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Clinical efficacy of dual trigger with human chorionic gonadotropin and a gonadotropin-releasing hormone agonist for women undergoing fertility preservation

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Abstract

Purpose: To determine the optimal maturation method to increase the yield of mature oocytes, especially for cancer patients with fewer chances of fertility preservation (FP) before gonadotoxic therapy.

Methods: A total of 373 cycles in 293 patients undergoing controlled ovarian stimulation (COS) for FP using a gonadotropin-releasing hormone (GnRH) antagonist protocol were enrolled. The control group (n = 225) received 250 μg of recombinant human chorionic gonadotropin (rhCG) while the study group (n = 148) received 250 μg of rhCG and 0.2 mg of triptorelin for triggering. Subgroup analyses were performed for stimulation cycles with diminished ovarian reserve (DOR; anti-Müllerian hormone (AMH) levels <1.1 ng/ml, n = 86), with endometrioma (n = 104), or with breast cancer and endometrial cancer using 5 mg of letrozole during the COS cycles (n = 84).

Results: There was no significant difference in the baseline characteristics or the number of total and mature oocytes between the two groups. Subgroup analyses for women with endometrioma or DOR showed similar results. However, the dual trigger group had a significantly higher number of mature oocytes than the rhCG trigger group in breast and endometrial cancer patients using letrozole during the COS cycles (6.9 ± 6.0 vs. 4.6 ± 3.6, p = 0.034). The maturation rate was higher in the dual trigger group, although the difference was not statistically significant (59.3 ± 26.7 vs. 50.0 ± 28.0, p = 0.124).

Conclusions: Dual triggering can be an efficient maturation method to maximize the yield of mature oocytes in breast or endometrial cancer patients using letrozole-combined GnRH antagonist protocol for FP.

KEYWORDS
dual trigger, fertility preservation, gonadotropin-releasing hormone agonist, human chorionic gonadotropin, mature oocytes

1 | INTRODUCTION

According to the national cancer statistics from Korea in 2016, breast cancer ranked first in the prevalence of female cancers. Endometrial, ovarian, and cervical cancers, all of which threaten female fertility, were also ranked in the top ten.[1] In 2021, the National Cancer Institute reported a 5-year survival rate of 50%–90% for these cancer patients, and the number of cancer survivors of reproductive age is increasing.[2] As the marriage age is delayed, pregnancy is attempted while the ovarian function is deteriorating. Furthermore, as the prevalence of diseases that impair ovarian function such as endometrioma has increased, fertility preservation (FP) has become a necessity.[3] For this reason, the search for patient-oriented FP methods and optimal controlled ovarian stimulation (COS) protocols are crucial for the field of FP.

Fertility in women can be preserved either by embryo or oocyte cryopreservation. Controlled ovarian stimulation in FP is performed in a similar manner as in vitro fertilization (IVF), wherein both methods aim to acquire oocytes. When FP is considered in cancer patients, they often deal with problems that are different from those of infertile patients. These patients usually have only one chance for FP before gonadotoxic treatment, making it necessary to obtain as many oocytes and mature oocytes as possible in this attempt. Patients with benign disease have more opportunities of FP than cancer patients. Even so, there are limitations in the number of oocyte collections or acquisitions due to factors such as surgery, age, and costs.

To induce final oocyte maturation in COS cycles, recombinant human chorionic gonadotropin (rhCG) that mimics the luteinizing hormone (LH) surge should be administered 34–36 h before oocyte retrieval. However, many studies have suggested the use of a gonadotropin-releasing hormone agonist (GnRHa) for oocyte maturation due to the long half-life and continuous luteotrophic activity of rhCG, which could increase the risk of ovarian hyperstimulation syndrome (OHSS).[4,5] It has been reported that when using a GnRHa trigger, metaphase II oocytes yielded similar or better results compared to when rhCG is used.[6,7] However, in the case of embryo transfer (ET) after GnRHa trigger, impaired luteal function can lower the pregnancy and live birth rates, while the abortion rate is increased.[5,8,9] The disadvantage of the GnRHa trigger is that it cannot be used in the luteal long protocol that is already suppressed with GnRHa. However, patients undergoing FP are free from sequential ET because they are expected to become pregnant several years after treatment of the primary diseases. At present, the most crucial aspect for these patients is to obtain as many mature oocytes as possible.

