

Fertility Preservation in Breast Cancer Patients: A Prospective Controlled Comparison of Ovarian Stimulation With Tamoxifen and Letrozole for Embryo Cryopreservation

Kutluk Oktay, Erkan Buyuk, Natalie Libertella, Munire Akar, and Zev Rosenwaks

From The Center for Reproductive Medicine and Infertility, Joan and Sanford I. Weill Medical College of Cornell University, New York, NY.

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Address reprint requests to Kutluk Oktay, MD, The Center for Reproductive Medicine and Infertility, Department of Obstetrics and Gynecology, Joan and Sanford I. Weill Medical College of Cornell University, 505 E 70th St, HT-340, New York, NY 10021; e-mail: kuo9001@med.cornell.edu.

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A B S T R A C T

Purpose

To develop safe ovarian stimulation methods to perform in vitro fertilization (IVF) in breast cancer patients who wish to preserve their fertility via embryo cryopreservation before chemotherapy.

Patients and Methods

Sixty women (age range, 24 to 43 years) with breast cancer were prospectively studied. Twenty-nine patients underwent 33 ovarian stimulation cycles with either tamoxifen 60 mg/d alone (Tam-IVF) or in combination with low-dose follicle-stimulating hormone (TamFSH-IVF) or letrozole 5 mg in combination with FSH (Letrozole-IVF). After IVF, all resultant embryos were cryopreserved to preserve fertility. Recurrence rates were compared with controls ($n = 31$) who elected not to undergo IVF.

Results

Compared with Tam-IVF, both TamFSH-IVF and Letrozole-IVF patients had greater numbers of follicles (2 ± 0.3 v 6 ± 1 and 7.8 ± 0.9 , respectively; $P < .0001$), mature oocytes (1.5 ± 0.3 v 5.1 ± 1.1 and 8.5 ± 1.6 , respectively; $P < .001$), and embryos (1.3 ± 0.2 v 3.8 ± 0.8 and 5.3 ± 0.8 , respectively; $P < .001$). Peak estradiol (E_2) levels were lower with Letrozole-IVF and Tam-IVF compared with TamFSH-IVF. After 554 ± 31 days (range, 153 to 1,441 days) of follow-up, cancer recurrence rate was similar between IVF and control patients (three of 29 v three of 31 patients, respectively; hazard ratio, 1.5; 95% CI, 0.29 to 7.4), and this estimate was not affected by cancer stage.

Conclusion

The combination of low-dose FSH with tamoxifen (TamFSH-IVF) or letrozole (Letrozole-IVF) results in higher embryo yield compared with Tam-IVF. Recurrence rates do not seem to be increased, but the letrozole protocol may be preferred because it results in lower peak E_2 levels.

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INTRODUCTION

Breast cancer is the leading cancer in women of reproductive age. In the United States alone, 25% of all women diagnosed with breast cancer are premenopausal, and 15% are under the age of 45 years.¹⁻⁴ Breast cancer is commonly treated with surgery followed 4 to 6 weeks later by combination chemotherapy. Most combination chemotherapy regimens include the alkylating agent cyclophosphamide, which is

known to cause a significant loss in ovarian follicle reserve.³ This diminishment in ovarian reserve results in premature ovarian failure and infertility with serious consequences to the quality of life. One study showed that the likelihood of ovarian failure within 1 year of receiving cyclophosphamide, methotrexate, and fluorouracil or doxorubicin and cyclophosphamide increases with age and is 78% and 38%, respectively, for a 40-year-old breast cancer patient.³ Because each course of

chemotherapy will result in loss of a significant portion of ovarian reserve,⁵ even women who do not immediately become menopausal after chemotherapy are likely to experience infertility and early menopause.⁶ Those who survive without losing their fertility will not be able to attempt pregnancy in the short run either because they will have to receive continuous tamoxifen therapy for up to 5 years or because of the uncertainty regarding the safety of pregnancy shortly after breast cancer treatment. By the time these patients are allowed to attempt pregnancy, 5 or more years may have elapsed, and many more of these cancer survivors will be in menopause and suffer from infertility because of further diminishment of ovarian reserve with aging.

