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GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation

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Abstract

Aromatase inhibitors can be utilized to minimize oestrogen exposure in breast cancer patients undergoing gonadotrophin stimulation. This retrospective-prospective study determined whether using a gonadotrophin-releasing hormone agonist (GnRHa) trigger instead of human chorionic gonadotrophin (HCG) would reduce oestrogen exposure and improve cycle outcomes in aromatase inhibitor cycles. Seventy-four breast cancer patients who desired fertility preservation, with normal ovarian reserve and <45 years of age received letrozole 5 mg/day plus recombinant FSH 150–300 IU/day for ovarian stimulation. Subjects either received HCG 5000–10,000 IU ($n = 47$) or leuprolide acetate 1 mg (GnRHa, $n = 27$) as trigger. Oestradiol measurements were repeated 4 days after the trigger and subjects were evaluated for ovarian hyperstimulation syndrome (OHSS). In the GnRHa group, oestradiol concentrations dropped significantly after the trigger than the HCG group ($P = 0.013$) and there was a lower incidence of OHSS. GnRHa trigger resulted in a higher number and percentage of mature oocytes and a higher number of cryopreserved embryos or oocytes compared with HCG. GnRHa trigger improves outcomes by increasing the yield of mature oocytes and embryos in aromatase inhibitor cycles and also decreases the post-trigger oestradiol exposure as well as OHSS risks in women with breast cancer.

Keywords

aromatase inhibitors; cryopreservation; fertility preservation; GnRHa; GnRH antagonist; ovarian stimulation

Introduction

Breast cancer is the most common malignancy encountered during reproductive years. In general, 25% of breast cancers occur prior to menopause (Hankey *et al.*, 1994). Further, while the incidence of post-menopausal breast cancer appears to be on the decline, the incidence of breast cancer has not changed in young women (Brinton *et al.*, 2008). Thus the relative frequency of breast cancer may be on the rise in reproductive age women. Recognizing the importance of fertility issues in cancer patients, the American Society of

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Clinical Oncology has published guidelines for fertility preservation in cancer patients (Lee *et al.*, 2006).

Patients of reproductive age often find the prospect of infertility as one of the most devastating consequences of their cancer treatment (Partridge *et al.*, 2004) and, as a result, many young cancer patients explore their fertility preservation options before starting gonadotoxic treatments. Embryo and oocyte cryopreservation are the most common methods of fertility preservation, the former being an established method. Ovarian stimulation takes 2 weeks from the beginning of the menstruation and because there is a typical gap of 4–6 weeks between surgery and chemotherapy, women with breast cancer often have sufficient time to undergo this procedure. However, fear of increased oestrogen exposure during gonadotrophin stimulation performed during embryo and oocyte cryopreservation procedures has previously limited the use of these options for women with breast cancer.

To minimize oestrogen exposure during ovarian stimulation, a previous report utilized an ovarian stimulation protocol with an aromatase inhibitor (letrozole) along with gonadotrophins in women with breast cancer (Controlled Ovarian Stimulation Treatment with Letrozole Supplementation Study, COST-LESS) (Oktay *et al.*, 2005). The study showed that this protocol resulted in lower peak oestradiol concentrations (Oktay *et al.*, 2005) and similar outcomes to standard IVF cycles in non-cancer patients (Oktay *et al.*, 2006) and did not increase breast cancer recurrence rates (Azim *et al.*, 2008).

The original protocol used human chorionic gonadotrophin (HCG) to trigger the final maturation of oocytes as has been used in routine IVF cycles. However, HCG has a considerably longer half-life compared with endogenous LH and, as a result, further increases and prolongs production of oestradiol after the egg retrieval. Further, women who are triggered by HCG are at high risk of ovarian hyperstimulation syndrome (OHSS), a complication of gonadotrophin stimulation that is characterized by ovarian enlargement, pelvic discomfort and in severe cases, ascites, haemoconcentration, electrolyte imbalance and thrombosis. Development of OHSS may prompt physicians to delay chemotherapy until the patient is haemodynamically stable.

An additional drawback of the HCG trigger is its effect on the interpretation of a pregnancy test, which is often required before initiating chemotherapy. After i.m. injection, HCG remains in the circulation for nearly 12 days and results in a false positive pregnancy test, causing unnecessary delays in the initiation of chemotherapy in a number of cases.