Several studies have described the benefits of dual trigger in IVF/intracytoplasmic sperm injection–embryo transfer (ICSI-ET) cycles. The effect of dual trigger is seen not only in normal responders, but also in patients with diminished ovarian reserve (DOR) and a poor ovarian response (POR), in patients with many immature oocytes in the previous cycle, and in patients with suboptimal responses to GnRHa- or rhCG-only triggers in the previous cycles.[10–17] Concerning the oocyte acquisition index, Zhang et al.[10] reported that the number of mature oocytes, the ratio of mature oocytes, and the rate of oocytes recovered increased with dual trigger compared with the standard rhCG trigger in poor responders who met the Bologna criteria. Recently, similar results were reported by using dual trigger in normal responders.[18,19] The ratio of mature oocytes increased when dual trigger was performed in the following cycle in patients who had an immature oocyte ratio exceeding 25% or 50% in the previous cycle (75% vs. 35% or, 79.6% vs. 43.6%, respectively).[13,20] Castillo et al.[14] reported a case that reached final follicular maturation and succeeded in live birth using the dual trigger method in women with repeated immature oocytes and empty follicle syndrome. Considering the results of infertile patients, better COS outcomes could be obtained in patients for FP; however, few studies have been reported.

To the best of our knowledge, unlike in the general IVF protocol, there have been no studies reporting the efficacy of dual trigger for final oocyte maturation in patients with endometrioma, and especially in patients with breast or endometrial cancer using aromatase inhibitors.

In this study, we verified the effectiveness of dual trigger (rhCG combined with GnRHa) in final oocyte maturation compared with the standard rhCG trigger in women undergoing oocyte or embryo cryopreservation for FP. Subgroup analyses of patients with DOR or endometrioma or of those using aromatase inhibitors were performed to explore specific groups that could benefit from dual trigger. Therefore, this study aimed to establish a protocol that increases the yield of whole and/or mature oocytes in a limited number of COS cycles.

2 | MATERIALS AND METHODS

2.1 | Study design

This retrospective study analyzed patients with GnRH antagonist cycles between May 2010 and February 2021 at the Seoul National University Bundang Hospital (SNUBH). All information was obtained from electronic medical records. The institutional review board (IRB) of SNUBH approved the study (IRB No. B-2006/616-110).

2.2 | Subjects

All patients for whom COS cycles were attempted for oocyte retrieval for FP were enrolled without age limitation. For final oocyte maturation, the groups receiving rhCG alone or rhCG with GnRHa were selected as the physician's preference. Diminished ovarian reserve was defined as an anti-Müllerian (AMH) hormone level of <1.1 ng/ml within 1 year of the start of the cycle. In the case of embryo cryopreservation, procedural outcomes up to final oocyte

acquisition were analyzed. The exclusion criteria were cycles triggered by urinary hCG, GnRHa, a double dose of rhCG, and GnRHa plus a half dose of rhCG and natural cycles. Cases that were discontinued in the middle of the procedure, those with no oocyte retrieval cycles, those with no record of gonadotropin use, and those using other supplements, such as clomiphene citrate or growth hormones with gonadotropin, were also excluded from the final analysis. When one patient attempted multiple cycles, each cycle was considered an independent event.

