

# Gonadotropin-releasing hormone analog cotreatment for preservation of ovarian function during gonadotoxic chemotherapy: a systematic review and meta-analysis

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**Objective:** To determine whether gonadotropin-releasing hormone (GnRH) analog cotreatment with chemotherapy provides better reproductive outcomes for women at risk of premature ovarian failure (POF) as a side-effect of gonadotoxic chemotherapy.

**Design:** Systematic review and meta-analysis.

**Setting:** University-affiliated research centers.

**Patient(s):** None.

**Intervention(s):** Electronic and manual searches (e.g., MEDLINE, EMBASE, CENTRAL) up to January 2010 were performed to identify randomized controlled trials (RCTs) comparing GnRH cotreatment with chemotherapy alone in premenopausal women.

**Main Outcome Measure(s):** Incidence of POF after treatment, incidence of women with resumption of ovulation, POF after an initial normal cycle, normal cycles but abnormal markers of ovarian reserve, spontaneous occurrence of pregnancy after treatment, and time to reestablishment of menstruation; data also extracted to allow for an intention-to-treat analysis.

**Result(s):** Twenty-eight RCTs were identified, but only six met the inclusion criteria. Data were only available for the incidence of women with new onset of POF, resumption of ovulation, and occurrence of pregnancy. The incidence of POF or resumption of ovulation both demonstrated a statistically significant difference in favor of the GnRH cotreatment. The occurrence of spontaneous pregnancy showed no statistically significant difference between GnRH cotreatment and the control groups.

**Conclusion(s):** Evidence from RCTs suggests a potential benefit of GnRH cotreatment with chemotherapy in premenopausal women, with higher rates of spontaneous resumption of menses and ovulation but not improvement in pregnancy rates. Data relating to study quality and possible bias for the majority of the outcomes in this review were not available, denoting possible selective reporting of trial data. (Fertil Steril® 2011;95:906–14. ©2011 by American Society for Reproductive Medicine.)

**Key Words:** Chemotherapy, gonadotrophin-releasing hormone, meta-analysis, premature ovarian failure, randomized trial

The risk of women developing cancer before 40 years of age is approximately 1 in 49 (1). Although some of these cases occur during infancy and childhood, more than 99% will occur during the reproductive

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years. The most common malignancies in this age group affect the breast, cervix, colon, brain, and blood cells (e.g., leukemia). With continued treatment improvements, the number of long-term cancer survivors has dramatically increased. Over the last 30 years, the 5-year survival rate for children with cancer has improved from 58% to approximately 80%; and for adults from 50% to almost 70% (2, 3). Because many cancer survivors will eventually become interested in childbearing, it is important to maximize their chances for success.

Improved cancer survival rates are directly related to major advances in our understanding of cell division, multiplication, and growth, which has led to the development of more effective chemotherapeutic agents that selectively target rapidly multiplying cells (4, 5). However, few chemotherapeutic agents are cell cycle-specific; they

therefore inflict damage on a wide range of rapidly dividing cell types, such as bone marrow, thymus, and gastrointestinal mucosa. Female germ cells are also very sensitive to these agents. However, in contrast to other cell types, female germ cells are incapable of regeneration after injury and thus gonadotoxic agents can result in permanent ovarian damage. Up to two-thirds of adult female patients undergoing chemotherapy for malignancies eventually develop premature ovarian failure (POF) (6). Chemotherapeutic agents most likely to induce POF include cyclophosphamide, L-phenylalanine mustard, busulfan, and nitrogen mustard (7). Because most cancer patients today get combination chemotherapy, it is difficult to estimate an individual's risk of subsequent infertility or POF.

Several approaches have been used in an effort to preserve fertility in cancer patients who must undergo chemotherapy. One of the most effective approaches has been retrieval and fertilization of oocytes before chemotherapy followed by cryopreservation of embryos (8). Other experimental approaches include removal and cryopreservation of unfertilized eggs (9) or whole tissue (10). However, all of these options are expensive, delay treatment for weeks to months, and are not currently available in many countries and regions of the world.

A simpler and more expedient approach is ovarian suppression, either by pituitary down-regulation with gonadotropin-releasing hormone (GnRH) agonists or the use of GnRH antagonists before and during chemotherapy. The theoretical basis behind this approach is the observation that ovarian function is less likely to be destroyed when chemotherapy is given before puberty (11, 12). The proposed mechanisms by which cotreatment with a GnRH agonist (GnRH-a) may decrease follicle depletion are suppression of the pituitary ovarian axis, decreased ovarian perfusion, and a direct gonadal effect that may prevent cellular apoptosis.

