Protective effect of gonadotropin-releasing hormone agonist against chemotherapy-induced ovarian dysfunction: A meta-analysis

FEI ZHENG[1], BIN ZHU[1], QINGJING FENG[2], LILI WU[1], YUECHONG CUI[3], YUMO LIU[4] and YINGQIAN WANG[5]

Departments of [1]Obstetrics and Gynecology, [2]Galactophore and [3]Human Health and Human Service, Family Planning Service Center of Yiwu Maternity and Child Health Care Hospital, Yiwu, Zhejiang 322000; [4]Department of Public Health, Southwest Medical University, Luzhou, Sichuan 646600; [5]Department of Obstetrics and Gynecology, The Third Hospital of Hebei Medical University, Shijiazhuang, Hebei 050035, P.R. China

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Abstract. The protective effects of gonadotropin-releasing hormone agonist (GnRHa) against ovarian chemotherapy induced-toxicity have not completely been demonstrated and the impact of chemotherapy on ovarian dysfunction remains unclear. The present meta-analysis aimed to evaluate the efficiency of GnRHa and to determine whether GnRHa could influence the long-term survival rate of patients with cancer. A total of 12 clinical randomized controlled trials were included, consisting of 1,413 patients who were divided into the GnRHa group (n=705) and the control group (n=708). The meta-analysis revealed that GnRHa may significantly improve the menstrual function recovery rate in patients who received chemotherapy [RR=1.29, 95% confidence interval (CI)=1.09-1.54, P=0.004] and reduce the rate of premature ovarian failure (RR=0.47, 95% CI=0.31-0.71, P=0.0004). However, it had no effect on the pregnancy rate (RR=1.40, 95% CI=0.98-1.98, P=0.06), on the rate of disease-free survival and overall survival of patients (disease-free survival rate: RR=1.04, 95% CI=0.95-1.13, P=0.40; overall survival rate: RR=1.02, 95% CI=0.90-1.16, P=0.72). In conclusion, GnRHa may reduce chemotherapy-induced ovarian dysfunction without compromising or influencing the therapeutic effects of chemotherapy.

Introduction

Chemotherapy is a widely used tumor treatment; however, it can cause various degrees of ovarian dysfunction, which can be irreversible. It is therefore important to protect ovaries during chemotherapy to avoid compromising pregnancy rate, considering the gradual improvement of women's survival following chemotherapy.

In 1985, Ataya *et al* (1) demonstrated that long-acting gonadotropin releasing hormone (GnRH) agonist (GnRHa) significantly protects rat ovaries against cyclophosphamide-induced toxicity. Blumenfeld and Eckman (2) performed a prospective clinical study on fertile women undergoing chemotherapy, and reported similar results. However, subsequent clinical studies have revealed different results and opposite conclusions (3,4). At present, reports on the protective effects of GnRHa on ovarian function and whether it alters chemotherapeutic efficiency are lacking.

In the present meta-analysis, clinical randomized controlled trials of premenopausal women using GnRHa to protect ovarian function during chemotherapy were systematically retrieved and collected. Menstrual function recovery rate, premature ovarian failure rate and pregnancy rate were analyzed. In addition, the influence of GnRHa on long-term survival rate was evaluated. This work may provide an effective strategy to protect ovarian function in premenopausal women undergoing chemotherapy.

Materials and methods

Strategy for retrieving literature. By the end of December 2017, the following key words were used in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Embase database (https://www.embase.com/) and Cochrane library (https://www.cochranelibrary.com/advanced-search/search-manager) to retrieve and collect clinical randomized controlled trials in which GnRHa was administered to premenopausal women undergoing chemotherapy: 'GnRH agonist', 'GnRH analog', 'chemotherapy', 'ovarian damage', 'ovarian suppression', 'ovarian protection', 'ovarian function', 'ovarian dysfunction', 'fertility' and 'fertility preservation'.

Literature search. The following inclusion criteria ware applied in the meta-analysis: i) Premenopausal women with

Correspondence to: Dr Yuechong Cui, Department of Human Health and Human Service, Family Planning Service Center of Yiwu Maternity and Child Health Care Hospital, 320 South Gate Street, Yiwu, Zhejiang 322000, P.R. China
E-mail: 1026984758@qq.com

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malignant tumors, systemic lupus erythematous or other diseases requiring chemotherapy (according to characteristics including age, menstrual function history, ultrasound and hormone levels); ii) a control group with the same disease who did not receive GnRHa treatment; and iii) no limits to ethnicity or language. The following exclusion criteria were applied in the meta-analysis: i) The test design in the original reference was not rigorous and the results were not reliable; ii) the indispensable analytical data were not provided; iii) case reports; iv) patients with metastatic advanced malignant disease or malignant tumors; and v) patients who were under hormone therapy or replacement therapy 3 months prior to treatment with chemotherapy. The studies consisted of randomized controlled trials of premenopausal women undergoing treatment with GnRHa to protect ovarian function during chemotherapy.