With increasing survival rates and the heightened awareness on quality of life of the consequences of cancer therapy, fertility preservation has gained further importance. An increasing number of breast cancer patients are seeking assisted reproductive technologies to preserve their fertility. Although ovarian tissue and oocyte freezing are still experimental,⁷⁻⁹ embryo cryopreservation is an established clinical procedure after in vitro fertilization (IVF). However, IVF typically requires ovarian stimulation with a resultant increase in estrogen levels. Because a high-estrogen milieu is not considered safe for breast cancer patients, many patients had been offered IVF during unstimulated cycles (natural-cycle IVF) in the past. In a previous preliminary study, we used tamoxifen as an ovarian stimulant in breast cancer patients to perform IVF and cryopreserve embryos for fertility preservation. We compared these patients with breast cancer patients undergoing natural-cycle IVF. Although the results of natural-cycle IVF were poor, resulting in an average of 0.6 embryos per patient, tamoxifen stimulation resulted in a 2.5-fold increase in embryo yield without cancer recurrence in short-term follow-up.¹⁰

Prospective pregnancy rates would increase with the availability of a higher number of cryopreserved embryos. Therefore, we conducted the current prospective controlled study to develop more effective ovarian stimulation protocols that will improve embryo yield without increasing cancer recurrence.

Tamoxifen is a nonsteroidal triphenylethylene antiestrogen that was first introduced in the United Kingdom as a postcoital contraceptive.¹¹ It was then used as an ovulation induction agent in Europe.¹² When used as an ovulation induction agent, tamoxifen was typically administered at 20 to 60 mg for 5 days. Subsequent work showed that tamoxifen suppressed breast carcinogenesis,¹³ which led to its worldwide use in breast cancer treatment and prophylaxis.^{14,15}

Another hormonal treatment agent that is increasingly more commonly used in breast cancer is letrozole, an aromatase inhibitor.¹⁶ Aromatase, an enzyme of the cytochrome P-450 super family and the product of the *CYP19* gene, catalyzes the reaction that converts androgenic substances to estrogens in many tissues, including granulosa

cells of ovarian follicles.¹⁷ Letrozole is a potent and highly selective third-generation aromatase inhibitor that was developed in the early 1990s. It competitively inhibits the activity of aromatase enzyme and has a half-life of approximately 48 hours.¹⁸ A single dose of letrozole 0.5 mg produces a potent long-lasting suppression in the plasma levels of estradiol (E_2), and recently, it was claimed to be superior to tamoxifen in the treatment of advanced-stage postmenopausal breast cancer.^{17,19,20}

Recent reports have also shown that aromatase inhibitors can be used as ovulation induction agents. In cycling bonnet monkeys, letrozole resulted in the formation of multiple follicles.²¹ Clinical studies in which letrozole was typically administered at doses of 2.5 to 5 mg for 5 days have also shown its benefit in ovulation induction alone or in combination with follicle-stimulating hormone (FSH). These studies also showed that peak E_2 levels were lower when letrozole, alone or in combination with FSH, was compared with stimulation with FSH or clomiphene. E_2 levels have been found to be even lower than in natural cycle in patients stimulated with letrozole.²² Because letrozole can induce ovulation without raising estrogen levels, we hypothesized that it can be safely used in patients with breast carcinoma undergoing IVF.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board at the Weill Medical College of Cornell University (New York, NY). Patients were referred by their medical or surgical oncologists, and patients with stage IV cancer were excluded based on the poor prognosis, general health status of the patient, and the higher uncertainty regarding delaying chemotherapy. Treatment allocation was not randomized based on ethical reasons because the tamoxifen arm of the study had already started and provided promising results by the time the letrozole arm was added to the study. Instead, the protocol was determined by patient self-selection based on physician-patient communication, including the oncologist. Because the protocols of tamoxifen 60 mg/d alone (Tam-IVF) or in combination with low-dose follicle-stimulating hormone (TamFSH-IVF) were initiated earlier during the study than the letrozole protocol, initial patients were only counseled regarding protocols involving tamoxifen, resulting in a sequential cohort design and a significantly shorter follow-up in letrozole patients. Patients with a history of breast cancer and who attempted pregnancy with tamoxifen using fresh embryos were reported in a previous publication and were not included in the current study.¹⁰

