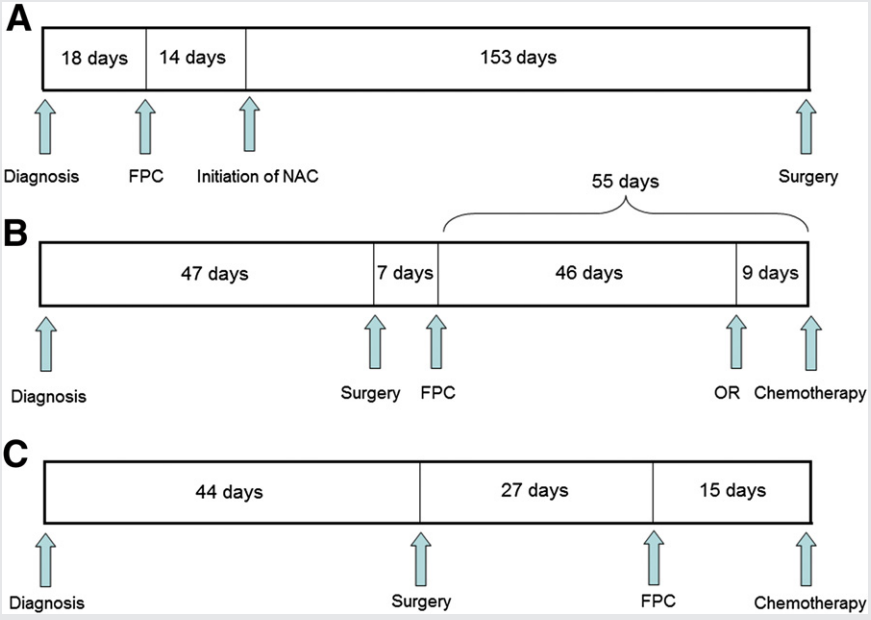
FIGURE 1



Comparison of clinical course between patients who underwent NAC and did not undergo NAC. (A) Clinical course of the patients who underwent NAC and no FPT. (B) Clinical course of the patients who had adjuvant chemotherapy and FPT. (C) Clinical course of the patients who had adjuvant chemotherapy but did not undergo FPT. OR = oocyte retrieval.

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multivariable logistic regression models, a negative association persisted between NAC and FPT (odds ratio 0.091, 95% confidence interval 0.009–0.904) after adjusting for BMI, income, center, and cancer stage. Mean time from FPC to oocyte retrieval was 32 days (range, 9–69 days).

DISCUSSION

In this multicenter analysis, we evaluated variables associated with the likelihood of pursuing FPT. Body mass index, income, cancer stage, center, and NAC seem to predict the likelihood of undergoing FPT. Interestingly, receiving NAC was associated with not undergoing FPT, even when we controlled for other significant variables. Predictors differed by center: center 1 had the lowest utilization rate of FPT and the highest rate of administration of NAC compared with centers 2 and 3.

We found that several variables are related to utilization of FPT. First, BMI was lower in the FPT group compared with the no-FPT group; this may be confounding, because BMI has been reported to have a significant positive correlation with stage of cancer (10). Second, a higher annual income logically correlates with increased FPT utilization, because FPT may be cost-prohibitive for those without insurance coverage and low income. Third, patients with more advanced disease were less likely to undergo FPT; these patients may need to quickly proceed with cancer treatments and/or have less concern about quality of life issues. Fourth, each center had different rates of FPT utilization. Several factors should be considered to interpret this finding. For example, each center's physicians might counsel the patients in different ways. Additionally, each center had a different rate of administration of NAC (NAC is used broadly under study protocols at center 1). Fifth, we found that women in the FPT group tended to be older, compared with women in the no-FPT group ($P=.05$). We can speculate that, generally, older patient may be more stable financially or regarding relationships, and therefore FPT may be a more feasible option in this age bracket. In addition, parity in the FPT group had a tendency to be lower compared with the no-FPT group ($P=.05$). This finding is similar to results from a study reporting that women who were childless at the time of their cancer treatments were more likely to undergo counseling and treatment with FPT (3).

One of our most novel findings was that NAC was a negative predictor of FPT even after adjusting other significant variables, which may be related to time-constraints, safety concerns, or characteristics of patients who receive NAC. First, there is a short time interval between diagnosis and the initiation of NAC. Generally, NAC is preferred in patients with advanced disease, and patients planning NAC initiate treatment soon after cancer diagnosis (11, 12). Thus, these patients would have only a limited time window for ovarian stimulation. Several studies have shown that if the time interval between breast cancer surgery and adjuvant chemotherapy is as long as 12 weeks, there is no detrimental effect on survival or recurrence, compared with women who have a shorter time interval (13, 14). However, to date, there are no studies that show the effect of delaying the initiation of NAC on treatment outcome in women with breast cancer, and therefore we are not proposing delaying NAC for FPT. Our data demonstrate that the mean time

interval from FPC to the initiation of NAC was 14 days. Considering that an FPT protocol takes approximately 2 weeks but initiation depends on the woman's cycle (15), 14 days is likely insufficient time for FPT. However, the mean time interval from cancer diagnosis to FPC was 18 days in the patients who underwent NAC, indicating that if the patient was referred for FPC earlier (e.g., immediately after diagnosis), she may have enough time for FPT before NAC, without delaying the start of chemotherapy. In our data, there was only one patient who underwent FPT followed by NAC, and she was referred only 3 days after her cancer diagnosis, consistent with a recent study by Lee et al. demonstrating the benefit of early referral in patients with cancer (16). The present study only includes women who presented for FPC; however, it is possible that a significant number of women who were planning NAC did not consider an FPC at all or the oncologists treating these women did not refer them for FPC, owing to perceived time constraints.

