

## Random-start controlled ovarian hyperstimulation for emergency fertility preservation in letrozole cycles

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**Objective:** To report an emergency approach of random-start controlled ovarian hyperstimulation (COH) in the late follicular or luteal phase of the menstrual cycle for embryo cryopreservation in patients with cancer.

**Design:** Case series.

**Setting:** Academic tertiary referral centers.

**Patient(s):** Three patients with a diagnosis of breast cancer requiring emergency fertility preservation in the late follicular or luteal phase of the menstrual cycle.

**Intervention(s):** After baseline pelvic ultrasound and hormonal evaluation, random-start COH was commenced immediately on menstrual cycle days 11, 14, or 17 with use of letrozole 2.5 mg/d and recombinant FSH 150 to 300 IU/d. Gonadotropin-releasing hormone antagonist was administered to prevent ovulation in all cases. Ovulation was triggered with either 250 µg of recombinant hCG or 10,000 IU of urinary hCG.

**Main Outcome Measure(s):** Number of oocytes harvested, maturity and fertilization rates, number of embryos frozen.

**Result(s):** Nine to 17 oocytes were harvested, resulting in the freezing of seven to 10 embryos with the mean maturity and fertilization rates of 58.8% to 77.7% and 69.2% to 87.5%, respectively.

**Conclusion(s):** In an emergent setting, ovarian stimulation can be started at a random cycle date for the purpose of fertility preservation without compromising fertilization rates in letrozole cycles. (Fertil Steril® 2011;95:2125.e9–e11. ©2011 by American Society for Reproductive Medicine.)

**Key Words:** Breast cancer, emergency fertility preservation, embryo freezing, letrozole

As the concept of fertility preservation becomes widely accepted, increasing numbers of patients with cancer are being referred by cancer specialists, hematologists, and other medical and surgical specialties to IVF centers (1). Various fertility preservation options are now available ranging from well-established techniques such as embryo cryopreservation to more experimental novel technologies including ovarian tissue cryopreservation. When appropriate, embryo cryopreservation is the most preferred method because of its high success rates (2). However, in the conventional approach, approximately 2 weeks of ovulation induction is required from the beginning of the menstrual cycle. This could mean up to 6 weeks of delay in starting cancer treatments depending on where in the cycle the patient presented.

The importance of early referral to fertility preservation cannot be understated. Patients referred earlier in the process had less delay in chemotherapy and were able to cryopreserve larger numbers of

oocytes and embryos (3). Currently, if there is insufficient time for ovarian stimulation, these women typically are offered more experimental approaches such as ovarian tissue cryopreservation, as well as in vitro maturation (4, 5). Recent evidence indicates that there are multiple major follicle recruitment waves during a normal menstrual cycle, and hence the concept of a narrow window of opportunity for follicle recruitment may not be accurate (5). Given the current availability of GnRH antagonists, the utility of these multiple recruitment waves throughout the menstrual cycle can be feasible especially in the fertility preservation setting where endometrial development is irrelevant. On the basis of this reasoning, we tried a new approach of a random-start controlled ovarian hyperstimulation (COH) in three patients with breast cancer who had a need for emergency fertility preservation. This case series reports the preliminary findings of this new approach.

### CASE REPORTS

Three patients aged 26, 26, and 29 years with breast cancer were referred for fertility preservation. The diagnosis was invasive ductal cancer in two patients and mixed invasive lobular and ductal cancer in the other. All patients were scheduled to undergo four to six cycles of cyclophosphamide-based cytotoxic therapy, and because of a late referral in the process patients did not have sufficient time to wait for

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the onset of the next menstrual period. The details of initial ultrasound examination and hormonal assessment of the patients are summarized in Table 1. The referral of the patients coincides with their menstrual cycle day 11 to 17. Antral follicle counts were 11, 20, and 20; endometrial thicknesses were 7 mm, 6.5 mm, and 9 mm at the time of the initiation of the stimulation. Serum FSH level ranged between 2.8 and 6.2 mIU/mL, LH ranged between 1.2 and 5.8 mIU/mL, E<sub>2</sub> ranged between 50 and 269 pg/mL, and P ranged between 0.4 and 2.5 ng/mL.