In patients with breast cancer and endometrial cancer, 5 mg of letrozole (Femara; Novartis) was co-administered with gonadotropins from the cycle start day and continued until the triggering day. The day after triggering, letrozole was skipped for one day. The drug was resumed after oocyte retrieval and continued at least one week until the serum estradiol (E2) levels remained lower than 50 pg/ml.[21] For the letrozole protocol, triggering was performed when two or more leading follicles reached diameters of 20 mm. The COS schedule used for each patient group is shown in Figure 1.

2.3 | Controlled ovarian stimulation protocol

All cycles (n = 373) adhered to GnRH antagonist protocols. Controlled ovarian stimulation was performed using either recombinant follicle stimulating hormone (rFSH; Gonal-F; Merck Serono) or a gonadotropin mixed with LH. The latter contains a purified human menopausal gonadotropin (Menopur; Ferring) or rFSH plus recombinant LH (Pergoveris; Merck Serono). The starting dose of gonadotropin was determined according to age and ovarian reserve. When the leading follicle reached a mean diameter of 13–14 mm, a GnRH antagonist (Cetrotide, 0.25 mg; Merck Serono) was added to inhibit a premature LH surge. When two or more leading follicles reached a mean diameter of ≥18 mm, either 250 μg of rhCG (Ovidrel; Merck Serono) or 250 μg of rhCG plus 0.2 mg of triptorelin (Decapeptyl; Ferring) was administered for final oocyte maturation according to the physician's decision. Oocytes were retrieved 36 h after triggering under ultrasound guidance. After oocyte acquisition, oocyte maturity was assessed by two skilled embryologists. The total dose of gonadotropins used was calculated only for the FSH dose apart from the LH dose.

2.4 | Cycle outcomes

The primary outcomes were the total number of retrieved oocytes, the number of mature oocytes, and the maturation rate. As a secondary outcome, we reported the incidence of OHSS. Other cycle outcome parameters, such as the duration of stimulation, total dose of gonadotropins, and peak estradiol level at the triggering day, were also compared. Subgroup analyses were performed for patients with DOR or endometrioma or those using letrozole.

2.5 | Statistical analysis

All statistical analyses were performed using the SPSS package version 25.0 (SPSS Inc.). Quantitative variables were presented as mean ± SD, and categorical variables were presented as "the number (percentage)" in the tables. The Student's t-test was used to compare the data between the two groups. The chi-square test or Fischer's exact test was used for categorical variables. A p-value < 0.05 was considered statistically significant.