Quality assessment and statistical analysis. Two evaluators independently conducted literature screening, risk assessment and data extraction. The risk assessment was conducted according to the clinical randomized controlled trial evaluation recommended by the Cochrane system evaluator manual 5.1 (5). RevMan 5.3 (http://ims.cochrane.org/revman/download) provided by Cochrane collaboration, was used to analyze data. The statistical heterogeneity of each result was analyzed using χ^2 test, and the significance level was set at P=0.1. P<0.1 was considered to indicate a statistically significant heterogeneity. I^2 was used to quantitatively evaluate the heterogeneity of the results. I^2<25% indicated that heterogeneity may not be important, I^2>50% indicated heterogeneity and I^2>75% indicated high heterogeneity. When heterogeneity was small, the fixed effect model was adopted. When heterogeneity was high among the literature, the random effect model was adopted and subgroup analysis was carried out. All participants were included in the analysis, and divided into various treatment groups, including the GnRHa group (chemotherapy combined with GnRHa) and control group (chemotherapy not combined with GnRHa) according to the type of intervention. Relative risk (RR) and 95% confidence interval (CI) were calculated for the following variables: Menstrual function recovery rate, pregnancy rate, premature ovarian failure (POF) incidence, tumor-free survival rate, total survival rate.

Results

Features of the included study. A total of 492 references were retrieved and 12 references were included in the present meta-analysis following accurate selection (3,4,6-15) (Fig. 1). A total of 1,413 premenopausal patients with breast cancer or lymphoma undergoing chemotherapy were included in the selected studies. All studies selected included a comparison between the GnRHa group (705 patients) and control group (708 patients). No significant difference in baseline data between the GnRHa and control groups was observed in these 12 studies. The GnRHa drugs used were triptorelin, goserelin or leuprolide. GnRHa was used either at the beginning of chemotherapy or prior to it. Basic features of the included literature are presented in Table I. Quality assessment is shown in Fig. 2.

Meta-analysis results. With regards to the effect of GnRHa on the menstrual function recovery rate, 10 references provided evidence of menstrual function recovery in both the GnRHa and control groups. In the GnRHa group (561 patients), 429 presented menstrual function recovery. In the control group (561 patients), 335 had menstrual function recovery. The results exhibited the following RR and CI: RR=1.29, 95% CI=1.09-1.54, P=0.004, with a statistically significant difference, suggesting that chemotherapy combined with GnRHa may significantly improve menstrual function recovery rate (Fig. 3). The scattered points of the inverted funnel plot were less symmetrical and the aggregation was more concentrated; therefore, some publication bias may be present as certain negative results may not be published, as presented in Fig. 4.

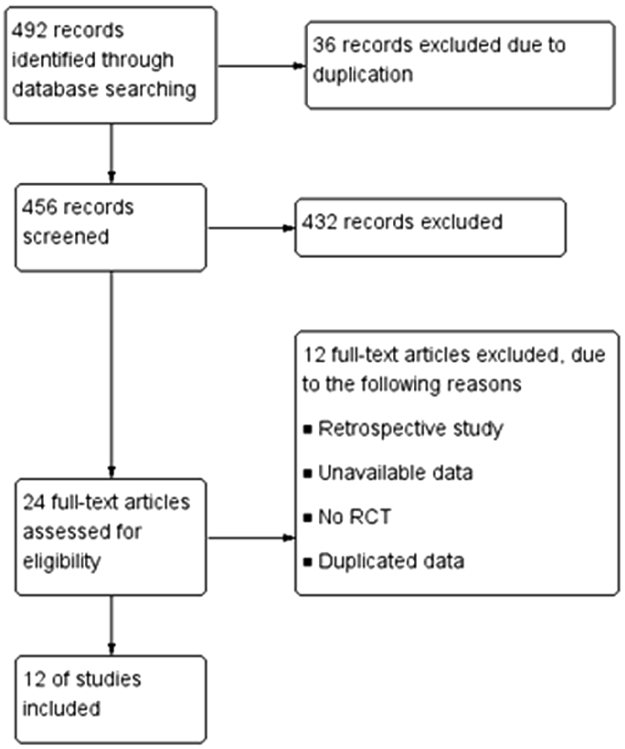

Figure 1. Flowchart of studies selected. RCT, randomized controlled trial.

The effects of GnRHa on POF incidence were then analyzed. Among the 12 references, nine provided evidence of POF incidence in both GnRHa and control groups. The total number of patients in the GnRHa group was 373, with 61 patients with POF, whereas the total number of patients in the control group was 377, with 135 patients with POF. The results were as follows: RR=0.47, 95% CI=0.31-0.71, P=0.0004, with statistically significant differences, suggesting that chemotherapy combined with GnRHa may significantly reduce POF incidence (Fig. 5).