Theoretically, reversibly returning ovaries to an inactive state by inhibition of the pituitary–gonadal axis before chemotherapy might make the germ cells less susceptible to the effects of alkylating agents (11). Originally, GnRH agonists were used for this purpose. These agents are begun in the luteal phase and must be administered several weeks until the initial increase in gonadal activity (“flare”) is followed by down-regulation. The required postponement in chemotherapy initiation can be avoided by the use of more recently developed GnRH antagonists (GnRH-antag), which do not have an initial flare phase. These agents immediately interfere with GnRH binding at the level of the pituitary and result in ovarian quiescence within a matter of days, regardless of when they are begun in relation to the menstrual cycle. In addition, GnRH analogue therapy in these patients could have other potential benefits, including menstrual suppression and reversal of menorrhagia-associated anemia, particularly in patients with hematologic cancers.

Studies of the effectiveness of GnRH analog cotherapy during chemotherapy to prevent ovarian damage have been inconsistent. Some prospective controlled studies of GnRH analog cotherapy have demonstrated a decrease in the ovarian failure rate after chemotherapy compared with controls (13). However, other studies have been unable to show a benefit (14). The primary objective of our systematic review of the literature was to ascertain the effectiveness of GnRH analogue cotherapy for the preservation of ovarian function during gonadotoxic chemotherapy.

## MATERIALS AND METHODS

To assess the efficacy and safety of GnRH cotreatment in preservation of ovarian function during gonadotoxic chemotherapy, we designed a systematic review of prospective randomized controlled trials. This review was conducted and reported according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (version 5.0.1) (15),

and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (16).

## Search Strategy

We searched for published, unpublished, and ongoing trials in MEDLINE (1960 to present), EMBASE (1980 to present), the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (issue 1, 2010), Ovid Healthstar (1999 to present), and [ClinicalTrials.gov](http://ClinicalTrials.gov) with no language restrictions. The search syntax was tailored individually for each database but included the following main Medical Subject Headings (MeSH) and text words: *gonadotropin releasing hormone*, *chemotherapy*, and *premature ovarian failure*. The last updated search was performed in January 2010. In addition, we performed a manual search of the grey literature (e.g., American Society for Reproductive Medicine [ASRM] and European Society of Human Reproduction and Embryology [ESHRE] conference abstracts) and the citation lists of the included studies and recent review articles for further trials.

Trials were excluded if they reported only on women who underwent bilateral oophorectomy (surgical castration), used different chemotherapy regimens in the GnRH and control groups, or did not provide data of relevance to this review. Finally, forward searching of trials was performed by cross-referencing the included trials with trials that cited them in Scopus and ISI Web of Science. One review author (AMAS) reviewed the identified reports, and this was confirmed by a second review author (MAB), with disagreements resolved by consensus.

## Outcomes Measures

The primary outcome for this review was the proportion of women who did not develop POF after treatment; as defined by the trials' investigators (Table 1). It should be noted that POF may occur without resumption of menstruation after chemotherapy, or may occur shortly after resumption of menstruation.

Secondary outcomes included the incidence of women with spontaneous ovulation, POF after an initial regular menstrual cycle, regular menstrual cycles but abnormal markers of ovarian reserve, spontaneous pregnancy during the follow-up period after cessation of treatment, and the time to reestablishment of a regular menstrual cycle. If more than one pregnancy was noted per patient, only the first would be included to avoid a possible unit-of-analysis error.

## Quantitative Data Synthesis and Statistical Analysis

A standardized data extraction sheet was developed and piloted for consistency. One review author (AMAS) took the lead in extracting data, which was confirmed by a second review author (MAB), with disagreements resolved by consensus.

Data management and statistical analyses were conducted using Review Manager (RevMan) 5.0.23. Where possible, data were extracted to allow for an intention-to-treat analysis, defined as including in the denominator the number of all originally included patients. If data from the trial reports were insufficient or missing, the investigators of the individual trials were contacted via E-mail for additional information.

For the meta-analysis, the number of participants experiencing the event in each group of the trial was recorded. Meta-analysis of binary data was performed with the DerSimonian and Laird method using a random-effects model, and the odds ratio (OR) and 95% confidence interval (95% CI) was reported. A random-effects model was determined to be more appropriate for this review because the protective effect of the GnRH analogue addition to multiple chemotherapy protocols is theorized to follow a similar pattern of distribution rather than the same treatment effect.

Homogeneity of the data from the included trials was performed by visual inspection of the outcomes tables and by using the chi-square test for heterogeneity with a 10% level of statistical significance. In addition, heterogeneity was quantified using the  $I^2$  test; where heterogeneity was found, the 95% CI for  $I^2$  (17) was calculated, and attempts to determine the possible source of heterogeneity was performed. A priori, the following factors of possible heterogeneity were considered to be relevant to this review: mean patient age, classification of disease process, type of chemotherapy regimens used, and type of GnRH analogue used. Publication bias assessment was planned but later cancelled owing to the small number of included trials and the associated low statistical power of reaching any firm conclusions.

**TABLE 1**

Description of reviewed prospective, randomized, controlled trials assessing the efficacy and safety of gonadotropin-releasing hormone cotreatment in preservation of ovarian function during gonadotoxic chemotherapy.