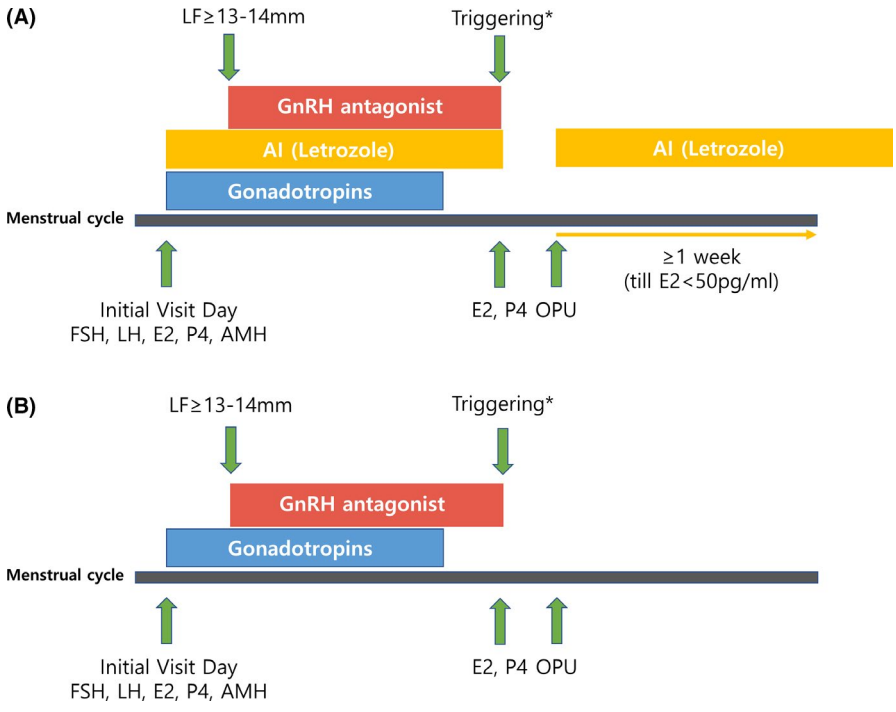

FIGURE 1 (A) A controlled ovarian stimulation protocol for patients with breast or endometrial cancer. (B) A controlled ovarian stimulation protocol, except for patients with breast or endometrial cancer. *Triggering with either recombinant human chorionic gonadotropin (rhCG) or dual triggering (rhCG + GnRHa). AI, aromatase inhibitor; AMH, anti-Müllerian hormone; E2, estradiol; FSH, follicle-stimulating hormone; GnRHa, gonadotropin-releasing hormone agonistLF, leading follicleLH, luteinizing hormone; OPU, ovum pickup; P4, progesterone

3 | RESULTS

Of the 373 cycles in 293 patients, 48 cycles were for embryo cryopreservation and 325 cycles were for oocyte cryopreservation. Among these cycles, 104 had endometrioma, 86 had DOR, and 84 underwent COS with letrozole. The rhCG group comprised 225 cycles, and the dual trigger group had 148 cycles. Concerning indications for breast cancer, hematologic malignancy, gynecologic malignancy, other solid tumor, benign diseases, and DOR or planned oocyte cryopreservation were noted in 82, 12, 43, 22, 137, and 77 cycles, respectively. Benign diseases included mainly endometrioma and other benign ovarian cysts. A total of 232 patients proceeded with only one cycle, and 44 patients continued until the 2nd cycle. Fifteen patients continued until the 3rd cycle, and only 2 patients continued until the 4th cycle. The mean age, body mass index (BMI), and AMH level for all cycles were 31.7 ± 6.0 years, 21.3 ± 2.9 kg/m2, and 2.5 ± 2.5 ng/ml, respectively.

Across all patients, there was no difference in the mean age, BMI, and mean AMH level between the rhCG and dual trigger groups. Fertility preservation in the rhCG and dual trigger groups was performed mostly for benign indications (79 (35.1%) versus 58 (39.2%)) and breast cancer (42 (18.7%) versus 40 (27.0%)). Regarding cycle outcomes, there were no significant differences between the two groups in terms of the total stimulation period, amount of gonadotropins used, peak E2 and progesterone levels on a triggering day, total number of oocytes obtained, oocyte maturation rate, and OHSS rate. The baseline characteristics and cycle outcomes for all cycles are summarized in Table 1. There were no significant differences between the two groups in cycle outcomes when separated by the start period, either the follicular or the luteal phase.

When the cycle outcomes in patients with breast cancer (82 cycles) and endometrial cancer (2 cycles) using letrozole during the COS cycles (84 total cycles) were analyzed, there was no difference between the dual and rhCG trigger groups in the age, BMI, and AMH level (Table 2). There was no difference in the total number of oocytes retrieved from the two groups (11.4 ± 8.6 vs. 8.8 ± 6.0, $p = 0.112$), but the number of mature oocytes in the dual trigger group was significantly higher than that in the rhCG trigger group (6.9 ± 6.0 vs. 4.6 ± 3.6; $p = 0.034$). The maturation rate was also

