

Protecting Ovaries During Chemotherapy Through Gonad Suppression

A Systematic Review and Meta-analysis

Eman Elgindy, MD, PhD, Hoda Sibai, MD, Amany Abdelghani, MD, and Magdy Mostafa, MD

OBJECTIVE: To estimate whether gonadotropin-releasing hormone (GnRH) analog administration during chemotherapy can protect against development of ovarian toxicity.

DATA SOURCES: MEDLINE (1966 to present), EMBASE (1980 to present), Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov were searched through March 2015 using the phrases: “gonadotropin-releasing hormone,” “chemotherapy,” and “premature ovarian failure.” Hand-search on conference abstracts, SCOPUS, and ISI Web of Science were also searched.

METHODS OF STUDY SELECTION: Published English-language randomized controlled trials comparing resumption of ovarian function between GnRH analogs plus chemotherapy with chemotherapy without GnRH analogs were included. Studies including women with pelvic metastases or recent history of receiving chemotherapy were excluded. Accordingly, 10 eligible trials (907 women) were analyzed.

TABULATION, INTEGRATION, AND RESULTS: Our primary outcome was the proportion of women with resumed ovarian function (defined as resumption of menstruation, prevention of chemotherapy-induced ovarian failure, or both) at the longest follow-up after

the end of chemotherapy. Secondary outcomes were evaluating ovarian reserve parameters and pregnancy. Risk ratio was used to integrate qualitative results and mean difference was used for quantitative data. Gonadotropin-releasing hormone analog cotreatment did not significantly increase ovarian function resumption (320/468 [68.4%] in GnRH analog arm and 263/439 [59.9%] in the chemotherapy alone arm; risk ratio 1.12, 95% confidence interval [CI] 0.99–1.27). No protective effect existed after subgroup analyses (type of malignancy [$P=.31$], age [$P=.14$], and GnRH analog type [$P=.44$]). Gonadotropin-releasing hormone analogs did not protect any of ovarian reserve parameters, whether follicle-stimulating hormone (mean difference -2.63 , 95% CI -7.33 to 2.07), antral follicle count (mean difference 1.66 , 95% CI -0.69 to 4.01), or anti-Müllerian hormone (mean difference 0.31 , 95% CI -0.41 to 1.03). Spontaneous pregnancy was also comparable (risk ratio 1.63 , 95% CI 0.94 – 2.82).

CONCLUSION: Gonadotropin-releasing hormone analog administration during chemotherapy does not appear to protect the ovaries from gonadal toxicity. It is not a reliable method for fertility preservation.

(*Obstet Gynecol* 2015;126:187–95)

DOI: 10.1097/AOG.0000000000000905

Recent years have witnessed marked improvement in cytotoxic treatments with a parallel increase in patient survival.¹ Ovarian damage, however, has been a major side effect of cytotoxic treatment.² The most important factors affecting the development of primary ovarian insufficiency are age of the patient, type of chemotherapy, and use of hormonal therapy, specifically tamoxifen.^{2,3} The American Society of Clinical Oncology in 2006 had emphasized the importance of integrating a fertility preservation measure as early as possible during planning for cancer treatment.⁴ The use of gonadotropin-releasing hormone (GnRH) analogs for ovarian suppression during chemotherapy is one of the suggested strategies to

From the Departments of Obstetrics and Gynecology, Zagazig University School of Medicine, Zagazig, and Cairo University Faculty of Medicine, El Manial, Cairo, Egypt; and the Department of Obstetrics and Gynecology, Maastricht University, Maastricht, the Netherlands.

The authors thank Professor Johannes Evers, MD, PhD, FRCOG, professor of obstetrics and gynecology at Maastricht University and editor-in-chief of Human Reproduction, for his valuable guidance and productive suggestions relative to this article.

Corresponding author: Magdy Mostafa, MD, Department of Obstetrics and Gynecology, Cairo University Faculty of Medicine, El Manial, Cairo, Egypt 115621; e-mail: imagdy@kasralainy.edu.eg.