The effects of GnRHa on pregnancy rate were also assessed. Eight references provided evidence of pregnancy in both the GnRHa and control groups. The total number of patients in the GnRHa group was 501, with 56 pregnant patients, whereas the total number of patients in the control group was 505, with 42 pregnant patients. The results were as follows: RR=1.40, 95% CI=0.98-1.98, P=0.06, without any statistically significant difference, suggesting that chemotherapy combined with GnRHa may have no effect on pregnancy rate (Fig. 6).

Table I. Basic features of the literature included in the present meta-analysis.

First author, year	Disease	Results	Drugs	Dose and interval	Start time	Follow-up time	(Refs.)
Badawy, 2009	Breast cancer	Menstrual recovery, POF	Goserelin	3.6 mg/28 days	2 weeks before chemotherapy	8 months	(3)
Demeestere, 2016	Lymphoma	POF, pregnancy, tumor-free survival, overall survival	Triptorelin	3.75 mg/28 days	2±0.51 days before chemotherapy	GnRHa group: 5.33 years Control group: 5.58 years	(4)
Elgindy, 2013	Breast cancer	Menstrual recovery, pregnancy	Triptorelin	3.75 mg/28 days	10 days before chemotherapy	1 year	(6)
Gerber, 2011	Breast cancer	Menstrual recovery, pregnancy	Goserelin	3.6 mg/28±3 days	At least 2 weeks before chemotherapy	2 years	(7)
Giuseppe, 2007	Lymphoma	Menstrual recovery, POF, pregnancy	Triptorelin	Triptorelin 3.25 mg/month Or Triptorelin 11.25 mg/3 months	Immediately after diagnosis	GnRHa group: 2.42±1.7 years Control group: 5.93±4.47 years	(8)
Karimi-Zarchi, 2014	Breast cancer	Menstrual recovery, POF	Triptorelin	3.75 mg/28 days	Same time as chemotherapy	6 months	(9)
Lambertini, 2015	Breast cancer	Menstrual recovery, pregnancy, tumor-free survival	Triptorelin	3.75 mg/28 days	At least 1 week before chemotherapy	7.3 years	(10)
Leonard, 2017	Breast cancer	Menstrual recovery, POF, pregnancy outcomes, overall survival	Goserelin	3.6 mg/28 days	At least 1-2 weeks before chemotherapy	2 years	(11)
Moore, 2015	Breast cancer	Menstrual recovery, POF, pregnancy, tumor-free, survival overall survival	Goserelin	3.6 mg/28 days	1 week before chemotherapy	5-7 years	(12)
Munster, 2012	Breast cancer	Menstrual recovery, POF, pregnancy	Triptorelin	3.75 mg/28-30 days	At least 7 days before chemotherapy	GnRHa group: 4.96 years Control group: 5.82 years	(13)
Song, 2013	Breast cancer	Menstrual recovery, POF	Leuprolide	3.75 mg/28 days	Before chemotherapy (if ovarian suppression was confirmed, patients started to receive chemotherapy)	1 year	(14)
Sverrisdotti, 2009	Breast cancer	POF	Goserelin	3.6 mg/28 days	Same time as chemotherapy	3 years	(15)

GnRHa, gonadotropin-releasing hormone agonist, POF, premature ovarian failure.