In standard IVF, patients typically receive a gonadotropin-releasing hormone agonist to suppress their ovarian function during the luteal phase preceding the ovarian stimulation, and the ovarian stimulation is begun on the second or third day of menstrual bleeding with an average dose of 300 U of gonadotropins. On average, patients will need 10 to 11 days of ovarian stimulation until the largest ovarian follicles (leading follicles) reach 17 to 18 mm in diameter by ultrasound examination. By this time, E_2 levels can exceed 3,000 pg/mL, which is 10 times higher than peak levels

of estrogen in an unstimulated cycle. At this time, typically 3,300 to 10,000 U of human chorionic gonadotropin (hCG) is administered to trigger final maturation of oocytes, and ultrasound-guided transvaginal retrieval is performed 34 to 36 hours later, just before ovulation. In the current study, we modified this protocol as follows.

In the tamoxifen-only group (Tam-IVF), patients were started on 60 mg/d of tamoxifen (AstraZeneca, Washington, DC) on the second or third day of their menstrual cycle, after baseline FSH, luteinizing hormone (LH), and E_2 levels were obtained. Tamoxifen was continued until the FSH level decreased below baseline value. In the tamoxifen-FSH combined-treatment group (TamFSH-IVF), 150 U of recombinant FSH (Gonal-F; Serono, Norwell, MA; or Follistim; Organon Inc, West Orange, NJ) injection was initiated simultaneously with tamoxifen 60 mg on the second or third day of the menstrual cycle. Tamoxifen and FSH were continued until the day of hCG administration, at which time all medications were discontinued. For patients receiving letrozole (Letrozole-IVF), 5 mg of letrozole was administered orally starting on the second or third day of the menstrual cycle. After 2 days of letrozole administration, 150 U/d of FSH (Gonal-F or Follistim) was added. Letrozole was continued until the day of hCG administration; the E_2 measurement was repeated 3 days after the oocyte retrieval, and if the E_2 level was more than 250 pg/mL, letrozole was continued until it decreased to less than 50 pg/mL.

Patients were monitored with ultrasound, and the E_2 , FSH, and LH measurements were taken every 1 to 2 days until the day of oocyte retrieval. When E_2 exceeded 250 pg/mL, a gonadotropin-releasing hormone antagonist (250 μ g, Antagon; Organon Inc) was administered to prevent a premature LH surge. When the largest (leading) follicle reached a mean diameter of 17 to 18 mm, 3,300 to 10,000 U of hCG (Profasi; Serono) was administered intramuscularly, and the oocyte retrieval was performed 36 hours later. IVF was performed via intracytoplasmic sperm injection, as reported previously.²³ Embryos were frozen at the 2-pronuclear stage (the earliest sign of fertilization). For each patient, peak E_2 was determined on the day of hCG administration. The control

group was made up of eligible women who were counseled about the protocol but who chose not to undergo ovarian stimulation. The reasons for not undergoing IVF varied but included the concern for cost, insufficient time to perform ovarian stimulation, unwillingness to delay chemotherapy, and willingness to consider alternatives, such as egg donation, if ovarian failure occurred. Recurrence information was obtained by telephone interview and mail-in questionnaires. In every case, including the recurrences, patients' oncologists were also contacted for follow-up information, and the pathology reports were reviewed for confirmation.

Analysis of variance was used to compare the ages between groups. Kruskal-Wallis nonparametric analysis of variance and Dunn's multiple comparisons tests were used for differences between groups and posttest comparisons, respectively. To compare recurrence rates, we used Kaplan-Meier analysis. We considered $P < .05$ as statistically significant.