© 2015 by The American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0029-7844/15



preserve fertility.^{5,6} This creates a pseudoprepubertal state with an overall decrease in ovarian function.^{7,8} A decrease in follicle-stimulating hormone (FSH) secretion occurs with the continuous use of analogs with subsequent prevention of secondary follicular recruitment and stopping the vicious circle of more follicular development and destruction.^{9,10} These mechanisms, however, have never been proven to be functional in human oocytes and the development from primordial follicle up to the small preantral follicle is a gonadotropin-independent process.¹¹

In fact, the protective effect of GnRH analog cotreatment during chemotherapy is quite debatable. Even in presence of meta-analyses suggesting a possible protective role, there are various limitations that could have affected the results.^{5,6,12}

Recent years have witnessed a number of well designed, multicenter, randomized controlled trials (RCTs). Therefore, the objective of the current systematic review and meta-analysis is to appraise the evidence as to whether coadministering GnRH analogs during chemotherapy could protect the ovaries from subsequent development of gonadal toxicity.

SOURCES

Our systematic review was conducted using only RCTs. We conformed methodologic approaches reported in the Cochrane Handbook for Systematic Reviews¹³ and the Methodological Expectations of Cochrane Intervention Reviews¹⁴ and complied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses¹⁵ and Methodological Expectations of Cochrane Intervention Reviews criteria. Our research question was "In chemotherapy-treated premenopausal women, does coadministration of GnRH analogs preserve ovarian function in comparison to no treatment?"

We searched MEDLINE (PubMed), EMBASE (Ovid), CENTRAL (Cochrane Library–Wiley), Global Health (Ovid), HealthStar (Ovid), the World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov from inception to March 2015. We also hand-searched relevant conference proceedings for the preceding 5 years to identify planned, ongoing, or recently completed but unpublished trials. In addition, we ran forward searches in Scopus and Web of Science to identify missed citations through previous searching techniques. The reference list of narrative and systematic reviews and included trials were finally hand-searched for any relevant citations.

Whatever the database, the search syntax included the following words: "gonadotropin/gonadotrophin/luteinizing hormone-releasing hormone

analogue," "gonadotropin/gonadotrophin/luteinizing hormone-releasing hormone agonist," "gonadotropin/gonadotrophin/luteinizing hormone-releasing hormone antagonist," "chemotherapy," "premature ovarian failure," "POF," "primary ovarian insufficiency," "POI," "fertility preservation," and "fertility reservation."

The primary outcome was the proportion of women with resumed ovarian function after the end of chemotherapy. We conformed to the most frequently used definitions, which were the resumption of menstruation, the prevention of chemotherapy-induced primary ovarian insufficiency at the longest available follow-up period, or both.

Secondary outcomes were measuring biochemical (FSH and antimüllerian hormone) ultrasonographic (antral follicle count) markers of ovarian reserve and occurrence of spontaneous pregnancy.

STUDY SELECTION

From a total of 1,300 screened records, 32 articles were assessed for eligibility and 10 studies were included (Fig. 1). Our review included RCTs studying women in their reproductive age receiving different chemotherapeutic regimens with or without adjuvant treatment for different types of malignancy. The inclusion criteria were: 1) English-language studies; 2) RCTs comparing GnRH analogs plus chemotherapy with chemotherapy alone in terms of resumption of menstruation, prevention of chemotherapy-induced primary ovarian insufficiency, or both; and 3) risk ratio (RR) for resumption of ovarian function could be computed from the presented results. Studies including women with pelvic metastases or with a recent history of receiving chemotherapy were excluded from the review.

Two authors (E.E. and M.M.) independently screened titles and abstracts of search results and then selected full-text articles to determine whether a citation met the inclusion criteria according to preprepared forms. Discrepancies between the two authors were resolved through consensus or by discussion with the other two authors (H.S. and A.A.), as required.

Internal validity assessment was done using Cochrane Collaboration's Risk of Bias tool.¹⁶

Two authors (E.E. and M.M.) independently extracted relevant data of all included trials using standardized data extraction form. Extracted data included characteristics of the enrolled patient population, details of interventions, study outcomes, and funding sources. Data processing was carried out using Microsoft Excel 2010 for MS Windows.