Study	Method	Participants	Intervention	Outcome
Waxman et al. (14), advanced Hodgkin disease	Design: Randomized trial Method of randomization: NA Allocation concealment: NA Blinding: NA Sample size calculation: NA	Country: U.K. No. of participants GnRH: 8 Control: 10 Age: mean (range) [y] GnRH: 28.5 (17–34) Control: 25.9 (17–46) Baseline FSH GnRH: NA Control: NA Follow-up: mean (range) [y] GnRH-a: 2.3 (1.8–2.5) Control: 2.0 (1–2.5)	Chemotherapy: Up to six cycles of MVPP Radiotherapy: Not used GnRH: Buserelin (200 µg) thrice daily intranasally for duration of chemotherapy Control: No GnRH analogue	Definition of POF: Cessation of menstruation Available outcomes: Incidence of spontaneous menstruation Incidence of return to spontaneous ovulation Incidence of spontaneous pregnancy
Gilani et al. (18), ovarian malignancy	Design: Randomized trial Method of randomization: Random-number table Allocation concealment: NA Blinding: “Open trial” with no blinding Sample size calculation: Performed	Country: Iran No. of participants GnRH: 15 Control: 15 Age: median (range) [years] GnRH: 21 (13–33) Control: 22 (15–35) Baseline FSH GnRH: NA Control: NA Follow-up: mean (y) GnRH-a: 0.5 Control: 0.5	Surgery: Conservative with preservation of one or two ovaries Chemotherapy: Up to 6 cycles of alkylating or alkylating-like MCT Radiotherapy: Not used GnRH: Diphereline (3.75 mg)/28 days for duration of chemotherapy Control: No GnRH analogue	Definition of POF: Early, permanent cessation of menstruation after 6 months of chemotherapy and a serum FSH level >20 mIU/mL Available outcomes: Incidence of spontaneous menstruation
Giuseppe et al. (19), Hodgkin disease	Design: Randomized trial Method of randomization: NA Allocation concealment: NA Blinding: NA Sample size calculation: NA	Country: Italy No. of participants GnRH: 14 Control: 15 Age: mean ± SD (y) GnRH: 24.3 ± 5.3 Control: 24.26 ± 7.92 Baseline FSH GnRH: NA Control: NA Follow-up: mean ± SD (y) GnRH-a: 2.4 ± 1.7 Control: 5.93 ± 4.47	Chemotherapy: Up to 6 cycles ABVD; ABVD, alternating with C(M)OPP; or C(M)OPP alternating with ABV. Additional DHAP in cases of incomplete remission Radiotherapy: No pelvic radiotherapy; supradiaphragmatic radiotherapy in 82.8% of patients GnRH: Triptorelin (3.25 mg)/month or depot triptorelin (11.25 mg)/3 months for duration of chemotherapy Control: No GnRH analogue	Definition of POF: Cessation of menstruation Available outcomes: Incidence of spontaneous menstruation Post-CHT markers of ovarian reserve (FSH, LH, inhibin B, AMH, AFC)

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**TABLE 1****Continued.**

Study	Method	Participants	Intervention	Outcome
Badawy et al. (13), unilateral adenocarcinoma of the breast	Design: Randomized trial Method of randomization: Unclear Allocation concealment: Sealed, dark envelopes Blinding: NA Sample size calculation: Performed a priori	Country: Egypt No. of participants: GnRH: 40 Control: 40 Age: mean $\pm$ SD (y) GnRH: 30.00 $\pm$ 3.51 Control: 29.20 $\pm$ 2.93 Baseline FSH: mean $\pm$ SD (mIU/mL) GnRH: 4.3 $\pm$ 1.11 Control: 5.7 $\pm$ 1.30 Mean follow-up (y) GnRH-a: 0.66 Control: 0.66	Surgery: Modified radical mastectomy or breast-conserving surgery plus full axillary lymph node dissection Chemotherapy: Up to 6 cycles of FAC regimen Radiotherapy: Not used GnRH: Goserelin (3.6 mg)/28 days for 6 months Control: No GnRH analogue	Definition of POF: Early cessation of menstruation, ovulation and increased serum FSH level (hypergonadotropic amenorrhea) Available outcomes: Incidence of spontaneous menstruation Incidence of spontaneous ovulation
Gerber et al. (21), receptor-negative breast cancer	Design: Randomized trial Method of randomization: NA Allocation concealment: NA Blinding: NA Sample size calculation: NA	Country: Germany No. of participants GnRH: 30 Control: 30 Age: median (range) [years] GnRH: 35.1 (26–44) Control: 38.2 (29–47) Baseline FSH: mean $\pm$ SD (mIU/mL) GnRH: NA Control: NA Mean follow-up (y) GnRH-a: 0.5 Control: 0.5	Surgery: NA Chemotherapy: Up to 12 cycles of anthracycline/taxane polychemotherapy Radiotherapy: NA GnRH: Goserelin (3.6 mg)/28 days until the end of chemotherapy Control: No GnRH analogue	Definition of POF: Cessation of menstruation Available outcomes: Incidence of spontaneous menstruation Incidence of spontaneous pregnancy