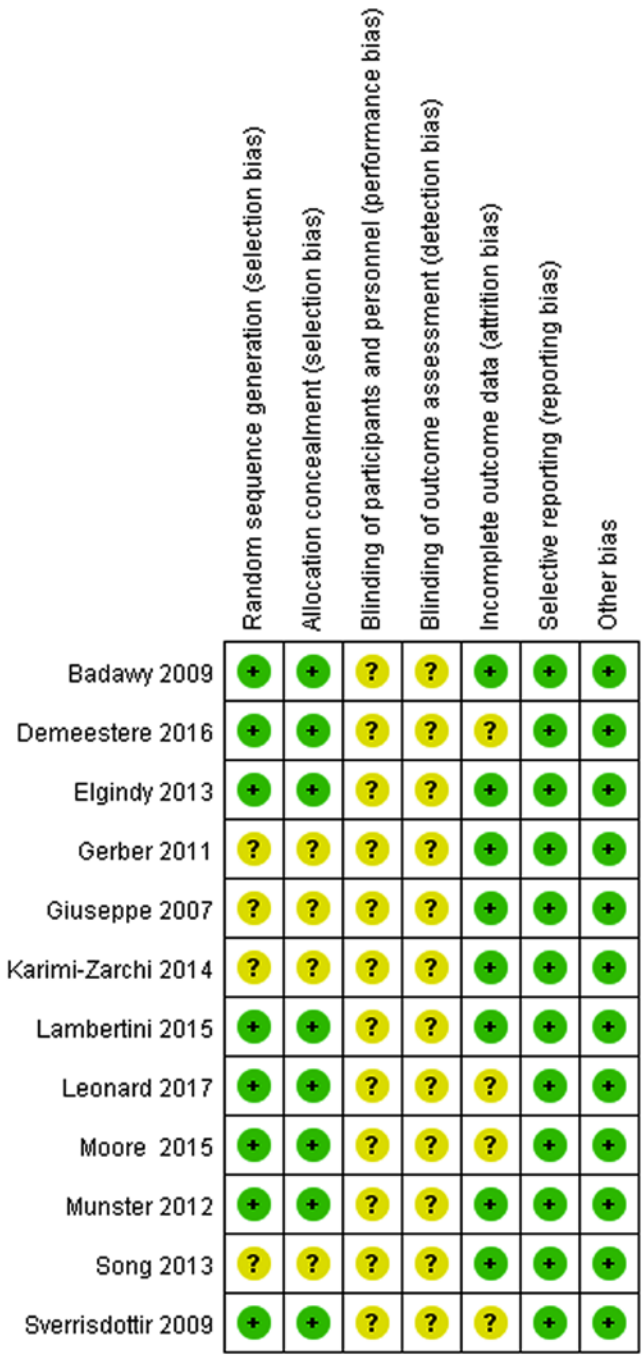

Figure 2. Summary risk of bias assessment, according to the Cochrane handbook.

The effects of GnRHa on the menstrual function recovery rate, POF incidence and pregnancy rate were also determined on patients <40 years old. This subgroup analysis was conducted because the literature was heterogenous. Results revealed that GnRHa improved the menstrual function recovery rate of patients undergoing chemotherapy (RR=0.16, 95% CI=0.07-0.38, P<0.0001) and reduced POF incidence (RR=1.51, 95% CI=1.02-2.23, P=0.04), with no effect on pregnancy rate (RR=0.36, 95% CI=0.06-2.27, P=0.28; Fig. 7).

With regards to the effects of GnRHa on the long-term tumor-free survival rate, three references provided evidence of long-term tumor-free survival in both the GnRHa and control groups. The total number of patients in the GnRHa group was 318, with 263 cases of survival without tumor, and 310 in the control group, with 249 cases of survival without tumor. The results were as follows: RR=1.04, 95% CI=0.95-1.13, P=0.40, with no statistically significant difference, suggesting that the combination of chemotherapy and GnRHa may have no effect on long-term tumor-free survival rate (Fig. 8).

With regards to the effect of GnRHa on long-term overall survival rate, two references provided evidence of long-term survival in both the GnRHa and control groups. The total number of patients in the GnRHa group was 170, of which 158 survived, whereas the number of patients in the control group was 177, of which 158 survived. The results of the meta-analysis were as follows: RR=1.02, 95% CI=0.90-1.16, P=0.72, without any statistically significant difference, suggesting that chemotherapy combined with GnRHa may have no effect on long-term overall survival rate (Fig. 9).

Discussion

The results of the present meta-analysis revealed that GnRHa may reduce ovarian function damage caused by chemotherapy-induced toxicity, and may significantly improve the menstrual function recovery rate and reduce POF incidence in patients undergoing chemotherapy. A previous study (16) has also analyzed the influence of GnRHa on the therapeutic effects of chemotherapeutic drugs. Cuzick *et al* (16) performed a meta-analysis on 16 randomized controlled trials, and evaluated a total of 11,906 premenopausal women who required chemotherapy for early breast cancer. The study revealed that GnRHa as an adjuvant chemotherapy for cancer patients does not affect chemotherapy. The present meta-analysis analyzed long-term tumor-free survival rate and overall survival rate of patients, and demonstrated that GnRHa had no effect on long-term chemotherapy.

Chemotherapy can cause several collateral effects to the ovaries, resulting in damage, including irreversible ovarian dysfunction, amenorrhea and infertility, thus compromising the health and quality of life of patients. There are three main types of chemical drugs that can cause damage to ovarian function (3). The first group comprises nitrogen mustard, cyclophosphamide and other alkylating agents, which have effects on cells in any cell cycle phase; these are the most harmful drugs. The second group of chemotherapeutic drugs includes cisplatin and adriamycin, which mainly affect proliferative cells. These drugs have minor effects on the primordial follicle, do not induce ovarian damage and only result in short-term amenorrhea. The third chemotherapeutic drugs group, including the methotrexate-treated group, exerts only minor or no damage to the ovaries. Overall, the effects of chemotherapy on ovarian function are influenced by numerous factors: i) The concentration of chemotherapeutic drugs; ii) the duration of chemotherapy; iii) drug superposition; and iv) age of the patient at the beginning of chemotherapy and the type of disease.