After a comprehensive consultation, a letrozole (2.5 mg/d, Femara; Novartis, Suffern, NY) plus recombinant FSH (150–300 IU/d, Gonal-f; Merck Serono, Rockland, MA) protocol was planned (6). A GnRH antagonist (Cetrotide; Merck Serono) also was administered to prevent LH surge from the first day of COH onward in one patient and fifth day of COH in the remaining two. The total duration of COH ranged between 9 and 12 days, and peak E<sub>2</sub> ranged between 478 and 988 pg/mL. After ovulation trigger with either 10,000 IU of urinary hCG (Pregnyl; Schering-Plough, Kenilworth, NJ) or 250 µg of recombinant hCG (Ovidrel; EMD Serono, Rockland, MA), nine to 17 oocytes were harvested, resulting in seven to 10 embryos to be frozen. In the first patient with breast cancer, embryos were frozen at the cleavage stage, whereas, in the others, embryos were frozen at the two-pronuclei stage according to the clinician's discretion. In the first case, four of seven embryos were grade A, and the remaining three were grade B. Notably, in all of the patients, one or two additional embryos were generated through in vitro maturation (IVM) of immature oocytes. All of the mature or IVM oocytes underwent intracytoplasmic sperm injection (ICSI) with a fertilization rate ranging between 69.2% and 87.5%.

## DISCUSSION

In the present case series, we demonstrated that COH can be started at any time during the menstrual cycle in the setting of urgent fertility preservation. In three cases, seven to 10 embryos were frozen with favorable fertilization rates. Moreover, we were able to generate additional embryos by IVM in all cases. Notably, presence of a dominant follicle measuring 20 mm in one patient and very recent ovulation with a serum P level of 2.5 ng/mL in another patient did not affect the outcomes of our random-start COH protocol.

There are limited data regarding late-follicular or luteal-start COH and emergency fertility preservation in the literature. Bedoschi et al. (7) described emergency COH in two cases with breast cancer and Hodgkin lymphoma. Both patients underwent ovarian stimulation with recombinant FSH along with GnRH antagonists during the luteal phase of the cycle. Twelve mature oocytes were retrieved in both cases. All mature oocytes were subjected to ICSI, with fertilization and cleavage rates of 83.3% and 70%, respectively. In the second case all mature oocytes were cryopreserved (7).

Another strategy is IVM of oocytes after immature oocyte retrieval. Oktay et al. (5) reported an emergency case where four immature oocytes were retrieved from a woman with breast cancer immediately after premature LH surge during letrozole stimulation. Of those, two matured in vitro and were vitrified (5). Demirtaş et al. (8) reported three patients aged 21, 30, and 40 years, without male partners, seeking fertility preservation before chemotherapy. They underwent immature oocyte retrieval in the luteal phase and seven, five, and seven immature oocytes were recovered. After IVM, five, three, and five metaphase II oocytes were vitrified (8). In another study, Oktay et al. (9) assessed IVM as a complementary strategy

**TABLE 1**

**Baseline characteristics and COH outcome of the patients with breast cancer undergoing emergency fertility preservation.**

Characteristic	Case 1	Case 2	Case 3
Age (y)	29	26	26
Stage	I	II	II
Histology	Invasive ductal	Mixed invasive ductal + lobular	Invasive ductal
COH start day	14	11	17
FSH (mIU/mL)	6.2	2.8	4.6
LH (mIU/mL)	5.8	2.8	1.2
E <sub>2</sub> (ng/mL)	62	269	50
P (pg/mL)	1.2	0.4	2.5
Endometrial thickness (mm)	7	6.5	9
Antral follicle count (n)	11	20 <sup>a</sup>	20 <sup>b</sup>
GnRH antagonist start day	5	1	5
Peak E <sub>2</sub> (pg/mL)	499	988	478
Duration of COH (d)	9	12	9
Oocytes retrieved (n)	9	17	16
Metaphase II, no. (%)	7 (77.7)	10 (58.8)	11 (68.75)
Metaphase I + germinal vesicle, no. (%)	2 (22.3)	7 (41.2)	5 (31.25)
Fertilization rate, no. (%)	7/8 (87.5)	10/12 (83.3)	9/13 (69.2)
Cleavage rate (%)	7/7 (100)	NA	NA
Embryos frozen (n)	7	10	9

Note: GnRH antagonist start day was defined as the day of COH start. Fertilization rate was calculated as the ratio of number of two-pronuclei embryos divided by the sum of number of metaphase II plus IVM metaphase I oocytes. NA = not applicable.