RESULTS

Cancer and treatment characteristics of all patients are listed in Table 1. There were 13 cycles in 12 patients in the Tam-IVF group, nine cycles in seven patients in the TamFSH-IVF group, and 11 cycles in 11 patients in the Letrozole-IVF group. All patients reported normal menstrual cycles before chemotherapy.

The mean age and baseline FSH levels of treatment groups were similar (Table 2). Mean age of control patients was similar to the age of patients who underwent IVF (37.7 ± 0.8 v 36.5 ± 0.7 years, respectively; $P = .2$). On average, patients received 7.8 ± 0.5 days of tamoxifen (range, 5 to 12 days) in the Tam-IVF group, 8.9 ± 0.8 days of tamoxifen (range, 5 to 13 days) in TamFSH-IVF group, and 9.1 ± 0.5 days of letrozole (range, 7 to 13 days) in the

Table 1. Receptor Status, Vascular Invasion, Median Grade, and Recurrences According to the TNM Stage of Cancer in IVF (tamoxifen, tamoxifen-FSH, or letrozole) and Control Patients

Stage	Total No. of Patients		No. of Patients						Vascular Invasion (No. of patients)		Median Grade		Recurrence (No. of patients)	
	IVF	Control	IVF			Control			IVF	Control	IVF	Control	IVF	Control
			ER	PR	H	ER	PR	H						
0														
Tis	1	2	1	1	1	1	0	1	0	0	NA	NA	0	0
I														
T1N0M0	9	15	7	7	3	10	7	5	2	1	3	2	1	2
IIA														
T1N1M0	8	7	7	6	3	6	3	3	3	1	2	2	1	1
T2N0M0	3	2	2	2	1	1	0	1	0	0	3	2	0	0
IIB														
T2N1M0	7	2	4	2	3	1	1	0	3	1	3	3	0	0
T3N0M0	0	2	0	0	0	2	0	2	0	0	0	2	0	0
IIIB														
T4 Any NM0	1	1	1	1	0	1	0	0	1	1	3	3	1	0

Abbreviations: TNM, tumor-node-metastasis; IVF, in vitro fertilization; FSH, follicle-stimulating hormone; ER, estrogen receptor positive; PR, progesterone receptor positive; H, Her2/Neu positive; NA, not available.

Table 2. Comparison of Cycle Characteristics and Embryo Yield Among Tam-IVF (12 patients, 13 cycles) TamFSH-IVF (seven patients, nine cycles), and Letrozole-IVF (11 patients, 11 cycles) Patients*

Variable	Mean \pm Standard Deviation			<i>P</i>		
	Tam-IVF (a)	TamFSH-IVF (b)	Letrozole-IVF (c)	a v b	a v c	b v c
Age, years	36.6 \pm 1.6	38.3 \pm 1.9	38.5 \pm 1	NS	NS	NS
Baseline FSH, mU/mL	9.4 \pm 1.5	9.4 \pm 1.5	6.2 \pm 1.1	NS	NS	NS
PeakE ₂ , pg/mL†	419 \pm 39	1,182 \pm 271	380 \pm 57	< .05	> .05	< .05
Total follicles, No.	2 \pm 0.3	6 \pm 1	7.8 \pm 0.9	< .01	< .001	> .05
Follicle > 17 mm, No.	1.2 \pm 0.1	2.6 \pm 0.4	3.2 \pm 0.4	< .05	< .001	> .05
Total oocytes, No.	1.7 \pm 0.3	6.9 \pm 1.1	12.3 \pm 2.5	< .05	< .001	> .05
Mature oocytes, No.	1.5 \pm 0.3	5.1 \pm 1.1	8.5 \pm 1.6	< .05	< .001	> .05
Total embryos, No.	1.3 \pm 0.2	3.8 \pm 0.8	5.3 \pm 0.8	< .05	< .001	> .05

Abbreviations: Tam-IVF, tamoxifen alone followed by in vitro fertilization; TamFSH-IVF, tamoxifen combined with low-dose follicle-stimulating hormone followed by in vitro fertilization; Letrozole-IVF, letrozole combined with follicle-stimulating hormone followed by in vitro fertilization; NS, not significant; E₂, estradiol.