The protective effects of GnRHa on ovarian function have been extensively studied. GnRHa can be combined with the GnRH receptor, which inhibits the secretion of lutein hormone and follicle-stimulating hormone (FSH), thus inhibiting gonadotropin. Numerous mechanisms explain ovarian protection. Primordial follicle maturation and growth depends on FSH, and it has been demonstrated that these follicles

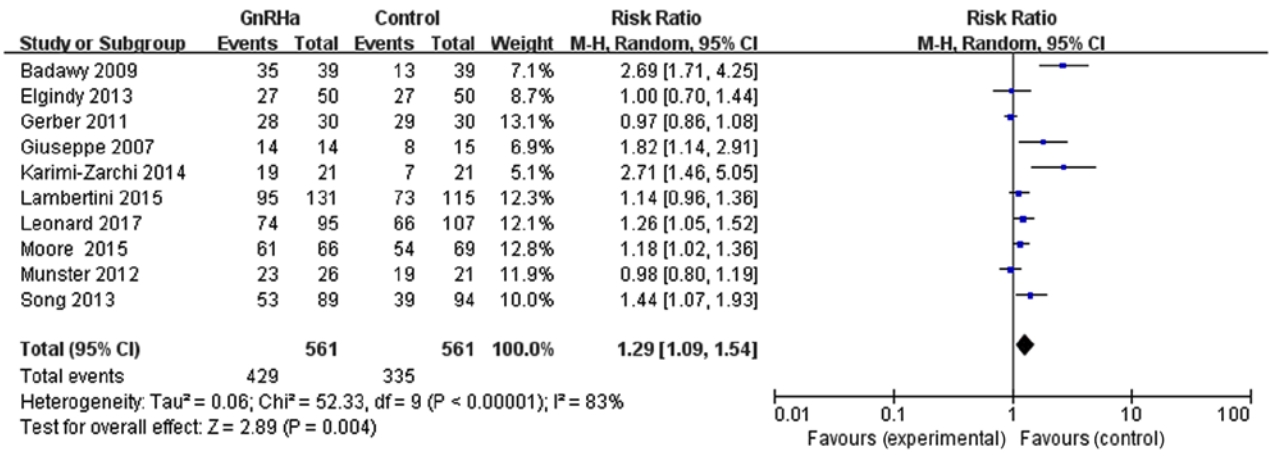

Figure 3. Forest plot of meta-analysis for the effects of GnRHa on menstrual recovery rate. CI, confidence interval; GnRHa, gonadotropin-releasing hormone agonist.

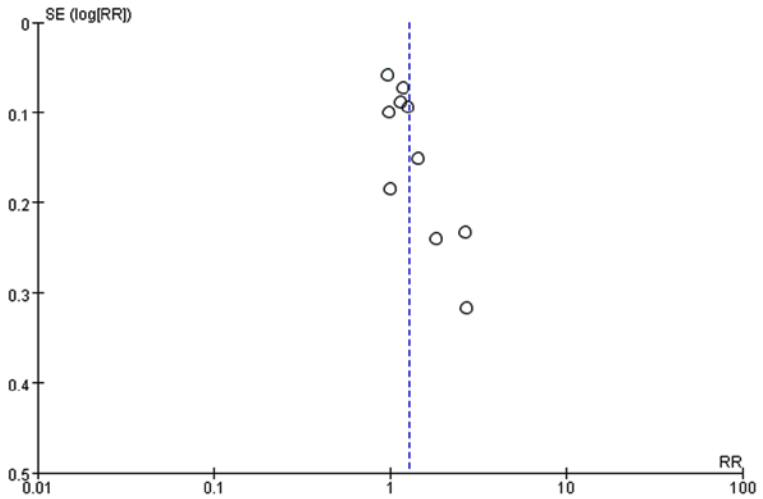

Figure 4. Funnel plot of meta-analysis for the effects of GnRHa on menstrual recovery rate. GnRHa, gonadotropin-releasing hormone agonist; SE, standard error; RR, relative risk.