TABLE 1 Comparison of baseline characteristics and COS outcomes between the rhCG and dual trigger groups in all stimulation cycles

	rhCG trigger (*n* = 225)	Dual trigger (*n* = 148)	*p*-Value
Age (y)	31.3 ± 6.2	32.2 ± 5.7	0.142
BMI (kg/m^2)	21.3 ± 2.8	21.3 ± 3.1	0.925
AMH (ng/ml)	2.6 ± 2.5	2.4 ± 2.5	0.502
Fertility preservation indication			0.048
Breast cancer	42 (18.7%)	40 (27.0%)	
Hematologic malignancy	8 (3.6%)	4 (2.7%)	
Gynecologic cancer	30 (13.3%)	13 (8.8%)	
Other solid tumor	16 (7.1%)	6 (4.1%)	
Benign diseases	79 (35.1%)	58 (39.2%)	
Planned oocyte cryopreservation	50 (22.2%)	27 (18.2%)	
Duration of stimulation (days)	8.3 ± 1.6	8.6 ± 1.7	0.185
Total dose of FSH (IU)	2243.6 ± 646.5	2241.4 ± 672.4	0.975
Menstrual phase on start day			0.862
Follicular	164 (75.2%)	111 (76.0%)	
Luteal	54 (24.8%)	35 (24.0%)	
Trigger day leading follicle diameter (mm)	19.3 ± 1.6	19.1 ± 1.4	0.375
E2 on trigger day (pg/ml)	1225.3 ± 932.9	1164.6 ± 962.0	0.640
P4 on trigger day (ng/ml)	1.2 ± 1.7	1.2 ± 1.5	0.976
Total number of oocytes retrieved (*n*)	7.9 ± 5.7	8.8 ± 7.2	0.187
Number of mature oocytes (*n*)	4.8 ± 3.8	5.7 ± 4.9	0.052
Maturation rate (%)	60.1 ± 28.4	63.8 ± 24.9	0.205
OHSS rate (%)	2.2% (5/225)	4.7% (7/148)	0.232

Note: Data are shown as either mean ± SD or *n* (%).

Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; COS, controlled ovarian stimulation; E2, estradiol; FSH, follicle-stimulating hormone; OHSS, ovarian hyperstimulation syndrome; P4, progesterone.

higher in the dual trigger group, although it was not statistically significant. The frequency of OHSS was not significantly different between the two groups ($n = 2$ (5.0%) vs. $n = 0$ (0%), $p = 0.224$).

In patients with DOR, there was no significant difference between the two groups except for the BMI (Table 3). The same analysis was performed for patients with endometrioma, but there was

TABLE 2 Baseline characteristics and COS outcomes between the rhCG and dual trigger groups in cycles using letrozole in breast and endometrial cancer patients

	rhCG trigger ($n = 44$)	Dual trigger ($n = 40$)	p-Value
Age (y)	33.8 ± 4.8	34.0 ± 5.0	0.920
BMI (kg/m^2)	21.9 ± 2.1	22.0 ± 3.4	0.841
AMH (ng/ml)	3.0 ± 1.9	3.6 ± 3.6	0.360
Duration of stimulation (days)	8.4 ± 1.9	8.8 ± 1.8	0.308
Total dose of FSH (IU)	2229.5 ± 729.4	2394.4 ± 659.6	0.282
Menstrual phase on start day			0.061
Follicular	26 (59.1%)	15 (37.5%)	
Luteal	18 (40.9%)	25 (62.5%)	
Trigger day leading follicle diameter (mm)	19.5 ± 1.4	19.3 ± 2.0	0.727
E2 on trigger day (pg/ml)	482.4 ± 309.6	386.4 ± 313.4	0.262
P4 on trigger day (ng/ml)	1.7 ± 2.5	1.2 ± 0.6	0.306
Total number of oocytes retrieved (n)	8.8 ± 6.0	11.4 ± 8.6	0.112
Number of mature oocytes (n)	4.6 ± 3.6	6.9 ± 6.0	0.034
Maturation rate (%)	50.0 ± 28.0	59.3 ± 26.7	0.124
OHSS rate (%)	0% (0/44)	5.0% (2/40)	0.224

Note: Data are shown as either mean ± SD or n (%).

Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; COS, controlled ovarian stimulation; E2, estradiol; FSH, follicle-stimulating hormone; OHSS, ovarian hyperstimulation syndrome; P4, progesterone.