Another possible reason that NAC may negatively predict FPT is related to safety concerns. To date, there is only one study that evaluated the safety of FPT in breast cancer patients (17). This study demonstrated no increased risk of recurrence (hazard ratio 0.56, 95% confidence interval 0.17–1.9) and no difference in relapse-free survival ($P=.36$) with FPT with a letrozole–gonadotropin protocol in women receiving adjuvant chemotherapy after initial surgery, although "overall survival" was not a reported outcome. The median follow-up after chemotherapy was 23.4 months (range, 7.5–63.6 months) in the women who underwent FPT and 33.05 months (range, 4.5–63.6) in the women who did not undergo FPT. However, the risks associated with FPT in women receiving NAC (with the primary tumor in place) are unknown. Future studies about the feasibility and safety of FPT in breast cancer patients before the initiation of NAC are needed. That being said, if a patient is interested in FPT, working with the oncology team to alter the treatment plan (for example pursing adjuvant vs. NAC, when survival outcomes are equivalent) can allow interested women the opportunity to pursue FPT.

Finally, the characteristics of patients who receive NAC may help explain the negative association between NAC and FPT. In general, NAC is the preferred treatment for patients with inoperable inflammatory or locally advanced breast cancer (stage IIIa and above) because it has several advantages in this subgroup of patients. These advantages may include allowing patients with inoperable cancers to become candidates for surgical resection (11, 12), targeting clinically occult micrometastases (18), and providing an opportunity to deliver cytotoxic agents to the tumor with intact native vasculature (19). Additionally, several studies have shown that NAC is tolerable and significantly improves outcomes compared with surgery alone in patients who had inflammatory or locally advanced breast cancer (20, 21). Because NAC tends to be offered to patients with advanced disease, perhaps our finding that NAC is a negative predictor of FPT may be related to the fact that oncologists treating women with advanced cancer defer the discussion about fertility issues when the prognosis is poor (22). However, we find in multivariate regression models that NAC has an independent inverse association with pursing FPT, even after controlling for cancer stage and other significant predictors from our univariate analysis. Another interesting finding was that NAC has a broader use under research protocols at center 1 and a higher utilization rate at that institution, even in lower-stage breast cancers. At center 1, only 35.2% of the patients in NAC group met the informal criteria (inoperable inflammatory or locally advanced breast cancer) for NAC use (21, 23). On the other hand, NAC was used only with advanced-stage cancers at centers 2 and 3, where only 3 patients received NAC, all of whom had stage III disease, large tumors (4–6 cm), and lymph node involvement. Given these data, we conclude that NAC is an independent negative predictor of FPT in women with breast cancer.

Our study is unique for several reasons. This is the first study to evaluate which variables predict the utilization of FPT in patients with breast cancer. Although a few studies have assessed the characteristics of female patients *counseled* for fertility preservation (3, 24), no study investigated predictors of *treatments*. Second, this is a multicenter study that involves three tertiary academic hospitals in three different states. This enables our study to evaluate patients with a wide variety of sociodemographic backgrounds. Third, we confined the definition of FPT to embryo and/or oocyte cryopreservation, and more than 90% of the FPT group underwent embryo cryopreservation. We believe that this is a clinically significant outcome to study, because embryo cryopreservation is the most established assisted reproductive technique for fertility preservation for female patients (1). Other studies have included experimental fertility preservation techniques when assessing utilization, such as GnRH agonist treatment and ovarian tissue cryopreservation (3), even though these options have not been proven to improve fertility chances.

Our study has several limitations. Because it was conducted retrospectively, the specific reasons that contribute to the patient's decision to undergo FPT cannot be ascertained. Another limitation is that annual income and insurance information is estimated according to the patient's ZIP code, which may limit accuracy. Other variables, such as education level and patient comprehension of FP choices, were not available. Subtle differences in cancer treatments and oncology attitudes at different centers are difficult to assess and may influence the decision to pursue FPT.

To our knowledge, this is the first multicenter study that shows the predictors of pursuing FPT in patients with breast cancer. Specifically, here we report for the first time that administration of NAC is an independent negative predictor of FPT. NAC restricts the time available for FPT. It is noteworthy that although BMI, income, cancer stage, and NAC seem to predict the likelihood of undergoing FPT, NAC is the only "modifiable" variable in certain patients. The use of NAC varies by center: center 1 has a broader use of NAC under research protocols, and many patients who received NAC had early-stage disease (Stage I–II). In general, although NAC can alter surgical options, allowing women to undergo a lumpectomy rather than a mastectomy, the lack of survival benefit of NAC compared with adjuvant chemotherapy has

been demonstrated (25–27). Except in cases in which NAC clearly improves survival, oncologists may consider offering adjuvant chemotherapy, rather than NAC, in women who are interested in FPT. Surgery before chemotherapy may be an option for these patients, giving them time to pursue FPT.

In conclusion, we found that several factors are associated with undergoing FPT, and administration of NAC was the only modifiable and independent negative predictor. Understanding these factors may help oncologists and fertility preservation specialists to better target counseling and possibly tailor treatments so that FPT options can be maximized.

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