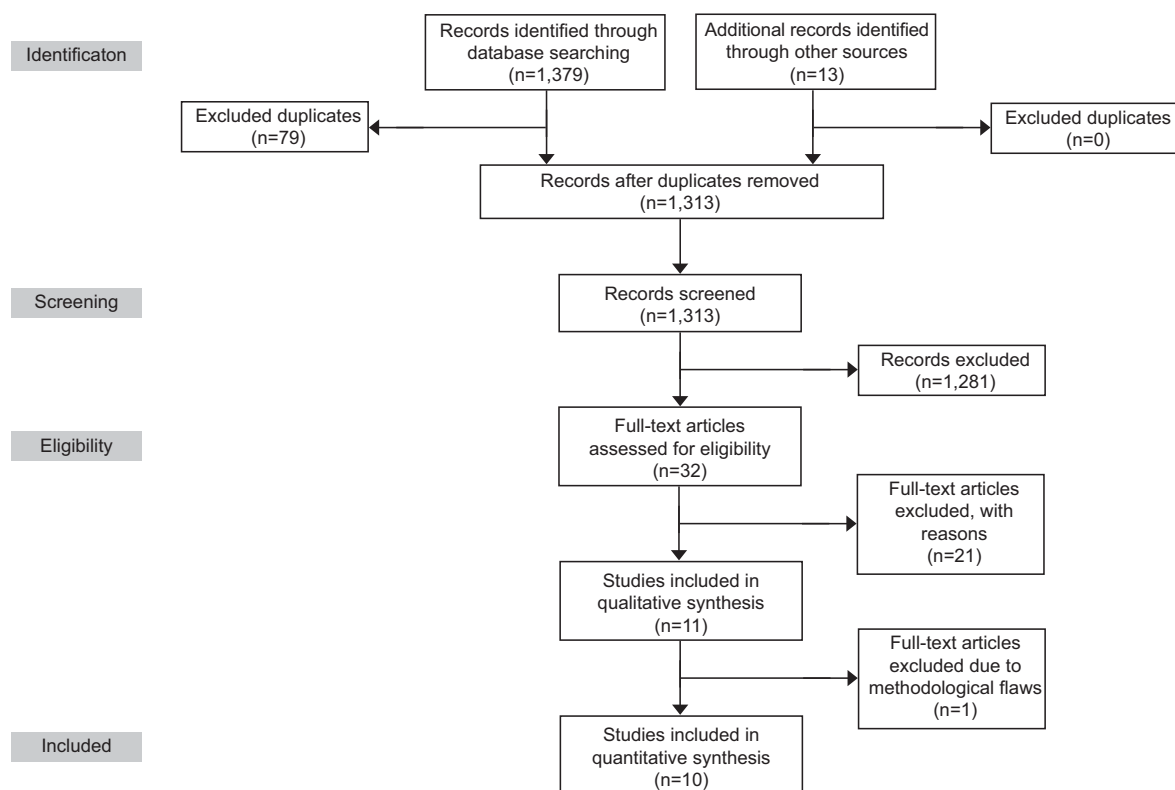


Fig. 1. Flowchart showing the identification of studies to include in the quantitative synthesis.

Elgindy. GnRH Analog Coadministration During Chemotherapy. Obstet Gynecol 2015.

RESULTS

We analyzed data from the included studies using Review Manager (RevMan 5.2) and Microsoft Excel 2010. A formal meta-analysis was conducted for all outcomes if data were sufficient. We expressed pooled dichotomous data as RR with 95% confidence intervals (CIs), whereas pooled continuous effect measures were expressed as mean difference with 95% CI. Because of considerable heterogeneity across the studies, we used the Der Simonian and Laird¹⁷ random-effects model for all analyses. We explored and quantified between-study statistical heterogeneity using the I^2 test. If I^2 was less than 25% in any analysis, calculation of the 95% uncertainty CIs was added.^{18,19} Subgroup analysis was conducted if significant heterogeneity was detected, P was greater than 50%, or both provided availability of enough number of trials. Accordingly, we performed subgroup analyses on type of malignancy (breast, lymphoma, and ovarian), age groups (40 years or younger and older than 40 years), and type of used GnRH analogs (agonist alone and agonist and antagonist combination).

We assessed publication bias using funnel plot technique, Begg's rank test,²⁰ and Egger's linear

regression test.²¹ We considered two-sided statistical testing setting the α error level at 0.05.

We tested the preferential effect of each study on overall result of our meta-analysis through performing multiple sensitivity analyses removing one study in each step.