TABLE 3 Baseline characteristics and COS outcomes between the rhCG and dual trigger groups in stimulation cycles with DOR

	rhCG trigger ($n = 50$)	Dual trigger ($n = 36$)	p-Value
Age (y)	32.0 ± 6.2	34.6 ± 6.0	0.053
BMI (kg/m^2)	20.6 ± 2.2	21.9 ± 3.7	0.039
AMH (ng/ml)	0.6 ± 0.3	0.6 ± 0.3	0.785
Duration of stimulation (day)	8.5 ± 2.1	8.7 ± 2.0	0.651
Total dose of FSH (IU)	2241.0 ± 890.1	2181.3 ± 781.4	0.748
Menstrual phase on start day			0.647
Follicular	39 (78.0%)	27 (75.0%)	
Luteal	9 (18.0%)	8 (22.2%)	
Trigger day leading follicle diameter (mm)	18.9 ± 1.2	18.9 ± 0.9	0.877
E2 on trigger day (pg/ml)	999.2 ± 678.1	657.0 ± 607.8	0.082
P4 on trigger day (ng/ml)	1.3 ± 2.7	1.5 ± 2.4	0.841
Total number of oocytes retrieved (n)	3.7 ± 2.7	3.8 ± 2.2	0.817
Number of mature oocytes (n)	1.9 ± 1.9	2.2 ± 1.4	0.473
Maturation rate (%)	51.1 ± 35.9	56.5 ± 27.7	0.436
OHSS rate (%)	2.0% (1/50)	0% (0/36)	1.000

Note: Data are shown as either mean ± SD or n (%).

Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; COS, controlled ovarian stimulation; DOR, diminished ovarian reserve; E2, estradiol; FSH, follicle-stimulating hormone; OHSS, ovarian hyperstimulation syndrome; P4, progesterone.

no significant difference between the two groups except for the proportion of the start day of stimulation (Table 4).

4 | DISCUSSION

The present study offered a more efficient strategy for the acquisition of mature oocytes, especially for breast and endometrial cancer patients using letrozole combined with GnRH antagonist downregulated COS cycles. Dual trigger with rhCG plus GnRHa for final oocyte maturation results in a higher number of mature oocytes than with the rhCG-only trigger. These results confirm the rationale for setting up a standard protocol for breast and endometrial cancer patients using letrozole in COS cycles.

Dual trigger generates an endogenous midcycle FSH and LH surge to form a hormone milieu, similar to the natural cycle.[12] It has been suggested that FSH increases the yield of mature oocytes by promoting the resumption of oocyte meiosis,[22] cumulus cell expansion,[23] plasminogen activator activity,[24] and formation of LH receptors in luteinizing granulosa cells (GCs),[25] which are all essential steps in oocyte maturation.[12] The LH surge occurs 4 h after the GnRHa trigger, and the FSH surge occurs 8 h after injection. In the case of rhCG injection, the LH surge occurs 24 h later.[26] Therefore, in the case of dual trigger, the two agents act synergistically as rescue triggers, compared with a single rhCG or GnRHa trigger. This effect might contribute to further oocyte maturation.[27] Similar results showing that the dual trigger group was superior in terms of mature oocyte acquisition and fertilization have also been reported.[28] Asynchrony of the nuclear and cytoplasmic maturation may frequently occur in COS cycles; cytoplasmic maturation may not be achieved even if with complete nuclear maturation in the case of a single trigger.[29] Dual triggering increases this ooplasmic maturity.[28]