Leuprolide acetate is a gonadotrophin-releasing hormone (GnRH) analogue which acts as an agonist in the first 72 hours of administration, before it shuts down the hypothalamic–pituitary axis. Thus, when administered to an oestrogen-primed woman, it triggers an LH surge and initiates oocyte maturation and ovulation. Recent studies showed that GnRH agonist (GnRHa) trigger instead of HCG may in general yield similar results in infertile women undergoing IVF treatment with or without donor eggs (Fauser *et al.*, 2002; Kol, 2004; Kolibianakis *et al.*, 2005; Erb *et al.*, 2009). The purpose of the current study was to determine whether the utilization of GnRHa instead of HCG as a trigger would reduce the post-HCG oestrogen exposure and lessen the likelihood of OHSS and, as a result, increase the overall safety and acceptability of the COST-LESS protocol.

Materials and methods

Subjects

The letrozole-IVF protocol was approved by the institutional review board. The study subjects were referred by their breast oncologist for fertility preservation. Given the recent

data showing the effectiveness of GnRHa as a trigger in infertile women undergoing IVF (Olivennes *et al.*, 1996), GnRHa instead of HCG was used as the trigger in women with breast cancer who were being stimulated with the COST-LESS protocol. Starting in January 2008, all but three patients received GnRHa. Those three patients received HCG because GnRHa was not covered under the Sharing Hope grant (Fertile Hope, NY, USA). The results were then retrospectively compared with those from women who had undergone treatment with the original COST-LESS protocol, which utilized HCG as the trigger between January 2006 and December 2007 (NCT00504699).

Inclusion criteria

The inclusion criteria were: (i) histologically proven breast cancer diagnosis; (ii) age 18– 45 years; (iii) no prior chemotherapy; (iv) normal basal concentrations (day 2 or 3) of FSH (<13 mIU/ml) and oestradiol (<75 pg/ml); (v) no prior history of infertility; and (vi) absence of hypothalamic dysfunction.

Ovarian stimulation with COST-LESS protocol

The details of the COST-LESS protocol have been reported previously (Oktay *et al.*, 2005). Briefly, 5 mg letrozole was administered orally starting on cycle day 2 or 3. After 2 days of letrozole administration, 150–300 IU/day rFSH (Gonal-F or Follistim; Serono, Rockland, MA, USA) was added to the stimulation depending on the age of patient and antral follicle count on cycle day 2 or 3. When the oestradiol concentration exceeded 250 pg/ml (917 pmol/l) or the leading follicle reached 13 mm in diameter, a GnRH antagonist (Antagon 250 μg; Organon, Roseland, NJ, USA; or Cetrotide 250 μg; Serono) was administered to prevent premature LH surge. All medications, i.e. letrozole, gonadotrophins and GnRH antagonist were discontinued on the day of the trigger. GnRH antagonists were always administered in the evening; hence, the trigger was usually within 24 hours of the last GnRH antagonist injection. When at least two leading follicles reached 20 mm, oocyte maturation was triggered by HCG (5000–10,000 IU HCG (Organon) or 250 μg recombinant HCG (Serono) or GnRHa (leuprolide acetate 1 mg (Ferring Pharmaceuticals, Parsippany, NJ, USA). The HCG dose was adjusted based on peak oestradiol concentrations and the type of HCG was chosen based on patients' medical insurance or participation in the Sharing Hope programme. Oocyte retrieval was performed 34–36 hours after ovulation trigger transvaginally. Oocytes were either cryopreserved without fertilization if the patient had no partner or did not want to use donor spermatozoa, or fertilized *in vitro* by intracytoplasmic sperm injection if patients had a partner or wanted to use donor spermatozoa. For patients without a partner and who wished to use donor spermatozoa to cryopreserve embryos but wanted to spare some oocytes for a potential future partner, both oocyte and embryo cryopreservation were performed. Letrozole was reinitiated on the day of retrieval and continued until oestradiol concentrations fell below 50 pg/ml (183 pmol/l).

Patient follow-up

Each patient underwent baseline evaluation with ultrasound, oestradiol, FSH and LH measurements on cycle day 2 or 3. Subsequently, patients were monitored by pelvic ultrasound and oestradiol measurements until the oocyte retrieval (peak oestradiol). Oestradiol, FSH and LH measurements were performed by chemiluminescent immunoassay (Immulite 2000); Diagnostic Products Corporation, Los Angeles, CA, USA). The oestradiol assay had a minimum sensitivity of 10 pg/ml, an intra-assay coefficient of variation (CV) of 4.2–16% and an inter-assay CV of 7.3–15.3%. The FSH assay had a sensitivity of 0.1 mIU/ml, an intra-assay CV of 2.1–2.9% and an inter-assay CV of 4.3–6.3%. The LH assay had a sensitivity of 0.05 mIU/ml, an intra-assay coefficient of variation (CV) of 3.04–3.71% and an inter-assay CV of 6.2–6.7%.