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**TABLE 1****Continued.**

Study	Method	Participants	Intervention	Outcome
Sverrisdottir et al. (22), node-positive breast cancer <sup>a</sup>	Design: Randomized trial Method of randomization: Permuted blocks Allocation concealment: Central randomization Blinding: NA Sample size calculation: NA	Country: Sweden No. of participants: GnRH A: 29 GnRH B: 37 Control A: 28 Control B: 29 Age: median (range) [y] GnRH A: 45 (36–51) GnRH B: 46 (35–54) Control A: 45 (29–53) Control B: 45 (29–53) Baseline FSH: mean ± SD (mIU/mL) GnRH A: NA GnRH B: NA Control A: NA Control B: NA Mean follow-up (y) GnRH-a: 1.0 Control: 1.0	Surgery: breast conserving Chemotherapy: Up to 6 cycles of CMF regimen ± tamoxifen Radiotherapy: Performed in patients with breast conserving surgery and/or four or more positive lymph nodes GnRH: Goserelin (3.6 mg)/28 days for 2 years Control: No GnRH analogue ± tamoxifen	Definition of POF: Cessation of menstruation Available outcomes: Incidence of spontaneous menstruation

*Note:* ABV = doxorubicin, bleomycin, and vinblastine hybrid regimen; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine regimen; AFC = antral follicle count; AMH = antimüllerian hormone; CHT = chemotherapy; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil regimen; C(M)OPP = cyclophosphamide, Oncovin (vincristine), procarbazine, and prednisone regimen; DHAP = dexamethasone, high-dose cytarabine (Ara-C), cisplatinum regimen; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide regimen; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; MCT = multi-agent chemotherapy; MVPP = mustine, vinblastine, procarbazine, and prednisone regimen; NA = information not available; POF = premature ovarian failure; SD = standard deviation.

<sup>a</sup> This study has four arms: arm A received only chemotherapy ± GnRH analogue; arm B received chemotherapy + tamoxifen ± GnRH analogue.

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Risk of Bias Assessment

To assess the validity of studies regarding the risk of bias (RoB) in their results, (e.g., risk of overestimation or underestimation of the true intervention effect), we performed a domain-based risk of bias assessment according the principles of the Cochrane Collaboration’s Risk of Bias tool (15).