Eleven studies had been identified.^{22–32} One of these studies, the study by Badawy et al,²⁷ was excluded because of major flaws, whether in study methods or results, with strong doubts about randomized nature of this study. Ten studies were therefore included in analysis (907 analyzed patients). Characteristics of included studies are in the Appendix, available online at <http://links.lww.com/AOG/A649>.

All included trials were published between 1987 and 2015 in peer-reviewed journals; six studies on breast carcinomas,^{22,24–26,28,32} three studies on lymphomas,^{23,30,31} and one trial on conservatively treated primary ovarian carcinoma.²⁹ A wide variety of chemotherapeutic regimens was included in the review's articles, and three trials^{24,25,28} studied addition of anti-estrogen tamoxifen as well. Six trials^{22,23,25,26,28,32} were multicenter and five^{22,23,25,26,32} were funded through industry and governmental grants.



Sample size of included studies ranged from 18 to 281 participants with a median of 72 and interquartile range of 34–117. The mean age of study participants ranged from 23 to 44 years (median 35, interquartile range 27–39). The follow-up period ranged from 6 to 60 months with a median of 24 months and interquartile range of 14–29 months.

All included studies were classified as “probable risk of bias” as a result of absence of blinding.

At the longest follow-up, women receiving GnRH analog cotreatment did not achieve a significant increase in resumption of ovarian function (320/468 [68.4%] in GnRH analog arm and 263/439 [59.9%] in chemotherapy alone arm; RR 1.12, 95% CI 0.99–1.27; $P=.07$) with a significant heterogeneity across the included studies ($P=63\%$, $P=.004$). Four studies^{25,29,30,32} showed a significant benefit of using GnRH analog, whereas the other six did not show any significant benefit (Fig. 2).

In breast cancer,^{22,24–26,28,32} resumed ovarian function was reported in a total of 251 of 386 (65%) in the GnRH analog arm compared with 207 of 360 (57.5%) in the chemotherapy alone arm with no significant difference ($P=.25$). In lymphoma,^{23,30,31} RR for preserved ovarian function also showed no significant difference (54/67 [80.6%] and 46/64 [71.9%], respectively, $P=.51$). Gilani²⁹ was the only study on conservatively treated ovarian cancer and showed a significant benefit of using GnRH analogs. The subgroups were not significantly different ($P=.31$) (Table 1).

Four trials included patients 40 years of age or younger^{22,24,29,30} and one study²⁴ performed a subgroup analysis on patients 40 years of age or older. In women 40 years of age or younger, GnRH analog cotreatment showed no significant benefit in resuming ovarian function (87/98 [88.8%] in GnRH analog arm

and 71/95 [74.7%] in chemotherapy alone arm). No significant benefit was also detected in women 40 years of age or older.²⁴ No significant difference was found across the subgroups ($P=.14$) despite moderate heterogeneity as shown in Table 1 ($P=54\%$).

Elgindy²² was the only trial that used an antagonist and agonist combination; all other studies used an agonist only. The analog did not protect the gonads, irrespective of the type used ($P=.44$).

Sensitivity analysis showed marginal, nonsignificant fluctuations when one study was excluded at a time, except on removing Gerber et al²⁶ (Table 2). P value, however, was 49%.

Furthermore, we assessed probability of publication bias first by observing evident overlap of CIs of the included trials, visual inspection of spread of studies in a funnel plot (Fig. 3), and finally using Begg’s rank correlation tau ($\tau=0.087$, $P=.77$) and Egger’s regression (intercept 0.397, 95% CI -0.930 to 1.706 ; $P=.50$) tests. No significant publication bias was detected.

Postchemotherapy FSH level was reported in three studies^{22,23,30} with a mean difference of -2.63 milliinternational units per milliliter that was nonsignificant (Table 3).

Posttreatment antimüllerian hormone was also reported in three studies^{22,23,30} with a mean difference of 0.31 ng/mL and a statistically nonsignificant P value (Table 3).

Only two studies,^{22,30} compared antral follicle count between the treatment groups with a reported mean difference of 1.66 , which was statistically nonsignificant as in Table 3.