The occurrence of OHSS was also evaluated for each patient, typically at the time of the return visit for repeat oestradiol measurement post trigger. This involved symptom assessment, a physical examination, ultrasound evaluation of the adnexa and, when indicated, assessment of haemoconcentration. OHSS was classified based on established clinical criteria (Schenker, 1999; Practice Committee of the American Society for Reproductive Medicine, 2003; Lunenfeld *et al.*, 1993; Whelan *et al.*, 2000; Elchalal *et al.*, 1997). Briefly, mild hyperstimulation was defined by bilateral ovarian enlargement up to 5 × 5 cm with mild to moderate abdominal discomfort. Moderate hyperstimulation was defined by ovaries enlarged up to 12 × 12 cm, accompanied by moderate to severe abdominal discomfort. Severe hyperstimulation was defined by the presence of ovaries larger than 12 × 12 cm, ascites, and, in some patients, pleural and/or pericardial effusion, electrolyte imbalance and haemoconcentration.

Statistical analysis

Comparison between groups regarding age, body mass index (BMI), baseline FSH concentrations, total gonadotrophin dose and FSH stimulation duration was performed by one-way analysis of variance (ANOVA). Cycle outcomes and the change in oestradiol concentrations were compared using the univariate analysis of variance (two-Way ANOVA) to control for the independent variables age, BMI, baseline FSH concentration and total gonadotrophin dose. Fertilization rates were compared between groups for the patients that underwent in-vitro fertilization by intracytoplasmic sperm injection for embryo cryopreservation only. Comparison of OHSS incidence between groups was carried out by Fisher's exact test. A P-value <0.05 was considered as statistically significant. An a-priori power calculation was not performed as this was a mixed retrospective-prospective study.

Results

Patient and cycle characteristics

Of the 92 patients who were stimulated with COST-LESS protocol, 74 met the inclusion criteria. Of those 74 women, 27 were triggered with GnRHa and 47 were triggered with HCG.

The two groups were comparable regarding age and baseline FSH concentrations. In the GnRHa and HCG groups, respectively, the mean ages were 33.6 ± 4.4 and 35.0 ± 4.3 years and mean baseline FSH concentrations were 8.2 ± 2.9 and 6.8 ± 2.7 mIU/ml. However, BMI was lower in the GnRHa group (21.5 ± 2.5 versus 23.3 ± 4.2 kg/m^2; P = 0.047). The mean duration of FSH stimulation (9.9 ± 1.6 and 9.6 ± 1.6 days) and the mean total amount of gonadotrophin administered (1994.4 ± 549.1 and 2012.8 ± 603.5 IU) were not significantly different between the GnRHa and HCG groups, respectively (Table 1).

Cycle outcomes

Mean peak oestradiol concentration (on the day of trigger) was significantly higher in the GnRHa group compared with HCG (695.5 ± 539.0 and 472.6 ± 345.5 pg/ml; P = 0.044) (Table 2). Mean total number of oocytes retrieved was similar in the GnRHa and HCG groups (16.4 ± 10.3 and 12.8 ± 7.7, respectively). However, the mean number of metaphase II (MII) oocyte (11.9 ± 6.6 and 7.4 ± 4.9; P < 0.001) and the mean maturation rate (77.3 ± 21.1% and 68.5 ± 23.3%; P = 0.049) were significantly higher in the GnRHa group compared with the HCG group. Mean fertilization rate was also higher in the GnRHa group (84.1 ± 11.1% and 74.0 ± 24.9%; P = 0.027). As a consequence, mean number of two pronuclei (2PN) embryos was higher in the GnRHa group (9.3 ± 5.7 and 6.3 ± 4.6; P = 0.008) (Table 2).