The suggested molecular mechanism of this effect could be explained by the gene expression changes in the GCs. Amphiregulin and epiregulin, which are involved in cumulus expansion, oocyte maturation, and meiosis resumption, are more highly expressed in the dual trigger group.[30–32] Ben-Ami et al.[33] reported that the enrichment of amphiregulin and epiregulin in the maturation medium significantly improved the maturation rate of human germinal vesicle (GV) oocytes. FSH increases the mRNA expression of amphiregulin and epiregulin in the GCs,[31,32] and hCG and FSH induce mRNA expression of these two genes through different pathways.[30] Furthermore, the mRNA expression of connexin 43, a constituent of gap junctions, in the cumulus cells was significantly lower in the dual trigger group compared to that in the rhCG trigger group.[30] Cumulus cells treated with FSH have a higher number of open gap junctions than the control group not treated with FSH.[34] Atef et al.[35] demonstrated that FSH helps to keep the gap junction open between the oocyte and the cumulus cells; thus, it may have an important role in signaling pathways. Dual trigger affects the mRNA expression of these GC genes, which can impact oocyte maturation.[30] A recent transcriptomic analysis shows that many genes are changed upon dual trigger, supporting key pathways of oocyte maturation and extracellular matrix remodeling for the growing follicles.[36]

TABLE 4 Baseline characteristics and COS outcomes between the rhCG and dual trigger groups in stimulation cycles with endometrioma

	rhCG trigger (n = 60)	Dual trigger (n = 44)	p-Value
Age (y)	32.2 ± 5.3	30.7 ± 5.2	0.148
BMI (kg/m^2)	20.9 ± 2.9	21.1 ± 3.0	0.780
AMH (ng/ml)	1.7 ± 1.0	1.8 ± 1.2	0.760
Bilaterality of endometrioma (%)	29 (48.3%)	22 (50.0%)	0.932
Diameter of largest endometrioma (cm)	5.0 ± 2.3	5.8 ± 2.3	0.085
Duration of stimulation (days)	8.4 ± 1.5	8.5 ± 1.4	0.659
Total dose of FSH (IU)	2480.0 ± 606.8	2215.9 ± 714.5	0.051
Menstrual phase on start day			0.029
Follicular	59 (98.3%)	39 (88.6%)	
Luteal	0 (0%)	4(9.1%)	
Trigger day leading follicle diameter (mm)	19.2 ± 1.0	19.1 ± 0.9	0.828
E2 on trigger day (pg/ml)	1358.1 ± 851.3	1183.7 ± 956.3	0.473
P4 on trigger day (ng/ml)	1.1 ± 1.4	1.0 ± 1.4	0.887
Total number of oocytes retrieved (n)	6.8 ± 4.8	6.6 ± 4.8	0.864
Number of mature oocytes (n)	4.1 ± 3.2	4.2 ± 3.5	0.836
Maturation rate (%)	60.8 ± 28.4	60.9 ± 26.3	0.996
OHSS rate (%)	0% (0/60)	6.8% (3/44)	0.073

Note: Data are shown as either mean ± SD or n (%).

Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; COS, controlled ovarian stimulation; E2, estradiol; FSH, follicle-stimulating hormone; OHSS, ovarian hyperstimulation syndrome; P4, progesterone.

