Protecting Effects of Gonadotropin-Releasing Hormone Agonist on Chemotherapy-Induced Ovarian Damage in Premenopausal Breast Cancer Patients: A Systematic Review and Meta-Analysis

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Keywords

Premenopausal breast cancer · GnRH agonist · Resumption of menses rate · Meta-analysis

Summary

Objective: There is no universal consensus on whether gonadotropin-releasing hormone (GnRH) agonist could protect chemotherapy-induced ovarian damage in premenopausal breast cancer patients. This meta-analysis was conducted to estimate the protective effects of GnRH agonist on premenopausal breast cancer patients in details. **Methods:** PubMed, Cochrane Library, Embase, CNKI and the Chinese Wangfang Database, conference proceedings and clinical trials were searched to find studies reported since 2000. Heterogeneity for the eligible data was assessed and a pooled odds ratio (OR) with 95% confidence interval (CI) was calculated. **Results:** Resumption of menses rate was improved in the GnRH agonist and chemotherapy-combination groups versus chemotherapy-alone groups (OR = 1.36, 95% CI: 1.19–1.56). Furthermore, the results indicated that spontaneous pregnancy rate was improved in the experimental groups versus the controls (OR = 1.90, 95% CI: 1.06–3.41). In addition, no publication bias was found using a Begg's funnel plot. **Conclusion:** The results of the current meta-analysis indicate that a GnRH agonist could im-

prove resumption of menses rate and pregnancy rate for premenopausal breast cancer patients. However, more evaluation may be considered to prove this theory.

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Introduction

According to the updated data of GLOBOCAN, there were 1,677,000 new cases of, and 522,000 deaths from, breast cancer worldwide in 2012, making it the most frequent type of cancer among women [1]. Chemotherapy has reduced the breast cancer death rate for breast cancer patients [2]. However, up to 60% of women treated with chemotherapy will experience periods of ovarian damage, which presents with a variety of symptoms, such as transient or permanent amenorrhea, infertility and early menopause, even premature ovarian failure (POF) and infertility. Each of these results in a significant financial and psycho-social burden [3–6]. As a consequence, preservation of ovarian function following adjuvant chemotherapy has raised great concern for both patients and clinicians/scientists. Fortunately, preclinical data have confirmed that temporary ovarian suppression with gonadotropin-releasing hormone (GnRH) agonist during chemotherapy reduces ovarian toxicity through mechanisms such as interruption of follicle-stimulating hormone (FSH) secretion, a decrease in utero-ovarian perfusion, the activation of GnRH receptors on the oocytes, the up-regulation of intragonadal-anti-apoptotic molecules and/or the protection of undifferentiated germ-line stem cells [7, 8]. However, from the clinical trials, it still remains controversial as to whether

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GnRH agonist can increase resumption of menses rate and pregnancy rate of premenopausal breast cancer patients. To help clarify this issue, we present a meta-analysis of 15 studies to give a quantitative assessment of the efficacy of GnRH agonists in protecting ovarian function in premenopausal breast cancer patients.

Materials and Methods

Search Strategy

Two investigators (F.B. and Y.L.) independently conducted a computerized search of all studies published since 2000 using the following databases: PubMed, Embase, Cochrane Library, CNKI and the Chinese Wangfang Database. In addition, we searched conference proceedings through online websites at www.asco.org and clinical trials through www.clinicaltrials.gov. A combination of Medical Subject Headings (MeSH) and text words was used to search the literature; these included gonadotropin-releasing hormone agonists, luteinizing hormone-releasing hormone agonists, triptorelin, goserelin, chemotherapy, ovarian preservation, premature ovary failure and premenopausal breast cancer.

Table 1. Check list for quality assessment

Items	Score
Randomization	0 = not randomized in inappropriate method of randomization 1 = study described as randomized 2 = method of randomization described and appropriate
Concealment of allocation	0 = method of allocation concealment not described 1 = study described as using allocation concealment method 2 = method of allocation concealment described appropriately
Double blinding	0 = not blind or inappropriate method of blinding 1 = study described as double blind 2 = method of double blind described and appropriate
Withdrawals and dropouts	0 = not described as follow-up 1 = description of withdrawals and dropouts