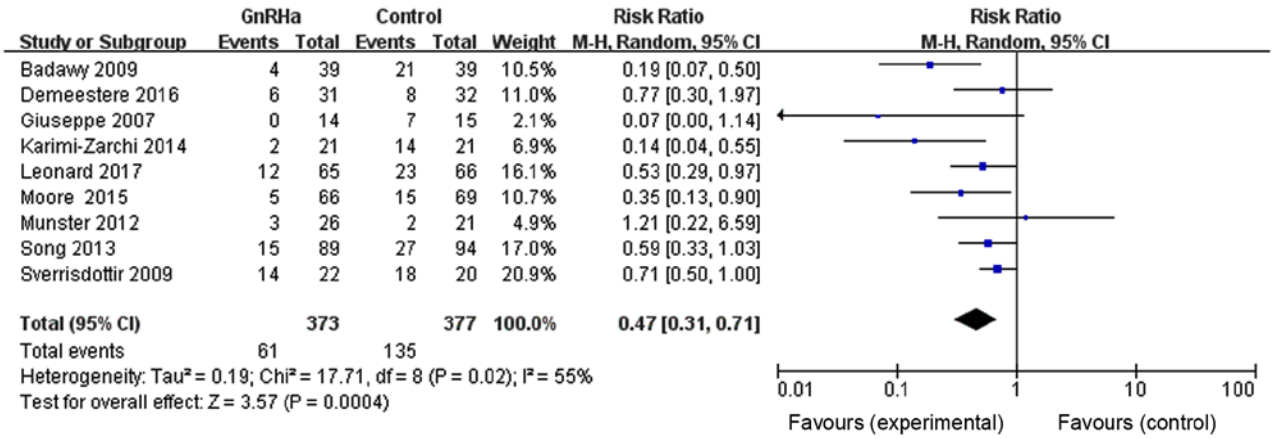

Figure 5. Forest plot of meta-analysis for the effects of GnRHa on premature ovarian failure incidence. CI, confidence interval; GnRHa, gonadotropin-releasing hormone agonist.

contain mRNA able to express FSH and lutein hormone receptors; this expression is dependent on gonadotropins (17). Furthermore, the chemical structure of GnRHa is similar to GnRH; however it has a stronger affinity to the receptors. When GnRHa is combined with the pituitary gland receptors, it can induce an increase in gonadotropin release, known

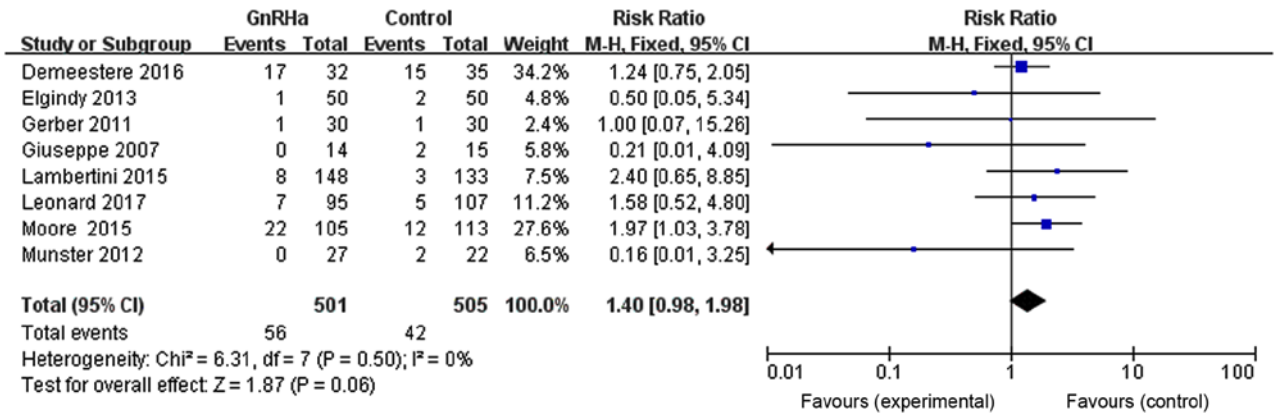

Figure 6. Forest plot of meta-analysis for the effects of GnRHa on the rate of pregnancy. CI, confidence interval; GnRHa, gonadotropin-releasing hormone agonist.