<sup>a</sup> One dominant follicle measuring 20 mm in diameter was observed.

<sup>b</sup> A corpus luteum was observed.

Sönmezer. Random-start ovarian hyperstimulation. *Fertil Steril* 2011.

to improve the mature oocyte yield of patients with breast cancer undergoing ovarian stimulation with aromatase inhibitors for fertility preservation. After IVM, mature oocyte yield increased 45% (from 274 to 399 of 464 oocytes retrieved,  $P < .0001$ ). The total number of oocytes and embryos frozen before IVM was 207 (45% of all oocytes retrieved). This number increased to 320 (69% of all oocytes retrieved) after IVM ( $P < .0001$ ) (9).

In a recent study, Maman et al. (10) compared the results of IVM of oocytes for fertility preservation performed during the luteal phase of the cycle with those of IVM performed during the follicular phase in a similar group of patients. Eighteen patients with cancer underwent IVM fertility preservation, five in their luteal phase and 13 in their follicular phase. The authors did not find significant differences in the number of oocytes retrieved, maturation rates, fertilization rates, or the total number of oocytes and embryos that were cryopreserved.

Although the timing of the initiation of GnRH antagonists is more straightforward in late follicular phase–start cases, the same timing in luteal starts is less clear. We chose to start GnRH antagonist on the first day of COH in one patient with late follicular start and on the fifth day of COH in two patients with luteal phase start. In the process of development of aromatase inhibitor protocols, we observed that premature LH surge can occur with very low  $E_2$  levels when follicle diameter exceeds 13 mm (5). Therefore, we recommend the initiation of gonadotropins when there is at least one leading follicle with diameter  $\geq 13$  mm regardless of whether the stimulation is started in the follicular or luteal phase.

It is, however, not yet known whether the oocytes and embryos obtained and frozen with late follicular or luteal phase–start ovarian stimulation will result in comparable pregnancy rates with those

originating from conventional stimulation cycles. The existing data, and confirmed by the findings of the current cases, demonstrated favorable fertilization rates after ICSI of oocytes collected after late follicular or luteal phase–start COH with letrozole. Nevertheless, given the young age of the presented cases with high ovarian reserve, we do not know the feasibility of random-start COH in older-aged women with low ovarian reserve. Larger, prospective studies are needed to assess the full potential of the protocol presented here.

The feasibility of random-start COH is on a sound scientific basis as recent research on healthy volunteers showed the presence of up to three major follicle recruitment waves during a normal menstrual cycle. Baerwald et al. (11) monitored 50 women by daily ultrasound examination and blood samples including  $E_2$ , LH, and FSH and observed that, whereas 34 of 50 women exhibited two follicle waves, 16 of 50 women exhibited three follicle waves. Further, the concept that the majority of the oocytes that are obtained during the luteal phase are atretic has been questioned. Similarly, in a recent report Bentov et al. (12) described a patient who successfully conceived after GnRH antagonist–induced demise of the first cohort of follicles and the emergence of a second wave of follicles followed by oocyte retrieval on cycle day 30 and fresh ET. Our case series is in line with these recent scientific observations and may help us take a fresh look at the way we approach ovarian stimulation in general. Such a fresh look, for example, can have practical application in egg donation cases where the donors can be stimulated without a need for delay. The latter becomes even more important given the increase in the success rates of egg freezing and given that donor egg banks are becoming a reality. In theory, with a random-start approach many young donors who usually have many schedule conflicts can be stimulated on a more practical schedule.

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