Table 2. Quality assessments of studies

Study	Randomization	Concealment of allocation	Double blinding	Withdrawals and dropouts	Total
Badawy et al. [10]	2	1	1	1	5
Munster et al. [15]	2	1	1	1	5
Sverrisdottir et al. [13]	2	1	1	1	5
Del Mastro et al. [11]	2	1	1	1	5
Zhao et al. [20]	2	1	0	1	4
Gerber et al. [14]	2	0	0	1	3
Elgindy et al. [12]	2	0	0	1	3
Sun et al. [19]	1	0	0	1	2
Li et al. [18]	1	0	0	1	2
Jiang et al. [17]	1	0	0	1	2
Gilani et al. [16]	1	0	0	1	2
Lambertini et al. [23]	2	1	0	1	4
Song et al. [22]	2	1	0	1	4
Moore et al. [21]	2	1	1	1	5
Zhang et al. [24]	2	0	0	1	3

We scanned the titles and abstracts to exclude any clearly irrelevant studies. The full texts of the remaining articles were reviewed to determine whether they contained information on the topic. In addition, the reference lists of the retrieved articles were checked to identify additional relevant publications.

Inclusion Criteria

The inclusion criteria were as follows: (1) the articles were published in English or Chinese; (2) the researches were restricted to those conducted on humans; (3) all the studies should have clear research objectives, designs and statistic methods; (4) the research subjects for the studies were female premenopausal breast cancer patients; (5) all of the studies should at least provide the statistics on the rate of resumption of menses, or it could be calculated; (6) the treatment of experimental group in all the included studies was a combination of GnRH agonist and chemotherapy, with the control group receiving chemotherapy therapy; and (7) the studies had to be randomized controlled trials (RCTs).

Data Extraction

Two independent reviewers (F.B. and Y.L.) extracted data from each eligible trial, including: (1) basic information, e.g. the year of publication, the name of first author and country of study; (2) study information, e.g. study population and type of study; (3) treatment information, e.g. regimen of both groups (dose, the time of administration, cycle and use of tamoxifen or radiation); and (4) other information, outcome measurement.

Quality Assessment of Included Studies

The quality of studies was assessed independently by 2 reviewers (F.B. and Y.L.) using the Modified Jadad Score [9]. In the assessment system, the quality of the studies was judged through 4 items: randomization, concealment of allocation, doubling blinding, and withdrawals and dropouts (table 1). The full score was 7, and high-quality studies were defined by a score of 4–7 (table 2).

Statistical Analysis

Data were collected and checked, and a database was set up as required for meta-analysis. The systematic assessment was performed using RevMan (Version 5.2). The comparison of the odds ratio (OR) of the rate of resumption of menses between experimental groups versus the control group in premenopausal breast cancer patients were the primary endpoints. Secondary endpoints were spontaneous pregnancy rate, and rate of resumption of menses among patients younger than 35 and for older patients. All the comparisons were calculated using the method for dichotomous data (assessment of OR; 95% confidence interval (CI)). Both the fixed-effect model/Mantel-Haenszel method with minimal heterogeneity in the variables among studies and the Der Simonian-Laird method (random effects model) when there was significant heterogeneity

were used. The Cochran's Q test, with a predefined significance p threshold of 0.05, was used to assess the statistical heterogeneity among the studies. The assumption of homogeneity was considered invalid for p values more than 0.05. Funnel plots was used to test for possible publication bias. The presence of asymmetry in the funnel plot indicates the occurrence of publication bias.

Results

Search Results

The study selection is presented as a flowchart in figure 1. 186 records were searched in the database. Of these, 162 studies were

Fig. 1. Flow diagram.

excluded after screening the title and abstract. Of the remaining 24, 15 records were included after full-text screening according to the inclusion criteria [10–24].

Quality Evaluation and Study Characteristics

Baseline characteristics of the 15 included studies are shown in online supplemental table 1 (www.karger.com/?DOI=454983). These studies were published between 2000 and 2015. Overall, 1,540 female premenopausal breast cancer patients were involved, and 786 of whom were in the experimental group, and 754 in the control group. All the studies were RCTs and were assessed through the Modified Jadad Score.

Meta-Analysis

According to the meta-analysis of the primary endpoint, there was between-study heterogeneity in the rate of resumption of menses (heterogeneity $\text{Tau}^2 = 0.04$, $\text{Chi}^2 = 51.98$ (d.f. = 14), $I^2 = 73\%$, $p < 0.00001$). Therefore, we used the random-effect model to analyze the data and found that the rate of resumption of menses was improved in the experimental groups versus the controls (OR = 1.36, 95% CI: 1.19–1.56) (fig. 2).