*One patient underwent both TamFSH-IVF and Letrozole-IVF treatments.

†Peak E₂ as measured on the day of human chorionic gonadotropin administration. TamFSH-IVF results in significantly higher peak E₂ levels compared with Tam-IVF and Letrozole-IVF.

Letrozole-IVF group. There were no cycle cancellations (zero of 20 cycles) in TamFSH-IVF and Letrozole-IVF groups compared with two cancellations in the Tam-IVF group (two of 13 cycles). The comparison of cycle characteristics between the three treatment groups is shown in Table 2. The number of follicles \geq 17 mm on the day of hCG administration, the oocytes retrieved, and the total number of mature oocytes were higher in the TamFSH-IVF and Letrozole-IVF groups compared with the Tam-IVF group, but there was no statistically significant difference between the Tam FSH-IVF and Letrozole-IVF groups. This resulted in a significantly higher number of embryos per retrieval in the TamFSH-IVF and Letrozole-IVF groups than in the Tam-IVF group (3.8 \pm 0.8 and 5.3 \pm 0.8 v 1.3 \pm 0.2 embryos, respectively; P < .001). The number of oocytes and embryos obtained with Tam-IVF and TamFSH-IVF was lower than the number obtained during standard IVF stimulation cycles in noncancer patients in our program (10.5 total oocytes, 8.5 mature oocytes, and 6.5 embryos on average). The mean number of oocytes and embryos obtained in the Letrozole-IVF group was comparable to the numbers obtained in noncancer patients, but this difference did not reach statistical significance compared with the TamFSH-IVF group because of the small sample size. Peak E₂ levels were lower in the Letrozole-IVF and Tam-IVF group compared with the TamFSH-IVF group (Table 2). Peak E₂ levels in an unstimulated cycle can be as high as 300 to 350 pg/mL,¹⁰ and thus, the mean levels seen in the Letrozole-IVF and Tam-IVF groups were minimally elevated. In contrast, peak E₂ levels in TamFSH-IVF group were three to four times higher than the levels seen in unstimulated cycles but lower than the peak E₂ levels seen in standard IVF cycles.

In the Tam-IVF group, two of 13 cycles were cancelled because of spontaneous ovulation a day before oocyte re-

trieval. In the TamFSH-IVF and Letrozole-IVF groups, none of the patients experienced cycle cancellation because of premature LH surge. However, in one patient in the TamFSH-IVF group, no fertilization occurred with two oocytes. The same patient underwent two repeat TamFSH-IVF cycles, and she produced a total of 15 mature eggs and 10 embryos.

Mean follow-up time for all patients including controls was 554 \pm 31 days (range, 153 to 1,441 days). Mean length and range of follow-up for the Tam-IVF, TamFSH-IVF, Letrozole-IVF, and control groups were 609 \pm 89 days (range, 169 to 1,015 days), 418 \pm 109 days (range, 153 to 1,237 days), 272 \pm 31 days (range, 157 to 474 days), and 660 \pm 71 days (range, 180 to 1,441 days), respectively. Although follow-up length was similar among the tamoxifen-treated patients and controls, the Letrozole-IVF group had a significantly shorter follow-up compared with controls. All patients had survived at the time of this report. The recurrence rate was similar between the patients who underwent IVF (three of 29 patients) and those who did not (three of 31 patients). Kaplan-Meier recurrence-free survival probabilities analysis did not show a difference between IVF and control patients (Fig 1). The hazard ratio for recurrence on IVF was 1.5 (95% CI, 0.29 to 7.4). This estimate was not importantly affected by inclusion of stage in the model; however, the number of events is low, and the CIs are too wide to rule out the effect of stage. Of the three patients who had recurrence after IVF, two were in the Tam-IVF group, and one was in the TamFSH-IVF group. There was no recurrence in the Letrozole-IVF group, but the follow-up was significantly shorter in the Letrozole-IVF group compared with controls (P < .001). The length of follow-up was similar among the other groups. It must be added that, in comparing self-reported data with chart review and pathology reports, we corrected few self-reporting errors; although this