Pregnancy was reported in eight studies.^{22–26,30–32} Thirty of 427 got pregnant in the GnRH analog arm compared with 20 of 412 in the chemotherapy alone

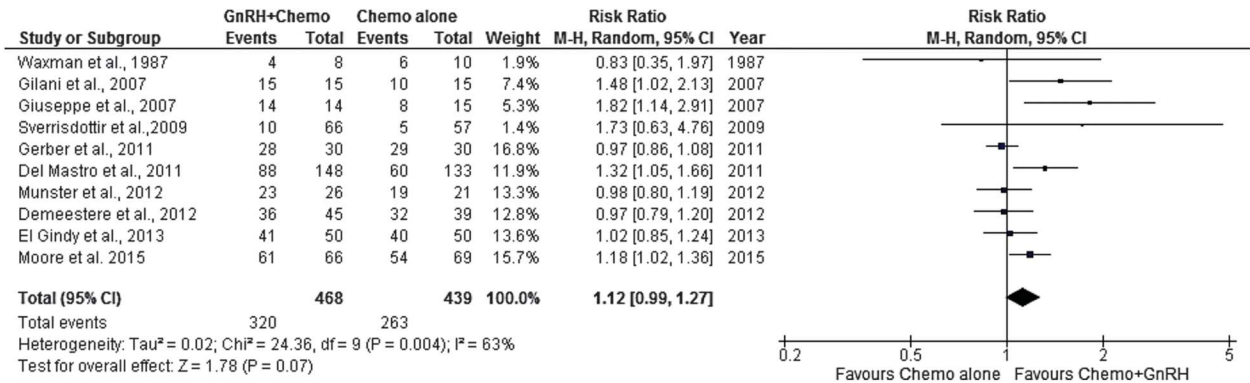


Fig. 2. Overall resumption of ovarian function at longest follow-up. GnRH, gonadotropin-releasing hormone; M-H, Mantel-Haenszel test; CI, confidence interval.

Elgindy. GnRH Analog Coadministration During Chemotherapy. *Obstet Gynecol* 2015.

Table 1. Subgroup Analyses for Resumption of Ovarian Function

Subgroup	Studies	No. of Participants	GnRH + Chemotherapy	Chemotherapy Alone	RR (95% CI)	I ² (%)	P
Type of malignancy							
Breast cancer	6	746	386	360	1.09 (0.94–1.25)	68	.25
Lymphoma	3	131	67	64	1.17 (0.73–1.87)	67	.51
Primary ovarian cancer	1	30	15	15	1.48 (1.02–2.13)	NE	.04
Women's age (y)							
40 or younger	4	193	98	95	1.22 (0.96–1.55)	62	.11
40 or older	1	15	8	7	0.89 (0.63–1.25)	NE	.50
GnRH analog type							
GnRH agonist only	10	857	443	414	1.13 (0.99–1.29)	64	.07
GnRH antagonist and agonist	1	50	25	25	1.00 (0.76–1.32)	NE	1.00

GnRH, gonadotropin-releasing hormone; RR, risk ratio; CI, confidence interval; NE, not estimable.

arm with no significant difference (RR 1.63, 95% CI 0.94–2.82) (Table 3).

DISCUSSION

Our meta-analysis showed that GnRH analogs during chemotherapy do not significantly increase resumption of ovarian function after the end of chemotherapy (RR 1.12, 95% CI 0.99–1.27). There is also no convincing evidence that the analog offers protection of ovarian reserve.

Significant heterogeneity existed across included studies; therefore, multiple subgroup analyses were done to explore possible causes. Noneffectiveness of analog coadministration persisted irrespective of age, type of malignancy, or type of analogs. Rates of resumed ovarian function were quite variable among included trials. Even in breast cancer, variations ranged from 8% up to 97%.^{26,28} However, rates were between

78% and 97% in studies not using tamoxifen,^{22,24,26,32} which signifies its effect on reported variations.

Evaluating ovarian reserve is important in determining gonadal dysfunction extent.³³ Ovarian reserve is commonly evaluated quantitatively using early follicular FSH, antral follicle count, and antimüllerian hormone^{34–36} and qualitatively by occurrence of pregnancy.^{34–36} All studied parameters were comparable and an analog cotreatment did not protect ovarian reserve. However, different antimüllerian hormone assays were used in included studies,^{22,23,30} making interpretation of combined results difficult. Antral follicle count was measured in the early follicular phase^{22,30}; however, only one of the two studies specified exact criteria for its determination.