RESULTS

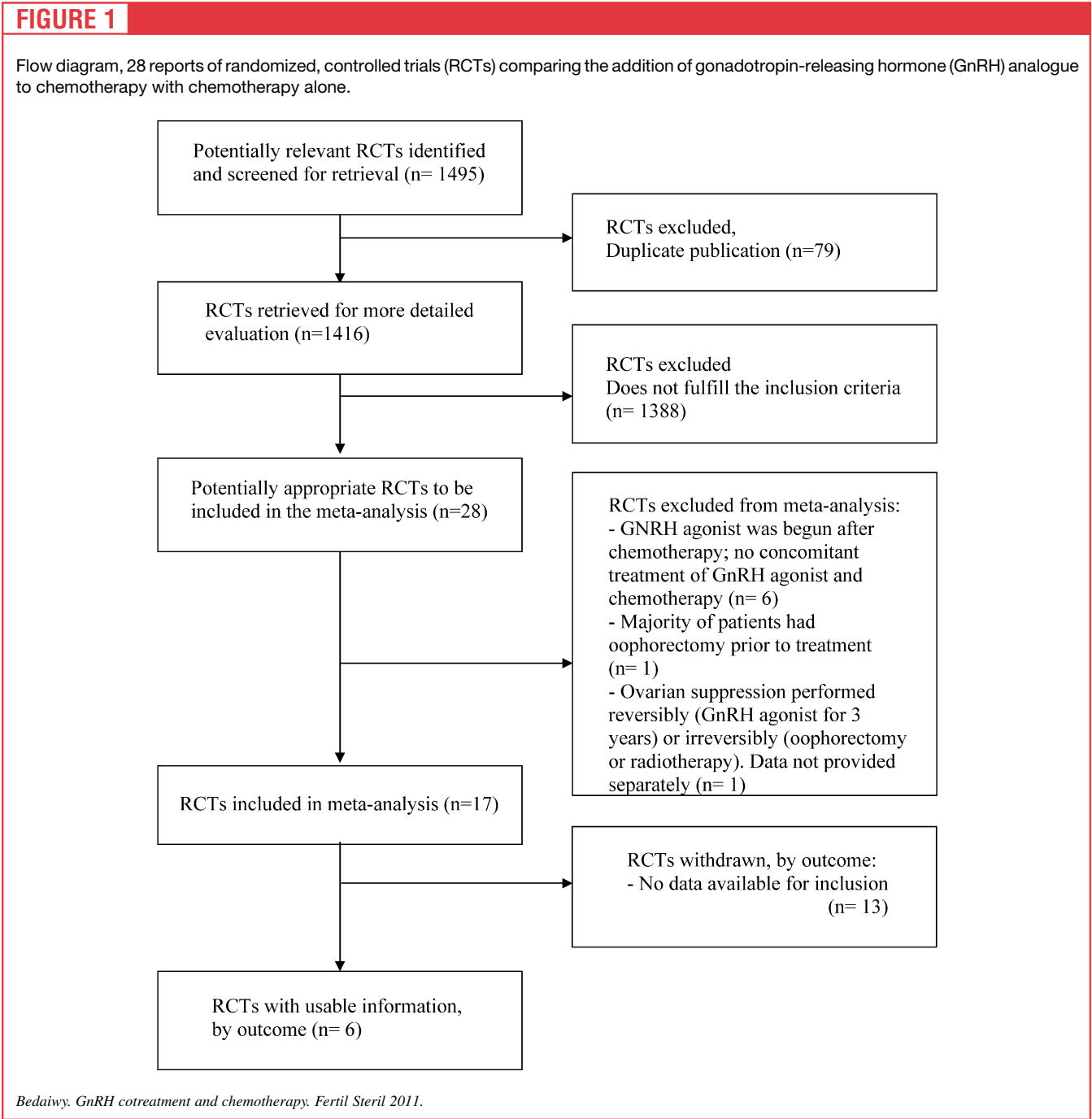
Search Results

The electronic and manual searches resulted in the identification of 28 reports of randomized trials comparing the addition of GnRH analogue to chemotherapy compared with chemotherapy alone

(Fig. 1). Of these trials, only six trials met the inclusion criteria (13, 14, 18–22).

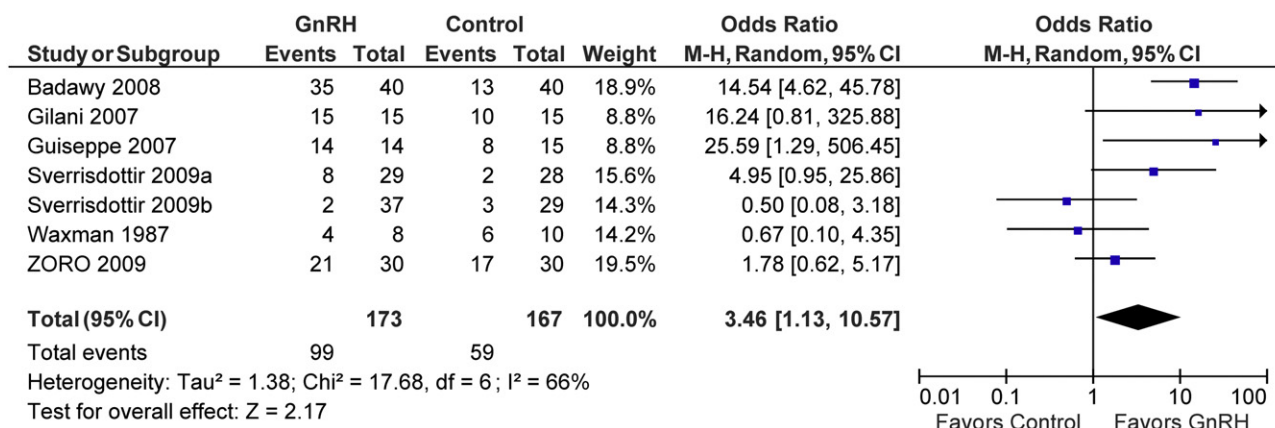
Description of Included Trials

Detailed description of the methods used in the included trials, including the type of chemotherapeutic drugs and type of GnRH analogue used, is provided (Table 1; Supplemental Table 1, available online). The results of the risk of bias assessment for the included studies are presented in Supplemental Table 2 (available online). It is noticeable that information relating to the methodology of patient randomization was rarely and incompletely reported (Supplemental Fig. 1, available online).



**FIGURE 2**

Forest plot demonstrating the incidence of not having premature ovarian failure. Heterogeneity:  $\text{Tau}^2 = 1.38$ ; chi-square = 17.68,  $df = 6$  ( $P = .007$ );  $I^2 = 66\%$ . Test for overall effect:  $z = 2.17$  ( $P = .03$ ).



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## Outcome Measures

Data were not available nor analyzable for the following outcomes: incidence of women with POF after an initial normal cycle, incidence of women with regular cycles but abnormal markers of ovarian reserve, and time to reestablishment of a regular menstrual cycle.