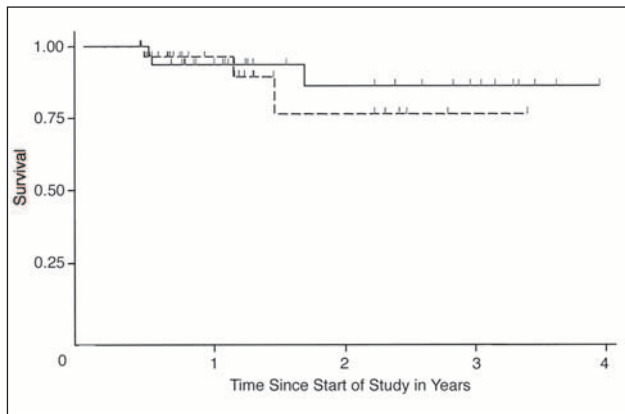


Fig 1. Kaplan-Meier analysis of recurrence-free survival analysis did not show a difference between in vitro fertilization (IVF; dotted line, $n = 29$) and control (solid line, $n = 31$) patients. The hazard ratio for recurrence on IVF was 1.5 (95% CI, 0.29 to 7.4). This estimate was not importantly affected by inclusion of stage in the model.

did not affect our results, it underscores the importance of validating self-reported data in future studies of fertility after cancer.

DISCUSSION

There are approximately 180,000 new patients with breast cancer each year in the United States alone, and 15% of these women are of reproductive age.¹⁻⁴ Consequently, at least 25,000 women may potentially suffer from ovarian failure and infertility because of exposure to gonadotoxic chemotherapy each year. In a previous study, we reported a novel use for tamoxifen to preserve fertility via embryo cryopreservation in women diagnosed with breast cancer and found that tamoxifen stimulation resulted in a higher yield of embryos than natural-cycle IVF.¹⁰ In the current report, we described two new approaches to preserve fertility in breast cancer patients by combining either tamoxifen or letrozole with low-dose FSH and compared this approach with stimulation with tamoxifen alone. We demonstrated that combination of tamoxifen or letrozole with FSH results in a higher number of embryos than tamoxifen stimulation alone. Even though we did not find an increase in the incidence of recurrence in breast cancer patients undergoing ovarian stimulation compared with a prospective control group, the study was not randomized and may lack the power to detect clinically significant differences.

Patients in the TamFSH-IVF group had significantly higher E_2 levels compared with patients in the Tam-IVF or Letrozole-IVF groups. Even though this may raise a doubt regarding the safety of this approach, these peak E_2 levels are not different from the levels seen during chronic administration of tamoxifen for breast cancer treatment.^{24,25} In TamFSH-IVF, a higher dose of tamoxifen than what is

administered for breast cancer treatment is used, exposure to higher estrogen levels is brief, and the patients usually start chemotherapy immediately after completion of IVF treatment. Nevertheless, further follow-up will be required to determine the long-term safety and efficacy of this protocol. In this study, we did not differentiate between receptor-positive and -negative patients because even the receptor-negative patients are likely to have a small fraction of cells staining for this receptor. However, if higher E_2 levels are of concern in estrogen receptor-positive patients, letrozole-FSH and tamoxifen-only protocols may be preferred to tamoxifen-FSH protocols.

Even though the mean E_2 levels were lower in the Letrozole-IVF group compared with the TamFSH-IVF group, two of the 11 patients in the Letrozole-IVF group had E_2 levels exceeding 600 pg/mL. These two patients were 33 and 37 years of age with polycystic ovaries and produced 31 and 20 oocytes, respectively. Thus, greater caution is required in younger patients with polycystic ovaries when using letrozole. The 33-year-old patient who produced 31 oocytes experienced symptoms of ovarian hyperstimulation, but these symptoms quickly resolved on reinstitution of letrozole treatment. The latter observation warrants a study to investigate the role of aromatase inhibitors in the treatment of ovarian hyperstimulation, especially because there is indirect evidence that estrogen may play a role in increased capillary permeability underlying this syndrome.²⁶