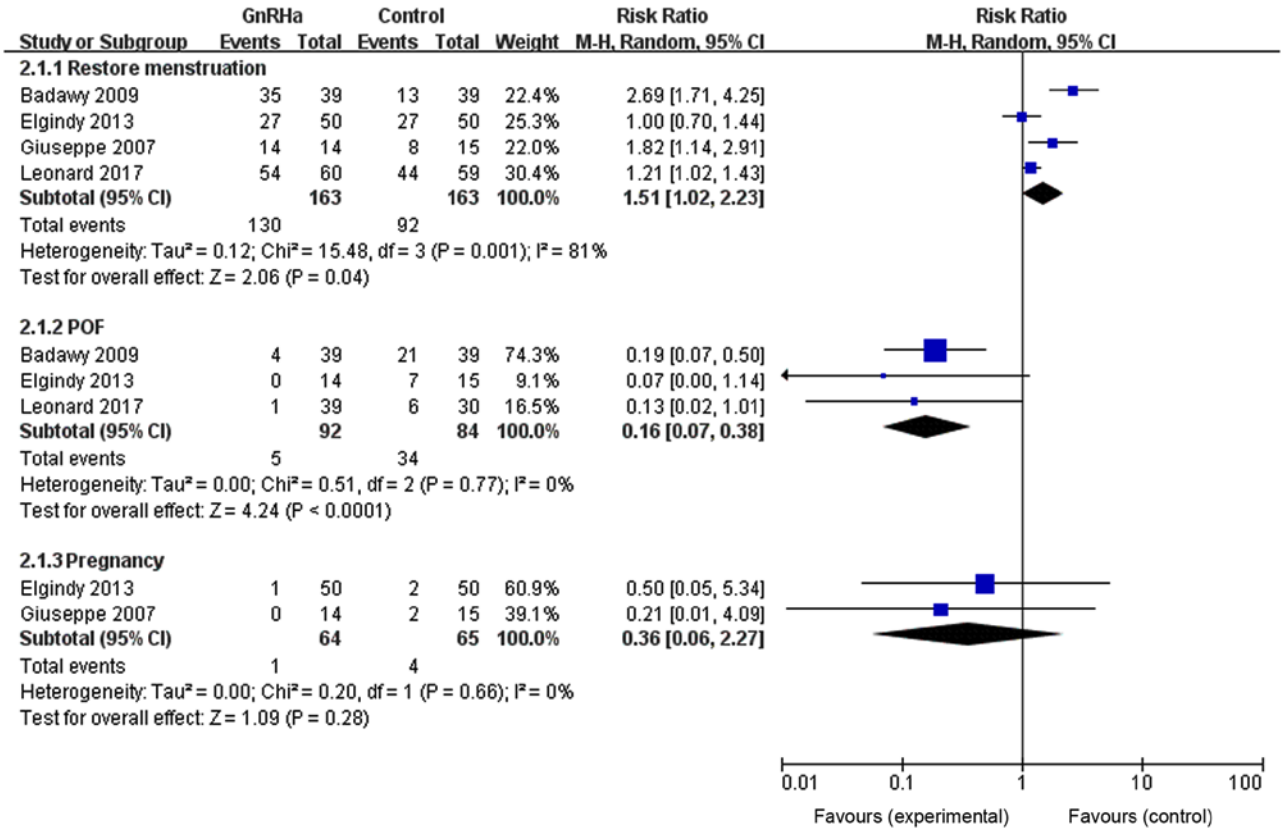

Figure 7. Forest plot of meta-analysis for the effects of GnRHa on menstrual recovery rate, POF incidence and pregnancy rate in patients <40 years old. CI, confidence interval; GnRHa, gonadotropin-releasing hormone agonist, POF, premature ovarian failure.

as the flare-up effect. The number of GnRH receptors then decreases, blocking the hypothalamus-pituitary-ovarian axis and subsequently decreasing the amount of FSH released, reducing the maturity and growth of original follicles, and reducing the sensitivity of the ovaries to chemotherapy (18). Badaru *et al* (19) demonstrated that this inhibition is positively correlated with the dosage of GnRHa, and that the inhibitory effect of GnRHa on the hypothalamus-pituitary-ovarian axis is increased when administered at 7.5 mg/month compared with at 3.75 mg/month. Previous studies have suggested that GnRHa reduces the amount of blood flowing through the ovaries, leading to a reduced concentration of topical drugs. However, few studies are available on this subject, and the results are contradictory. Kitajima *et al* (20) suggested that high levels of estrogen can significantly increase ovarian hyperstimulation and ovarian blood flow in a mouse model, whereas these effects are inhibited by GnRHa, and the degree of inhibition is positively associated with GnRHa dosage. A prospective study completed by Reinsch *et al* (21) revealed that after 3 months of continuous use of leuprorelin acetate, the blood flow to the uterus decreases by 21% and the signal of blood flow to the ovaries disappears. Conversely, Ng *et al* (22) and Jarvela *et al* (23) discovered that there is no alteration in ovarian blood flow before or after GnRHa treatment. The

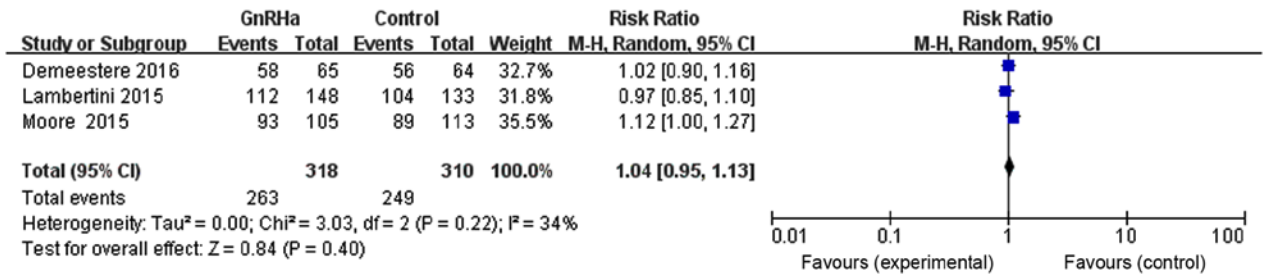

Figure 8. Forest plot of meta-analysis for the effects of GnRHa on the long-term tumor-free survival rate. CI, confidence interval; GnRHa, gonadotropin-releasing hormone agonist.