Both the incidence of women with spontaneous menstruation and incidence of spontaneous ovulation demonstrated a statistically significant difference in favor of the use of GnRH-a (OR 3.46; 95% CI, 1.13–10.57; and OR 5.70; 95% CI, 2.29–14.20, respectively) (Figs. 2, 3). It should be noted that data for the latter outcome came from only two studies (13, 14), but data for the former outcome came from all six included trials. The proportion of women with occurrence of spontaneous pregnancy during the follow-up period after cessation of treatment was available from three trial reports (14, 19, 21) (Supplemental Fig. 1). There was no statistically significant difference between treatment and the control groups in the incidence of a spontaneous pregnancy (OR 0.26; 95% CI, 0.03–2.52).

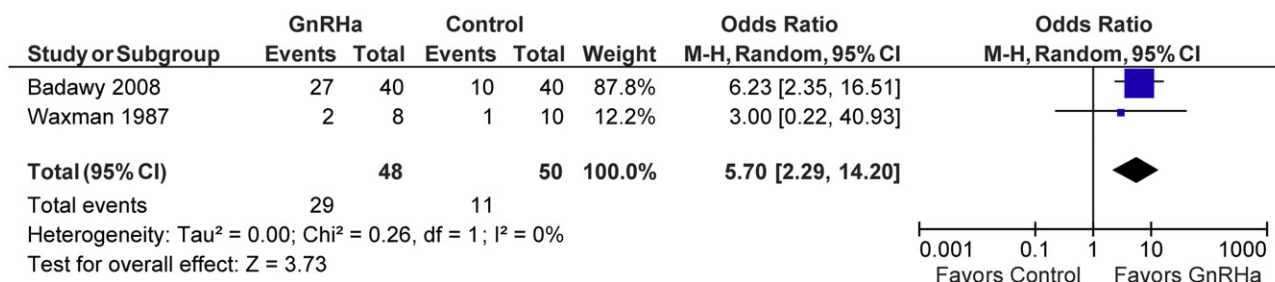
The tests for heterogeneity highlighted homogeneity among the included trials in all the outcomes with the exception of the incidence of women with spontaneous menstruation, which showed moderate heterogeneity ( $I^2 = 66\%$ ; 95% CI, 0–82.93%). Subgroup and sensitivity analyses could not determine the exact source of the heterogeneity nor were any of the studies considered as outliers. This may reflect the differing patient populations, chemotherapy regimens, or length of the follow-up period in the respective trials.

## DISCUSSION

The results of this systematic review demonstrate that the use of GnRH agonist cotreatment with chemotherapy may be beneficial in preserving future fertility in women treated with chemotherapeutic agents. The main observation of our analysis is that cotreatment with an agonist does seem to provide short-term return of ovulation and a menstrual cycle but not improved pregnancy rates. Because data on the use of GnRH-antagonist cotreatment were not available, no comment can be made on the possible benefit of this class.

**FIGURE 3**

Forest plot demonstrating the incidence of spontaneous ovulation. Heterogeneity:  $\text{Tau}^2 = 0.00$ ; chi-square = 0.26,  $df = 1$  ( $P = .61$ );  $I^2 = 0$ . Test for overall effect:  $z = 3.73$  ( $P = .0002$ ).



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Patients undergoing chemotherapy for breast cancer, choriocarcinoma, Hodgkin disease, acute lymphoblastic leukemia, and other tumors as well as systemic diseases are now expected to survive for prolonged periods after treatment (23). This has led to the introduction of less invasive techniques as well as awareness among physicians for the need to rethink the long-term strategy with regards to patient benefits as opposed to just the 5-year survival rates.

Gonadal tissue is highly sensitive to the effects of chemotherapeutics and radiotherapy. Preovulatory follicles are particularly sensitive to alkylating agents (24, 25). Therefore all options available should be investigated and compared to offer patients the best available outcomes for a normal reproductive future.

Only a hand-full of randomized trials were identified that discussed the issue of ovarian preservation with the use GnRH analogues. Of these, the majority have been either small in size, are still ongoing, and/or do not provide analyzable data. Furthermore, all these studies have a short follow-up period that limit any conclusions on their long-term efficacy. This dearth of information is partially to blame for the slow introduction of GnRH analogues into clinical trials and practice. In addition, in an early study by Waxman et al. (14) in women with advanced Hodgkin disease, no additional protective effect was observed in women randomized to buserelin cotreatment. This study was criticized for having a small sample size and inadequate down-regulation of the women as the follicle-stimulating hormone (FSH) levels were relatively unaffected by the addition of buserelin.

Recently, several investigators have demonstrated more promising results. In patients with Hodgkin disease, Blumenfeld et al. (26) noted that cotreatment with a GnRH agonist may reduce ovarian damage significantly. In addition, in women with systemic lupus, Blumenfeld et al. (27) demonstrated that the effect of GnRH agonists was not limited to hematologic malignant diseases but to any disease requiring exposure to alkylating agents such as cyclophosphamide and chlorambucil, including systemic lupus. In

women with breast cancer, Badawy et al. (13) demonstrated the administration of GnRH analogue in combination with chemotherapy is feasible, well tolerated, and protects long-term ovarian function. At the end of the observation period, almost 44% more patients were ovulating in the GnRH agonist group than among controls. However, this study generated a great deal of controversy (28, 29) and was criticized for the fact that all patients showed hormonal evidence of being in the luteal phase of their cycles, which is improbable if the patients were randomly selected. Moreover, the investigators did not account for the possible effects of tamoxifen therapy on the hormonal status of the study groups (28).