We encountered a high rate of immaturity and fertilization failure in the initial few patients who underwent ovarian stimulation with letrozole. Although ovarian follicle development can continue in the absence of estrogen production, as seen in patients with 17-hydroxylase deficiency,²⁷ there is some concern that low estrogen milieu may affect oocyte competence to undergo fertilization and embryo development.²⁸ In our protocol, we continued letrozole until the day of hCG, which was longer than the 5-day regimen used for ovulation induction, resulting in a prolonged period of low-estrogen environment. When we delayed our hCG injection criteria from 17 to 18 mm for leading follicles, the percentage of immature oocytes and fertilization failures were reduced.

All embryos reported in this study were cryopreserved, and only one patient, who was in the Tam-IVF group, returned to have embryo transfer. This was a 41-year-old patient whose three embryos were thawed, and the only surviving embryo was transferred to a gestational carrier. Gestational carrier was used because the patient's cancer treatment was completed 6 months earlier. This resulted in a pregnancy. Although the first ultrasound showed the presence of fetal cardiac activity, unfortunately the pregnancy resulted in a spontaneous abortion later during the first trimester. Embryo cryopreservation is an established clinical procedure, and for a patient with the mean age of the participants in this study (37 to 38 years), pregnancy rates

with transfer of three to four frozen-thawed embryos is approximately 35% in our program. Previous work showed that tamoxifen does not have a detrimental effect on oocyte and early embryo development,²⁹ and several other viable pregnancies and live births have been reported after use of tamoxifen with fresh embryo transfer.¹⁰ Previous reports of satisfactory pregnancy rates in noncancer patients undergoing ovarian stimulation with letrozole are also assuring.^{22,30} However, further confirmation is needed, especially with prolonged administration of letrozole, that embryo quality is not altered because, when used for ovulation induction in noncancer patients, this drug is typically administered for 5 days. Recently, we stimulated a 37-year-old patient with history of breast cancer using the prolonged letrozole protocol described here. Her surplus embryos were cryopreserved and later transferred to her uterus, resulting in a pregnancy, which is currently in its second trimester. Nevertheless, in the protocols described here, embryos are not exposed to tamoxifen or letrozole because fertilization takes place *in vitro*, and there is no evidence that these drugs have long-term effects on the children who are born when used in noncancer patients.

The age range of patients in this study was 24 to 43 years. It has been well established that the pregnancy rates are higher with IVF in younger patients. For example, the “take home baby rate” per embryo transfer exceeds 65% in patients younger than 33 years, but this rate declines to less than 10% in patients 43 years and older in our program. Thus, the techniques described here will have a higher likelihood of success in younger patients.

Our preliminary report has its limitations. The short follow-up and the low statistical power do not allow us to rule out clinically meaningful differences in survival between IVF and control patients. The study was not randomized. Longer follow-up and data on pregnancy outcome

with a larger number of patients will be needed to verify the safety and the efficacy of our approach. A multicenter prospective randomized trial is currently being sought to study the safety of IVF in breast cancer patients. That study will also take into consideration the effect of age on the feasibility of fertility preservation by the methods described here.

In summary, we described two new approaches to ovarian stimulation in breast cancer. Tamoxifen or letrozole can be used in combination with FSH to perform IVF to cryopreserve embryos for the purpose of fertility preservation before treatment of breast cancer. These protocols result in a higher yield of embryos than tamoxifen alone. On the basis of the established clinical experience with cryopreservation of surplus embryos in noncancer patients undergoing IVF for infertility,³¹ this is expected to translate into higher pregnancy rates in the future. Because IVF treatment is started with the onset of menses and may require a minimum of 2 weeks to complete, breast cancer patients of reproductive age should be immediately referred to an assisted-reproduction center. This may allow sufficient time to complete multiple IVF cycles before chemotherapy and maximize their future chance of pregnancy.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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