Gonadotropin-releasing hormone agonist trigger increases the number of oocytes and embryos available for cryopreservation in cancer patients undergoing ovarian stimulation for fertility preservation

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Objective: To compare the oocyte and embryo yield associated with GnRH-agonist triggers vs. hCG triggers in cancer patients undergoing controlled ovarian stimulation (COS) for fertilization preservation.
Design: Retrospective cohort study.
Setting: Academic center.
Patient(s): Cancer patients undergoing COS with letrozole and gonadotropins or gonadotropin-only protocols for oocyte or embryo cryopreservation.
Intervention(s): Gonadotropin-releasing hormone agonist or hCG trigger.
Main Outcome Measure(s): Number of metaphase II (MII) oocytes or two-pronuclei (2PN) embryos available for cryopreservation were primary outcomes. Separate multivariate linear regression models were used to assess the effect of trigger type on the primary outcomes, after controlling for confounders of interest.
Result(s): A total of 341 patients were included, 99 (29.0%) in the GnRH-agonist group and 242 (71%) in the hCG group. There was no difference in the baseline demographics of patients receiving GnRH-agonist or hCG triggers. Within the letrozole and gonadotropins group (n = 269), the number (mean ± SD, 11.8 ± 5.8 vs. 9.9 ± 6.0) and percentage of MII oocytes (89.6% vs. 73.0%) available for cryopreservation was higher with GnRH-agonist triggers compared with hCG triggers. Similar results were noted with GnRH-agonist triggers in the gonadotropin-only group (n = 72) (i.e., a higher number [13.3 ± 7.9 vs. 9.3 ± 6.0] and percentage of MII oocytes [85.7% vs. 72.8%] available for cryopreservation). Multivariate linear regression demonstrated approximately three more MII oocytes and 2PN embryos available for cryopreservation in the GnRH-agonist trigger group, irrespective of cancer and COS protocol type.
Conclusion(s): Utilization of a GnRH-agonist trigger increases the number of MII oocytes and 2PN embryos available for cryopreservation in cancer patients undergoing COS for fertility preservation. (Fertil Steril® 2017;108:532–8. ©2017 by American Society for Reproductive Medicine.)
Key Words: Breast cancer, cancer, fertility preservation, GnRH-agonist trigger, ovarian stimulation

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Reproductive-age women with a cancer diagnosis often find the risk of infertility to be one of the most distressing consequences of their cancer treatment (1). Recognizing the importance of this quality of life topic, the American Society of Reproductive Medicine and the American Society of Clinical Oncology recommend that fertility preservation be discussed as early as possible in treatment planning (2, 3). Currently oocyte and embryo cryopreservation are the most common methods used for fertility preservation. Unfortunately, in cancer patients there is often a limited window of time before the initiation of chemotherapeutic agents to undergo controlled ovarian stimulation (COS) and cryopreservation. For example, in breast cancer patients there is usually a time period of approximately 2-4 weeks between their initial surgery and the initiation of chemotherapy (3). Therefore, the establishment of an efficient and safe protocol that results in the largest yield of mature oocytes and embryos for cryopreservation is of utmost importance to improve the chances of future genetic parenthood in cancer patients.

Several studies have reported on the use of a GnRH-agonist ovulatory trigger to improve the safety of COS by reducing the incidence of ovarian hyperstimulation syndrome (OHSS) (4–8). Additionally, emerging data also suggest that the utilization of a GnRH-agonist trigger increases the yield of mature oocytes when compared with the utilization of a standard hCG trigger (9). Specifically, larger cohorts of metaphase II (MII) oocytes have been obtained in oocyte donors (10) and in patients undergoing IVF when they received GnRH-agonist triggers compared with standard hCG triggers (9, 11, 12).