In addition, the study population was relatively younger than any other breast cancer group ever studied before, with a mean  $\pm$  standard deviation (SD) of 30 ( $\pm 3.51$ ) and 29.2 ( $\pm 2.93$ ) years, respectively; which limits the generalizability of their findings as breast cancer populations in the United States and Europe have a higher mean age. Even more interesting is that they reported amenorrhea rates twice as high as other groups with even more gonadotoxic chemotherapy and older study populations (29). In the future, more well-designed, powered, and reported trials are needed to address all possible outcomes and strengthen the body of evidence.

## CONCLUSION

Evidence from RCTs suggests a potential benefit of GnRH cotreatment with chemotherapy in premenopausal women, with higher rates of spontaneous resumption of menses and ovulation but not improvement in pregnancy rates. Data relating to possible bias for the majority of the outcomes in this review were not available; denoting a possible selective reporting of trial data. Therapy with a GnRH analogue in this patient population could have other potential benefits, including menstrual suppression and reversal of menorrhagia-associated anemia, particularly in patients with hematologic cancers.

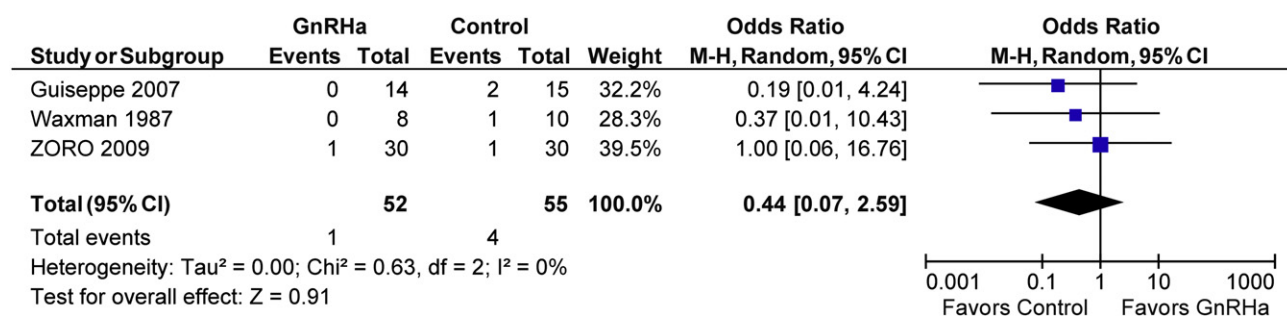
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# SUPPLEMENTAL FIGURE 1

Forest plot demonstrating the incidence of spontaneous pregnancy. Heterogeneity:  $\text{Tau}^2 = 0.00$ ; chi-square = 0.63,  $df = 2$  ( $P = .73$ );  $I^2 = 0$ . Test for overall effect:  $z = 0.91$  ( $P = .36$ ).



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# SUPPLEMENTAL TABLE 1

Description of chemotherapy regimens used in reviewed trials assessing the efficacy and safety of gonadotropin-releasing hormone cotreatment in preservation of ovarian function during gonadotoxic chemotherapy.

Study	Chemotherapy regimens	Components of each regimen
Waxman et al. (14), advanced Hodgkin disease	MVPP	Mustine, 6 mg/m <sup>2</sup> Vinblastine, 6 mg/m <sup>2</sup> Procarbazine, 100 mg/m <sup>2</sup> Prednisone, 40 mg
Gilani et al. (18), ovarian malignancy	VAC	Vincristine, 1.5 mg/m <sup>2</sup> Dactinomycin, 0.5 mg Cyclophosphamide, 5–7 mg/kg
	BEP	Bleomycin, 20 u/m <sup>2</sup> Etoposide, 100 mg/m <sup>2</sup> Cisplatin, 20 mg/m <sup>2</sup>
	TC	Taxol, 175 mg/m <sup>2</sup> Carboplatin with AUC 4
	CP	Taxol, 175 mg/m <sup>2</sup> Cisplatin, 75 mg/m <sup>2</sup>
	ABVD regimen	Adriamycin (doxorubicin), 25 mg/m <sup>2</sup> Bleomycin, 10 mg/m <sup>2</sup> Vinblastine, 6 mg/m <sup>2</sup> ; dacarbazine, 375 mg/sqm
Giuseppe et al. (19), Hodgkin disease	ABVD alternating with C(M)OPP	Cyclophosphamide (Endoxan), 600 mg/m <sup>2</sup> Oncovin (vincristine), 1.4 mg/m <sup>2</sup> Procarbazine, 100 mg m <sup>2</sup> Prednisone, 1 mg/kg
	C(M)OPP alternating with ABV hybrid	Adriamycin, 25 mg/m <sup>2</sup> Bleomycin, 10 mg/m <sup>2</sup> Vinblastine, 6 mg/m <sup>2</sup> Dexamethasone, 40 mg/m <sup>2</sup>
	DHAP	High-dose cytarabine (Ara-C), 2 g/m <sup>2</sup> Cisplatin, 100 mg/m <sup>2</sup>
	FAC regimen	5-Fluorouracil, 500 mg/m <sup>2</sup> Doxorubicin, 500 mg/m <sup>2</sup> Cyclophosphamide, 500 mg/m <sup>2</sup>
	NA	NA
Badawy et al. (13), unilateral adenocarcinoma of the breast	Anthracycline/taxane polychemotherapy	NA
Gerber et al. (21), receptor-negative breast cancer	CMF regimen	Cyclophosphamide, 600 mg/m <sup>2</sup> Methotrexate, 40 mg/m <sup>2</sup> 5-Fluorouracil, 600 mg/m <sup>2</sup>
Sverrisdottir et al. (22), node-positive breast cancer		

