Gonadotropin-releasing hormone agonists for the preservation of ovarian function among women with breast cancer who did not use tamoxifen after chemotherapy: a systematic review and meta-analysis

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Objective: To determine whether concurrent use of GnRH agonists with chemotherapy preserves ovarian function in women with breast cancer who did not use tamoxifen.
Design: Systematic review and meta-analysis.
Setting: University-based hospitals.
Patient(s): Premenopausal women with breast cancer treated with chemotherapy who did not receive tamoxifen.
Intervention(s): Randomization to concurrent GnRH agonists with chemotherapy or chemotherapy alone.
Main Outcome Measure(s): Odds ratio (OR) of resumption of menses 1 year or more after chemotherapy.
Result(s): Searches were conducted in PubMed, Scopus, Cochrane Trials Register, and the National Research Register through March 2014, and all randomized trials that reported resumption of menses 1 year or more after GnRH agonist with chemotherapy or chemotherapy alone among women with breast cancer who did not receive tamoxifen were included. Four studies were analyzed in the meta-analysis and included 252 patients (GnRH agonist with chemotherapy, n = 131; chemotherapy alone, n = 121). There was no significant difference in the rate of return of menses between the two groups (OR, 1.47; 95% confidence interval [0.60–3.62]). Heterogeneity among the trials was not significant ($I^2 = 16.6\%$).
Conclusion(s): Concurrent GnRH agonists with chemotherapy may not preserve ovarian function in women with breast cancer. Furthermore, randomized data are limited regarding fertility after concurrent use of GnRH agonists with chemotherapy. (Fertil Steril® 2014;102:808–15. ©2014 by American Society for Reproductive Medicine.)
Key Words: GnRH agonist, fertility preservation, breast cancer, systematic review, meta-analysis

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Reproductive-aged women account for 12% of newly diagnosed breast cancer cases (1). While adjuvant chemotherapy and endocrine therapy with tamoxifen have improved disease-free and overall survival, these therapies have been associated with an increased risk of premature ovarian insufficiency (POI) and delayed attempts at conception,

respectively. In addition to infertility, POI diminishes the quality of life among young women with breast cancer given the associated hot flashes, sleep disturbances, and sexual dysfunction (2). The variables of greatest importance in determining the risk of chemotherapy-induced amenorrhea include patient age, type of chemotherapeutic agent(s) used, cumulative chemotherapy dose, and use of tamoxifen (3–5).

Current neoadjuvant and adjuvant regimens for breast cancer management include combinations of taxanes, anthracyclines, alkylating agents, and pyrimidine analogs. Taxane use has increased since 2003 when improved outcomes in breast cancer were reported as a result of the sequential addition of paclitaxel to an adjuvant chemotherapy regimen (6). The platinum-containing agent carboplatin is used with increasing frequency for management of Her2/neu positive breast cancer (7). Increased use of carboplatin for treatment of estrogen receptor–, P receptor–, Her2/neu–negative breast cancer is anticipated with mounting evidence of efficacy (8, 9). A decreasing trend in methotrexate use is the direct result of anthracycline- and taxane-containing regimens supplanting the former standard regimen of cyclophosphamide, methotrexate, and fluorouracil (CMF). Despite the changing trends in the use of various chemotherapeutic agents, the rates of POI remain fairly stable over time. This may be the result of the relatively consistent use of the alkylating agent cyclophosphamide, which is common to both older and newer chemotherapy regimens. With respect to the risk of gonadal toxicity, cyclophosphamide is classified as high risk, since the non–cell cycle–specific effects of alkylating agents can damage primordial ovarian follicles. In contrast, cycle-specific chemotherapeutic agents such as fluorouracil and methotrexate are not thought to diminish ovarian reserve and accordingly are deemed low risk for development of POI (10).

While more than 50% of breast cancer survivors' rate future fertility as a major concern, less than 5% of young women with breast cancer preserve their fertility through oocyte or embryo banking (11, 12). Barriers to oocyte and embryo banking among young women with breast cancer include inadequate counseling, decisional conflict, inability to delay chemotherapy initiation, financial constraints, and concerns regarding the safety of controlled ovarian stimulation (13). Concurrent use of GnRH agonists with chemotherapy for ovarian protection is an attractive alternative to banking given that it is widely available, relatively inexpensive, and does not introduce the treatment delay and potential risks associated with controlled ovarian stimulation (14). In addition, preservation of ovarian function after chemotherapy may improve quality of life by avoiding the consequences of POI.

Observational trials have reported high rates of resumption of menses (67%–100%) and pregnancies after concurrent use of GnRH agonist with chemotherapy in young women with breast cancer (15–19), while randomized trials have reported conflicting results (20–27). Factors contributing to the conflicting results include heterogeneity of both study populations and treatment regimens. Most randomized trials include women with hormone receptor–positive and–negative breast cancer. Accordingly, the use of tamoxifen may confound analysis of these trials since its use is associated with higher rates of amenorrhea in women with hormone receptor–positive breast cancer who receive adjuvant chemotherapy (28, 29).

Given the importance of ovarian protection for young women with breast cancer, the conflicting data from randomized trials, and the inclusion of confounders such as tamoxifen use, we performed a systematic review and meta-analysis to determine whether concurrent use of GnRH agonists with chemotherapy preserves ovarian function in women with breast cancer who did not receive tamoxifen.

MATERIAL AND METHODS

Search Strategy

This systematic review and meta-analysis was exempt from Institutional Review Board approval. Literature searches without language restrictions were performed through March 2014 in PubMed, Scopus, Cochrane Clinical Trials, and the National Research Registry. A combination of Medical Subject Headings and text words was used to search the literature, including GnRH agonists ("gonadotropin releasing hormone/GnRH analogue/agonist/triptrorelin/goserelin/leuprolide/busselin/nafarenlin"), breast cancer ("breast cancer"), and randomized clinical trials ("clinical trials/random/cross over/double masked/double dummy/parallel group/sham controlled"). The three subsets were combined using "AND" to generate a set of citations relevant to the research question.

Study Selection

Inclusion criteria included randomized clinical trials of premenopausal women randomized to GnRH agonist and chemotherapy or chemotherapy alone. Outcomes for women who did not use tamoxifen were extracted from trials that included both hormone receptor–positive and hormone receptor–negative populations. Exclusion criteria included nonrandomized trials, inability to ascertain tamoxifen use among the population, inability to ascertain outcome data among the population without tamoxifen use, and trials presented in abstract form only. Inquiries were sent to investigators to collect additional and unpublished data. Two investigators (W.S.V. and C.F.) reviewed the titles and abstracts from the literature searches independently and identified trials that met the inclusion criteria. Inclusion and exclusion decisions were made by two investigators (W.S.V. and C.F.) after evaluating the manuscripts.

Data Extraction

Two investigators (W.S.V. and C.F.) independently extracted the data from each trial using predefined criteria that had been developed specifically for this review, which included the following items: [1] baseline demographics (author, country, year of publication, and period of study enrollment); [2] study population (age of patients, number of total patients, number of patients who did not receive tamoxifen, characteristics of breast cancer, and types of chemotherapy and breast surgery); [3] GnRH agonist intervention (type, duration, and schedule of administration); and [4] outcome measures