Despite this, there are limited data on whether a GnRH-agonist trigger can improve the yield of mature oocytes or embryos in cancer patients. To date, only a few studies have examined the use of a GnRH-agonist ovulatory trigger in the cancer patient population, but these investigations were generally limited to breast cancer patients undergoing COS with letrozole-based protocols (13, 14). Therefore, the primary objective of this study is to determine whether the utilization of a GnRH-agonist ovulatory trigger increases the yield of mature oocytes and embryos in patients undergoing COS for fertility preservation, irrespective of the cancer and protocol type.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

Women desiring cancer-related fertility preservation, referred to the Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine during a 10-year period by their oncologists, were assessed for potential inclusion. At our center ovarian stimulation for oocyte or embryo cryopreservation generally occurs in the 2–4-week interval between cancer diagnosis and initiation of cancer treatment. Thus, all patients undergoing oocyte or embryo cryopreservation for cancer diagnoses were included in the present study. Patients receiving neoadjuvant chemotherapy or radiation before ovarian stimulation were excluded from the analysis. Furthermore, patients undergoing fertility preservation for elective reasons or noncancer diagnoses were also excluded. Our study was approved by the institutional review board at Weill Cornell Medical College.

Clinical and Laboratory Protocols

Ovarian stimulation, oocyte retrieval, and oocyte or embryo cryopreservation were performed according to previously described protocols (15). Controlled ovarian stimulation was carried out to maximize follicular response while minimizing the risk of OHSS. Dosing of gonadotropins (Gonal-F [EMD-Serono] or Follistim [Merck]; and Menopur [Ferring Pharmaceuticals]) was based on age, body mass index (BMI, kg/m^2), antral follicle count (AFC), and serum antimüllerian hormone (AMH) level. The majority of cancer patients began COS on the second day of their menstrual cycle (i.e., conventional ovarian stimulation), whereas the remaining underwent random-start ovarian stimulation. Ovulation was suppressed using once-daily injections of Cetrotide (EMD-Serono) according to a previously described flexible protocol (15). Patients with estrogen-sensitive cancers (breast and endometrial) were given letrozole (Femara, Novartis), 5 mg once daily, for the entire duration of ovarian stimulation until the day of ovulatory trigger and then restarted after oocyte retrieval.

Human chorionic gonadotropin in the form of 250 μg Ovidrel (EMD-Serono) or 10,000 IU Novarel (Ferring Pharmaceuticals) was used as the ovulatory trigger in most patients. However, on the basis of independent studies reporting a higher oocyte yield in cancer patients receiving GnRH-agonist triggers (9–14), patients were prospectively treated with a 4-mg dose of GnRH-agonist (leuprolide acetate, Sandoz), generally according to physician preference. Patients were given the ovulatory trigger when the two lead follicles attained a mean diameter of $>$17 mm in gonadotropin-only protocols (15, 16). For letrozole-based protocols, ovulatory trigger criteria described by Azim et al. (17) was used (i.e., at least two lead follicles attained a mean diameter of $>$19 mm). All oocyte retrievals were performed approximately 35–36 hours after the ovulatory trigger under conscious sedation with transvaginal ultrasound guidance. To remove the cumulus cells, retrieved oocytes were exposed to 40 IU recombinant hyaluronidase (Cumulase, Halozyme Therapeutics) (18). Oocyte maturity was confirmed by the presence of a polar body. Intracytoplasmic sperm injection (ICSI) was performed on the oocytes retrieved from patients desiring cryopreservation of embryos as per our center's practice (19). These oocytes were examined 14–17 hours after fertilization for the presence of two distinct pronuclei (2PN) and two clear polar bodies, thereby confirming normal fertilization. Cryopreservation of oocytes or 2PN embryos was performed using slow-cooling before 2010 (20) and vitrification after 2010 (21).

Study Variables

Baseline demographics recorded were age, BMI (kg/m^2), FSH, AMH level (ng/mL), AFCs, type of cancer (solid vs. hematogenous), and type of ovarian stimulation (conventional vs.