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## SUPPLEMENTAL TABLE 2

**Risk of bias in reviewed trials assessing the efficacy and safety of gonadotropin-releasing hormone cotreatment in preservation of ovarian function during gonadotoxic chemotherapy.**

Study	Item	Judgment	Description
Waxman et al. (14)	Adequate sequence generation?	Unclear	Insufficient information about the sequence-generation process to permit judgment.
	Allocation concealment?	Unclear	Insufficient information available on allocation concealment to permit judgment.
	Blinding?	No	Blinding not possible because no placebo injection was used in control group.
	Incomplete outcome data addressed?	No	Data for noncompliant participants were not provided.
	Free of selective reporting?	Unclear	Mean baseline FSH levels were not presented.
	Free of other bias?	Yes	Study appears to be free of other sources of bias.
Gilani et al. (18)	Adequate sequence generation?	Yes	Reported that randomization was performed with the use of a random-number table.
	Allocation concealment?	Unclear	Insufficient information available on allocation concealment to permit judgment.
	Blinding?	No	Reported that this was an “open trial” and blinding was not performed.
	Incomplete outcome data addressed?	No	Data for participants who died or did not complete the oncologic and GnRH protocols were not provided.
	Free of selective reporting?	Unclear	Mean baseline FSH levels were not presented.
	Free of other bias?	Yes	Study appears to be free of other sources of bias.
Giuseppe et al. (19)	Adequate sequence generation?	Unclear	Insufficient information about the sequence-generation process to permit judgment.
	Allocation concealment?	Unclear	Insufficient information available on allocation concealment to permit judgment.
	Blinding?	No	Blinding not possible because no placebo injection was used in control group.
	Incomplete outcome data addressed?	Yes	Intention-to-treat principle was used, and all patients were included in the analyses.
	Free of selective reporting?	No	Majority of data reported for all participants together as one group in an observational fashion; data not available for each group separately.
	Free of other bias?	No	Period of follow-up was significantly different between the GnRH and control groups.
Badawy et al. (13)	Adequate sequence generation?	Unclear	Insufficient information about the sequence-generation process to permit judgment.
	Allocation concealment?	Yes	Used dark, sealed envelopes, an adequate method of allocation concealment.
	Blinding?	No	Blinding not possible because no placebo injection used in control group.
	Incomplete outcome data addressed?	No	Data for noncompliant participants were not provided.
	Free of selective reporting?	Unclear	Insufficient information available to permit judgment.
	Free of other bias?	No	Baseline FSH levels were significantly different between GnRH and control groups.

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## SUPPLEMENTAL TABLE 2

Continued.

Study	Item	Judgment	Description
Gerber et al. (21)	Adequate sequence generation?	Unclear	Insufficient information about the sequence-generation process to permit judgment.
	Allocation concealment?	Unclear	Insufficient information available on allocation concealment to permit judgment.
	Blinding?	No	Blinding not possible because no placebo injection used in control group.
	Incomplete outcome data addressed?	Unclear	Insufficient information available to determine if all patients were followed for evaluation and included in the analyses.
	Free of selective reporting?	Unclear	Insufficient information available to permit judgment.
	Free of other bias?	No	Financial support provided by a pharmaceutical company.
Sverrisdottir et al. (22)	Adequate sequence generation?	Yes	Reported that randomization was performed using permuted blocks.
	Allocation concealment?	Yes	Reported that allocation concealment was performed through the use of central randomization.
	Blinding?	No	Blinding not possible because no placebo injection used in control group.
	Incomplete outcome data addressed?	No	Data for participants who were lost for follow-up were not included in the analyses.
	Free of selective reporting?	Unclear	Insufficient information available to permit judgment.
	Free of other bias?	Yes	Study appears to be free of other sources of bias.

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