The percentage drop in oestradiol concentrations from trigger day (peak oestradiol) to 4 days after trigger was significantly higher in the GnRHa group compared with the HCG group (from 695.5 ± 539.0 to 59.2 ± 37.0 compared with 472.6 ± 345.5 to 86.34 ± 94.44 pg/ml; 89.5 ± 6.3% versus 79.0 ± 13.4%; $P = 0.013$) indicating that GnRHa had a suppressive effect on oestrogen production after trigger.

Only one patient (3.7%) in the GnRHa group and six patients (12.8%) in the HCG group developed mild OHSS. The only case of OHSS in the GnRHa group was classified as mild because the patient had a moderate amount of pain, which lasted briefly without significant enlargement of ovaries. Her peak oestradiol was 1746.8 pg/ml and 25 oocytes were retrieved. Moderate OHSS was encountered only in the HCG group in four patients (8.5%). There was no severe OHSS in either group. The incidence of mild and moderate OHSS was significantly lower in the GnRHa group compared with HCG (3.7 versus 21.3%; $P = 0.047$).

Discussion

This study reports for the first time the use of GnRHa as an oocyte maturation trigger in women with breast cancer undergoing IVF with aromatase inhibitor supplementation (COST-LESS). The study found that GnRHa trigger resulted in a greater drop in oestradiol concentrations and lower OHSS incidence indicating that the oestrogen exposure was lower compared with HCG trigger. Furthermore, following the GnRHa trigger in COST-LESS cycles, the oocyte maturation rate, the number of MII oocytes retrieved, fertilization rate and the number of 2PN embryos were significantly greater when compared with the HCG trigger and hence GnRHa both reduced oestrogen exposure and improved cycle outcomes.

This study showed that a significant advantage of the GnRHa trigger for women with breast cancer is diminished oestrogen concentrations in the luteal phase following the trigger. Lower oestrogen exposure in breast cancer should, at least in theory, make the protocol safer and more acceptable for breast cancer patients. The study found that the drop in oestradiol concentrations from trigger day to 4 days after trigger was significantly greater after the GnRHa trigger. This finding is supported by the study by Fauser *et al.* (2002) in infertility patients, which showed that oestradiol and progesterone concentrations were significantly lower in the GnRHa group during the luteal phase although these concentrations were comparable on the day of retrieval.

OHSS is a syndrome associated both with prolonged elevated oestrogen concentrations and potential medical complications requiring hospitalization and is therefore an important safety aspect of the treatment. In addition to the concern of prolonged oestrogen exposure with OHSS in breast cancer patients, development of OHSS may also result in the delay of the initiation of chemotherapy. Further, because cancer patients in general are at higher risk for thrombotic events, risk of thrombosis associated with OHSS may be higher in these patients. This study showed that GnRHa trigger decreased the incidence of mild/moderate OHSS. Reassuringly, it did not encounter severe OHSS in either group, probably owing to the fact that pregnancy was not attempted. Only one patient (3.7%) developed mild OHSS in the GnRHa group. In contrast, 21.3% of subjects developed either mild ($n = 6$) or moderate ($n = 4$) OHSS in the HCG group. Interestingly, despite significant suppression of oestradiol concentrations from letrozole supplementation, these patients still experienced OHSS symptoms. This observation suggests that high oestradiol concentrations do not have a causative relationship with OHSS.

In addition to reducing oestrogen exposure, the study also showed that the GnRHa trigger was associated with improved cycle outcomes. However, this study was not prospectively randomized and there are no pregnancy outcome data as many of these women have not yet

returned for embryo transfer. In the GnRHa group, the oocyte yield was marginally better and thus one can argue that the improved oocyte maturity and fertilization rates can be related to better stimulation in that group. The peak oestradiol concentration was slightly elevated in the GnRHa group. Although this may represent a stronger response to stimulation in the GnRHa group, this study controlled for any confounding factors such as age, baseline FSH, BMI and total gonadotrophin dose in the final analysis and this did not change the results. Nevertheless, the differences in BMI and MII oocyte yield might have been responsible for the difference in peak oestradiol concentrations.

