Tamoxifen co-administration during controlled ovarian hyperstimulation for in vitro fertilization in breast cancer patients increases the safety of fertility-preservation treatment strategies

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Objective: To evaluate the safety and efficacy of tamoxifen co-administration during conventional controlled ovarian hyperstimulation (COH) protocols for a fertility-preservation IVF cycle in breast cancer patients.
Design: Two groups: retrospective descriptive cohort study and prospective study.
Setting: Breast cancer oncology and fertility-preservation centers in a tertiary hospital.
Patient(s): Two groups of breast cancer patients: premenopausal patients treated with adjuvant tamoxifen; and patients undergoing in vitro fertilization (IVF) for fertility preservation.
Intervention(s): Fertility-preservation cycles, tamoxifen co-administration during conventional IVF.
Main Outcome Measure(s): Endocrine records, and IVF results.
Result(s): Estradiol (E_2) levels were chronically high (mean 2663 pmol/L, maximum: 10,000 pmol/L) in 38 of 46 breast cancer patients treated with adjuvant tamoxifen. Co-administration of tamoxifen (48 cycles) during conventional IVF or without tamoxifen (26 cycles), using either the long gonadotropin-releasing hormone–agonist or–antagonist protocols, resulted, respectively, in a mean of 12.65 and 10.2 oocytes retrieved, and 8.5 and 6.4 embryos cryopreserved. Average peak E_2 levels were 6,924 pmol/L and 5,093 pmol/L, respectively, but long-term recurrence risk (up to 10 years) was not increased.
Conclusion(s): In breast cancer patients, co-administration of tamoxifen during conventional COH for fertility preservation does not interfere with IVF results. The high serum E_2 levels during COH should be considered safe, as it simulates the high prevalence of persistently high serum E_2 levels in premenopausal breast cancer patients safely treated with adjuvant tamoxifen. (Fertil Steril® 2014;102:488–95. ©2014 by American Society for Reproductive Medicine.)
Key Words: IVF, breast cancer, controlled ovarian hyperstimulation, tamoxifen, fertility preservation

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Breast cancer is the most prevalent malignancy among women, with approximately 13% of patients being diagnosed between ages 20 and 34 years. Women aged younger than 40 years at diagnosis represent fewer than 7% of women diagnosed with breast cancer in developed

countries (1). In this age range, women are at the peak of their reproductive years. As the age at first birth has steadily increased in developed nations (2), with more than one quarter of deliveries in women age >35 years, many reproductive-age breast cancer survivors have not yet completed family planning. Survival rates after breast cancer have significantly improved, with more than 89% of women alive 5 years after diagnosis (3), and most young women with early breast cancer will in fact be cured by adjuvant therapy, despite the fact that young women tend to present with more-advanced disease and with biologically aggressive disease (4).

Newer treatments have improved outcomes among young women, and with some early-stage disease subtypes, outcomes are similar to those for older women (5). The increasing numbers of breast cancer survivors are concerned with post-cancer quality-of-life issues, such as the ability to have children after completing treatment (6, 7). The desire of former breast cancer patients to conceive is legitimate, and medical and public awareness is increasing; hence, it is critical that fertility issues be raised when breast cancer is diagnosed (8, 9).

Treatment for early breast cancer involves local therapy, including surgery and adjuvant radiation therapy, as well as systemic therapies, including chemotherapy, biological therapy, and hormonal therapy. The deleterious effects of chemotherapy on the ovary, ovarian reserve, and future fertility depend on the patient's age, previous chemotherapy exposure, the type of chemotherapeutic agent used, and the drug regime (10). Chemotherapy protocols for breast cancer include various combinations of alkylating agents, platinum derivates, and taxanes, which are toxic to the ovaries and destroy primordial follicle stockpiles, which directly represent ovarian reserve (11, 12).

Age determines how resilient the ovary will be to chemotherapy treatment, with older patients (>35 years) more likely to suffer from either complete sterility (13) or diminished ovarian reserve (14). Therefore, it is crucial to present this information to patients before chemotherapy administration and to offer young female cancer patients fertility-preserving options. Currently, these options include embryo, oocyte, or ovarian tissue cryopreservation (15, 16).

Conventional in vitro fertilization (IVF) before chemotherapy (after or sometimes before surgery) is the most effective, and success rates are known (17); however, no studies have shown that IVF in breast cancer patients, especially those with endocrine-responsive tumors, is safe. Concerns have been raised, although not based on direct studies, that the hyper-estrogenic state associated with controlled ovarian hyperstimulation (COH) for IVF could negatively affect cancer progression. At this stage, patients have not completed treatment for breast cancer, and it is plausible that cancer cells still present in the body will respond to high estradiol (E_2) levels, as documented in in-vitro studies (animals and human cultures), as well as in patients with metastatic disease (18–20).

Tamoxifen citrate, a selective estrogen receptor modulator (SERM), competes with estrogen for binding sites in the estrogen receptor (ER) in target tissues such as breast. The drug prevents proper binding of estrogen and subsequent transcription of deoxyribonucleic acid (DNA) to messenger ribonucleic acid (mRNA). Tamoxifen has been in use for more than 30 years with a proven high therapeutic index and significant efficacy in reducing breast cancer recurrence and improving patients' survival. Specifically, the drug is effective in young premenopausal breast cancer patients (21–23), in spite of occasional reports indicating significantly elevated estrogen levels during tamoxifen treatment (24, 25).

To investigate the safety and effectiveness of COH protocol in breast cancer patients undergoing fertility preservation with IVF cycles, the objectives of the present study were to: [1] systematically evaluate steroidogenesis, specifically serum E_2 levels in a group of premenopausal breast cancer patients under prolonged tamoxifen treatment; and [2] prospectively assess the effectiveness and safety of tamoxifen co-administration during COH for IVF in breast cancer patients undergoing a fertility-preservation cycle.

MATERIALS AND METHODS

In the present study, 2 groups of breast cancer patients were evaluated. In group 1 were premenopausal breast cancer patients undergoing prolonged chronic adjuvant tamoxifen treatment. Group 2 consisted of young breast cancer patients referred for fertility preservation before potentially sterilizing treatment by COH for IVF and embryo freezing. The study was conducted and monitored by specialists in reproduction and oncology in a tertiary center within the breast cancer unit of the oncology department and within the assisted reproductive techniques (ART) unit. The study was approved by the center's institutional review board.

Group 1: Serum Estrogen Levels in Young Breast Cancer Patients Treated with Tamoxifen

In this retrospective cohort study, all consecutive files of breast cancer patients, age <51 years, treated in our oncology department during an 8-year period, were evaluated. Only those treated with tamoxifen and who underwent assessment of their endocrine profiles were eligible for evaluation. Patients received 5 years of adjuvant tamoxifen at 20 mg per day. For patients who also received systemic chemotherapy, tamoxifen treatment began after completion of chemotherapy. During tamoxifen treatment, menstruation frequently ceases or is completely irregular; hence, E_2 serum levels were measured at various arbitrary times, months to years after initiation of treatment. As young breast cancer patients are commonly treated with chemotherapy, which often results in premature ovarian failure, only women showing proven functioning ovaries, by menstrual reports and/or E_2 and follicle-stimulating hormone (FSH) levels when tamoxifen was administered, were enrolled.

Group 2: IVF and Embryo Freezing for Fertility Preservation in Breast Cancer Patients

During a 10-year period, young women diagnosed with stage 1–3 breast cancer were referred by the oncology team to the fertility-preservation clinic. All patients were consulted about the prospect of future fertility in accordance with their age, ovarian reserve, and the risk of sterilization with the planned