As to the secondary endpoints, 5 studies [11, 14, 15, 21, 23] were included and there was no between-study heterogeneity in spontaneous pregnancy rate (heterogeneity $\text{Chi}^2 = 3.25$ (d.f. = 4), $I^2 = 0\%$, $p = 0.52$). Therefore, we used the fixed-effect model, and the results indicated that spontaneous pregnancy was improved in the experimental groups versus the controls (OR = 1.90, 95% CI: 1.06–3.41) (fig. 3).

In a subgroup analysis, we included 4 studies [18–20, 22] to compare the rate of resumption of menses among patients younger than 35 years, and there was no between-study heterogeneity (heterogeneity (d.f. = 4), $I^2 = 0\%$, $p = 0.47$). Using the fixed-effect model to analyze the data, we found that the difference between 2 groups was not significant (OR = 0.69, 95% CI: 0.27–1.74). As to the rate of resumption of menses among patients older than 35, there was between-study heterogeneity (heterogeneity (d.f. = 4),

Fig. 2. Forest plot of rate of resumption of menses.

Table 3. Subgroup analyses

Patient age	Studies*	Random effect		Heterogeneity p-value	I-squared, %
		OR (95% CI)	p-Value		
≤35 years	4	0.69 (0.27, 1.74)	0.43	0.47	0
>35 years	4	3.22 (0.56, 18.65)	0.19	0.0005	83

*Included studies: Li et al. 2013 [18], Song et al. 2013 [22], Sun et al. 2014 [19], Zhao and Jia 2012 [20].

Fig. 3. Forest plot of pregnancy rate. **Fig. 4.** Funnel plot of rate of resumption of menses. **Fig. 5.** Funnel plot of pregnancy rate.

$I^2 = 83\%$, $p = 0.0005$); using the random-effect model the difference between 2 groups was not significant (OR = 3.22, 95% CI: 0.56–18.65) (table 3).

Publication Bias

We performed the funnel plots to assess the publication bias. As a result, there was no publication bias in each for the primary endpoint analysis and the spontaneous pregnancy rate analysis (figs. 4 and 5).

Discussion

We included 15 studies in this meta-analysis, and the results indicate that GnRH agonist can significantly increase the rate of resumption menses. Subgroup comparison showed that the rate also increases in the patients younger than 35 years. In addition, the data prove that the spontaneous pregnancy rate improves significantly compared to control groups.

The fundamental reason why GnRH agonists can provide ovarian protection is that prepubescent children have different rates of infertility after treatment with chemotherapy, with the prepubescent state seeming to confer some protection to the female gonads. A possible mechanism is that a GnRH agonist-induced hypoestrogenic state could decrease ovarian perfusion and that the GnRH agonist-induced hypogonadotropic milieu could decrease the number of primordial follicles entering the differentiation stage. In addition, ovarian cell apoptosis is decreased through either activation of the GnRH receptors or up-regulation of intragonadal anti-apoptotic molecules. Furthermore, GnRH agonist may have certain protective effect on ovarian germline stem cells [25].

According to the NCCN Clinical Practice Guidelines in Oncology: breast cancer, version I 2016, randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with estrogen receptor-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea

[26]. Although resumption of menses is a clinically relevant and reproducible outcome, it is not necessarily linked to fertility restoration. Conversely, the presence of menses does not guarantee fertility. However, although ovarian suppression with GnRH agonist during chemotherapy has been studied as a strategy to preserve ovarian function and not fertility, there is evidence suggesting a possible utility of this technique to preserve fertility [27].

However, this meta-analysis still suffers from several limitations. First of all, different definitions of POF were used in different trials. Secondly, the limited length of follow-up in the RCTs precludes our ability to determine the long-term impact of GnRH agonists on preservation of ovarian function and fertility. Thirdly, because of lacking data, we were unable to compare the survival rates and hormones levels between patients with or without the use of GnRH agonist. Lastly, there was moderate heterogeneity among all included studies, for instance, the lack of uniform chemotherapy regimens.

In conclusion, GnRH agonists could be beneficial to premenopausal breast cancer patients by increasing the rates of resumption menses and pregnancy. To investigate this further, more research and high-quality homogeneous prospective clinical RCTs with larger populations and long-term follow-up are required.

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Online Supplemental Material

Supplemental Table 1. Characteristics of included studies

To access the online supplemental table please refer to www.karger.com/?DOI=454983.

Acknowledgments

The research was funded by Science and Technology Commission of Shanghai Municipality (No. 12JC1406800 and No. 14411950206).

Disclosure Statement

All authors declare that they have no financial or personal relationships with other people or organizations that could inappropriately influence their work.