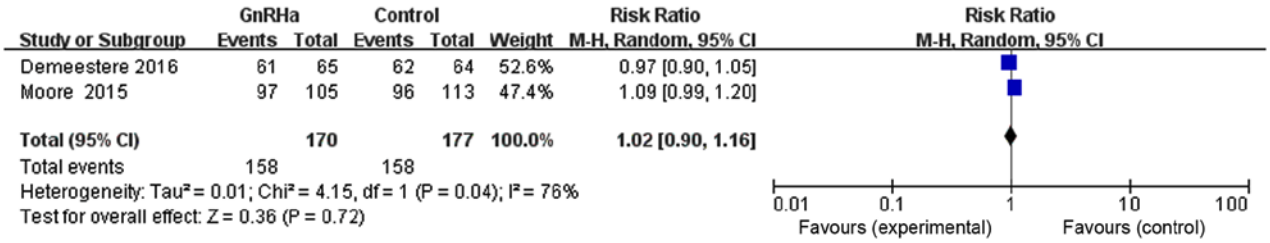

Figure 9. Forest plot of meta-analysis for the effects of GnRHa on the long-term overall survival rate. Leonard measured overall survival; however, this only demonstrated the short-term outcome. CI, confidence interval; GnRHa, gonadotropin-releasing hormone agonist.

effects of GnRHa on ovarian blood flow remain unclear and require further investigation.

There are two main types of GnRH receptors: GnRH receptor-I and GnRH receptor-II. Choi *et al* (24) discovered that GnRH receptors are present in ovarian cancer cell lines, ovarian surface epithelium, preovulatory follicles and corpus luteal cells, but are not detectable in the original follicles and early sinus follicles. Imai *et al* (25) reported that GnRHa acts directly on the granulosa cells, thus reducing the toxic effect of chemotherapy drugs.

Recent studies (26,27) have suggested that the damage induced by chemotherapy to female reproduction and endocrine function is due to cell apoptosis. GnRHa can be used to increase secretion of the gonadal protective molecule sphingosine-1-phosphate (S-1-P), which can prevent follicle injury or reproductive cell apoptosis. It has been demonstrated that S-1-P application to patients undergoing radiotherapy reduces ovarian damage (28).

The number follicles contained in the ovaries can reach 7,000,000 in a 28-week-old fetus, after which the follicles gradually die. No new cells are produced in the ovaries, and all cells stored will eventually disappear, resulting in perimenopausal symptoms. However, a recent study (29) has presented opposite results, indicating that the ovaries contain ovarian stem cells. Johnson *et al* (29) reported that rat ovaries have active germ line stem cells, which can continuously replace the immature ovarian follicles, allowing primordial follicular pool regeneration. Therefore, some researchers have hypothesized that GnRHa may preserve ovarian function by protecting the undifferentiated germ line stem cells. This hypothesis requires further investigation.

The present study had some limitations. Firstly, the 12 references included in this study had different definitions of POF and the follow-up time was markedly different, which potentially affects the results of this work. Secondly, eight references provided evidence of pregnancy in the GnRHa and control groups; however, no information was given on the use of contraception following cessation of chemotherapy and during follow-up. It was therefore difficult to evaluate the effects of chemotherapy combined with GnRHa on fertility. Thirdly, only three of the 12 references provided long-term tumor-free survival rate, which represented a small sample size that could potentially have led to a wrong conclusion. In addition, the 12 clinical randomized controlled trials included had an overall heterogeneity, and their differences in disease, chemotherapy, follow-up time and POF definition may have affected the results. A larger sample size, longer follow-up period and well-designed clinical randomized controlled trials are therefore required to further study and/or confirm the protective effects of GnRHa on ovarian damage induced by chemotherapy.

In conclusion, the present meta-analysis demonstrated that GnRHa may reduce ovarian function damage caused by chemotherapy. GnRHa significantly increased the rate of menstrual function recovery and reduced POF incidence; however, it had no effect on pregnancy rate, tumor-free survival rate and overall survival rate.

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Availability of data and materials

The analyzed datasets generated during the study are available from the corresponding author on reasonable request.

Authors' contributions

FZ and BZ designed the study and performed the literature review. YL and YW interpreted the data and wrote the manuscript. QF and LW performed the literature review, data collection and analysis, and wrote the manuscript. YC designed the the study, performed data analysis and wrote the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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