A protocol to suppress E2 level elevations by taking letrozole during the COS cycles to prevent the potential negative effect caused by the rise of supraphysiological levels of serum E2 in breast cancer patients was first proposed by Oktay.[37–39] Letrozole has additional benefits of reducing the required dose of gonadotropins by suppressing the negative feedback to the hypothalamic–pituitary axis along with E2-level inhibition.[38] In many studies comparing letrozole-combined protocols and conventional protocols in the COS cycles, the number of mature oocytes acquired and/or the oocyte maturation rate in the former was reported to decrease significantly.[38,40,41] The reason for this effect remains unclear, but the low intrafollicular E2 levels might be the main cause.[40] According to the in vitro study, aromatase inhibitors alter follicular fluid dynamics by promoting early antral cavity formation.[42] Reddy et al.[7] compared the final oocyte maturation effects of either GnRHa or rhCG triggers in breast cancer patients. The maturation rate and mature oocyte numbers were significantly higher, and the mild or moderate OHSS rate was lower in the GnRHa trigger group. Similarly, GnRHa in dual trigger induces endogenous FSH and LH surges that mimic the natural cycle, providing a more physiologic follicular fluid environment for the follicles. Low maturity is a challenge in the letrozole-combined COS regimens, and mature oocytes can be obtained by maintaining secondary maturation through rhCG while taking advantage of the physiologic benefits of GnRHa by applying the results in the IVF/ET cycle. While Revelli et al.[43] reported that 40% of lower mature oocytes were obtained in the letrozole regimen, the average maturation rate of the dual trigger group was 60% in our study. This is an encouraging outcome and is clinically meaningful for the letrozole-combined regimen compared to that of the rhCG trigger, where the maturation rate was 50%. As a result of the improved maturation rate, significantly more mature oocytes were collected in the dual trigger group. The reason for the statistically nonsignificant difference in the maturation rate might be due to the relatively small number of patients enrolled. There have been reports that a high maturation rate can be achieved by triggering when at least two leading follicles reach 20 mm.[38] We also used the same triggering criteria, and a synergistic effect is expected if dual triggering is performed together, as observed in our results. There may be concerns about whether differences in the menstrual cycle start day affects the FP outcomes. Although the duration of simulation and total dose of gonadotropins used were higher in the random-start group, the number of total and mature oocytes and the oocyte maturity rate were even higher in the random start group than in the conventional start group.[41] Furthermore, the addition of letrozole did not negatively affect the acquisition of total oocytes. However, oocyte maturity was slightly lower in the letrozole group compared to that in the conventional group, but this could be overcome by dual trigger, as presented here.

In DOR patients, the number of retrieved mature oocytes and maturation rates did not differ between the two groups, which is also consistent with the results of Lin et al. In DOR patients, low oocyte retrieval was expected, so it was challenging to derive meaningful results from the small sample size. Previous studies that reported the effect of dual trigger on the number of total oocytes obtained or the number of mature oocytes in DOR or POR patients had larger sample sizes and stricter inclusion criteria than our study. Zhang et al.[10] included 1350 patients who met the Bologna criteria, and Lin et al. enrolled 427 POR patients with an antral follicle count (AFC) of ≤5 and an AMH level of ≤1.1 ng/ml. Contrastingly, in our study, the definition of DOR was set to an AMH level of <1.1 ng/ml because fewer patients were enrolled in our study who met the Bologna criteria. In addition, it was difficult to recover an AFC value because some of the patients started their cycles in the luteal phase, and most cases were the first cycles without previous attempts. Therefore, our definition of DOR may be broader than in previous studies.

While previous studies have shown that COS outcomes could be worse if endometrioma is present,[3,44,45] there has been no previous study on the effect of dual triggering in patients with endometrioma. According to this study, dual trigger does not appear to be of great help in these patient groups. It is assumed that the harmful effects of the endometrioma cannot be recovered with dual triggering because the mechanism of the lower oocyte quantity and quality does not originate from an altered oocyte maturation process.

Our study has some limitations. Certain patient groups, such as patients with DOR, have a small sample size, and the study has a retrospective nature. Therefore, a prospective study with a large number of patients is needed in future.

To the best of our knowledge, this is the first study to report the effect of dual trigger on oocyte maturation in hormone-sensitive cancer patients using letrozole in COS cycles for fertility preservation, thereby helping to establish a patient-oriented COS protocol. The combination of a standard dose of rhCG and GnRHa for final oocyte maturation can improve the number of mature oocytes and the maturation rate in these patient groups.

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None.

CONFLICT OF INTEREST

None.

HUMAN RIGHTS STATEMENTS AND INFORMED CONSENT

Informed consent from the patients was waived due to anonymity, and the study protocol for this research project was approved by the appropriate ethics review board (Seoul National University Bundang Hospital Institutional Review Board (SNUBH IRB) No. B-2006/616-110).

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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