A number of prospective randomized studies have evaluated the effect of GnRHa trigger on the cycle outcomes in non-cancer infertility populations. Two of those studies showed that the number of oocytes and MII oocytes retrieved were similar when compared with HCG trigger (Fauser *et al.*, 2002; Kolibianakis *et al.*, 2005). In the study byHumaidan *et al.* (2005), the proportion of MII oocytes was significantly higher following GnRHa trigger, consistent with the present study's findings. All three studies reported similar fertilization rates between GnRHa and HCG trigger. Further, the study by Fauser *et al.* (2002) demonstrated similar pregnancy rates when proper luteal-phase hormonal support was provided to compensate the hormonal suppression caused by GnRHa administration. Likewise, Engmann *et al.* (2008) showed that pregnancy rates are similar to HCG-treated cycles with appropriate luteal-phase supplementation in embryo-transfer cycles. Nevertheless, the present study was not designed to assess the impact of leuprolide trigger on oocyte maturity; this was an incidental finding. Hence, larger prospective studies will be needed to determine whether leuprolide trigger improves mature oocyte yield in IVF cycles.

Concerns regarding the impact of GnRHa on oocyte and embryo quality and quantity were further addressed in patients undergoing IVF with donor oocytes whose donors were triggered with GnRHa.Acevedo *et al.* (2006) demonstrated that the number of total and mature oocytes and number of good-quality embryos were greater in the GnRHa group compared with the HCG group. The study byErb *et al.* (2009) did not find a difference in oocyte quality or fertilization when GnRHa or HCG was used as a trigger in donor oocyte cycles. Both studies reported similar fertilization, implantation and clinical pregnancy rates with GnRHa compared with HCG trigger (Erb *et al.*, 2009; Acevedo *et al.*, 2006). Thus, while there are no data on the pregnancy outcome when GnRHa trigger is used in aromatase inhibitor cycles, the above data is reassuring that the pregnancy outcome in GnRHa-triggered cycles is likely to be at least as good as in HCGed cycles.

In conclusion, GnRHa trigger in COST-LESS cycles in breast cancer patients undergoing fertility preservation appears to be associated with more favourable cycle outcomes compared with HCG cycles while resulting in more significant drop in oestradiol concentrations and lower incidence of OHSS. Lower incidence of OHSS and a more significant decline in oestrogen concentrations post GnRHa trigger suggests that oestrogen exposure may be less with this approach. Considering these advantages, it is proposed that a GnRHa trigger should be used in all women with oestrogen-sensitive cancer while undergoing ovarian stimulation.

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Biography

Table 1

Patient and cycle characteristics in COST-LESS (Controlled Ovarian Stimulation Treatment with Letrozole Supplementation Study) cycles triggered with human chorionic gonadotrophin (HCG) versus gonadotrophin-releasing hormone agonist (GnRHa).

Characteristic	**HCG (*n* = 47)**	**GnRHa (*n* = 27)**
Age (years)	35.0 ± 4.3	33.6 ± 4.4
Body mass index (kg/m^2)	23.3 ± 4.2[a]	21.5 ± 2.5[a]
Baseline FSH (mIU/ml)	6.8 ± 2.7	8.2 ± 2.9
FSH stimulation duration (day)	9.6 ± 1.6	9.9 ± 1.6
Total gonadotrophin dose (IU)	2012.8 ± 603.5	1994.4 ± 549.1

All values are mean ± SD.

[a] $P = 0.047$.

Table 2

Outcomes of the COST-LESS (Controlled Ovarian Stimulation Treatment with Letrozole Supplementation Study) cycles triggered with human chorionic gonadotrophin (HCG) versus gonadotrophin-releasing hormone agonist (GnRHa).

Parameter	**HCG trigger (*n* = 47)**	**GnRHa trigger (*n* = 27)**	***P*-value**
Peak oestradiol (pg/ml)	472.6 ± 345.5	695.5 ± 539.0	0.044
Endometrial thickness (mm)	8.8 ± 1.8	8.4 ± 2.3	NS
Total oocytes	12.8 ± 7.7	16.4 ± 10.3	NS
Mature oocytes	7.4 ± 4.9	11.9 ± 6.6	<0.001
Oocyte maturation rate (%)	68.5 ± 23.3	77.3 ± 21.1	0.049
Two-pronuclei embryo[a]	6.3 ± 4.6	9.3 ± 5.7	0.008
Fertilization rate (%)	74.0 ± 24.9	84.1 ± 11.1	0.027
Drop in oestradiol from day 0 to 4 (%)	79.0 ± 13.4	89.5 ± 6.3	0.013
Mild or moderate OHSS (%)	10 (21.3)	1 (3.7)	0.047

Values are mean ± SD or number (%).

[a]35 and 19 patients underwent embryo freezing in the HCG and GnRHa groups, respectively. Others underwent egg freezing.

NS = not statistically significant; OHSS = ovarian hyperstimulation syndrome.