Definition of resumed ovarian function and period of follow-up have been variable. In the current

Table 2. Sequential Sensitivity Analyses for Resumption of Ovarian Function

Excluded Studies	GnRH+Chemotherapy		Chemotherapy Alone		RR (95% CI)	P	I ² (%)
	Resumed Ovarian Function	Total	Resumed Ovarian Function	Total			
Waxman et al, 1987 ³¹	255	394	203	360	1.13 (0.99–1.29)	.07	67
Gilani et al, 2007 ²⁹	244	387	199	355	1.1 (0.97–1.24)	.16	62
Giuseppe et al, 2007 ³⁰	245	388	201	355	1.09 (0.97–1.22)	.15	56
Sverrisdottir et al, 2009 ²⁸	249	336	204	313	1.11 (0.98–1.26)	.09	64
Del Mastro et al, 2011 ²⁵	171	254	149	237	1.09 (0.97–1.23)	.17	55
Gerber et al, 2011 ²⁶	231	372	180	340	1.15 (1.01–1.31)	.03*	49
Demeestere et al, 2012 ²³	223	357	177	331	1.15 (1.00–1.33)	.06	67
Munster et al, 2012 ²⁴	236	376	190	349	1.15 (1.00–1.32)	.05	65
Elgindy et al, 2013 ²²	218	352	169	320	1.15 (0.99–1.33)	.14	68
Moore et al, 2015 ³²	259	402	209	370	1.12 (0.96–1.30)	.14	66

GnRH, gonadotropin-releasing hormone; RR, risk ratio; CI, confidence interval.

* Statistically significant.



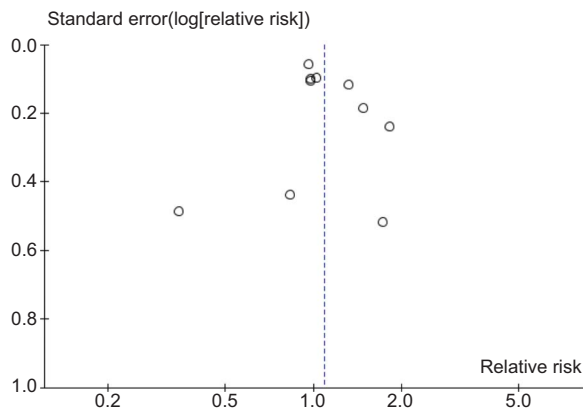


Fig. 3. Publication bias of the resumption of ovarian function at the longest follow-up.

Elgindy. GnRH Analog Coadministration During Chemotherapy. *Obstet Gynecol* 2015.

meta-analysis, five trials considered resumption of cycle as an indicator of resumed ovarian function,^{22,24,28,30,31} whereas one study²⁶ counted on the presence of two consecutive menstrual periods within 21–35 days. Three studies counted on resumed cycles in addition to absent postmenopausal levels of FSH.^{25,29,32} Demeestere et al²³ only counted on absent postmenopausal levels of FSH. Follow-up periods ranged between 6 months up to 5 years. The World Health Organization defines menopause as no menstruation for at least 12 months. There are 12-month or greater follow-up in all included trials, except one study in which women were followed for 6 months.²⁹ Sensitivity analysis, however, did not reveal significant fluctuations on excluding this study.

There is no consensus on the rationale behind using an analog for gonadal protection. Earlier studies suggested preserved ovarian function on prepubertal chemotherapy.^{7,8} A series of studies emerging from the U.S. Childhood Cancer Survivor Study reported contradictory results.^{37–39} In a study of 5,149 participants, there was emphasis on declining fertility of young survivors.³⁹

Furthermore, human gonads contain GnRH receptors. One study reported decreased apoptosis on agonist exposure,⁴⁰ whereas other studies reported contradictory results.^{41,42} Similarly, debate exists whether antagonists protect or suppress the ovaries.^{43,44} In the current meta-analysis, one study used an antagonist in addition to an agonist with no significant effect.²²

Indeed, the value of an analog for gonadal protection is quite controversial. Both randomized^{22–32} and nonrandomized^{45–52} studies failed to report consistent results. One RCT planned to enroll 124 patients was stopped for futility after enrolling 49 participants only.²⁴ Interim analysis showed comparable cycle resumption between analog and control groups.

Even for published meta-analyses, there are major inconsistencies and limitations that contradict extraction of reliable evidence. Three meta-analyses, including nonrandomized and randomized trials, reported a beneficial effect for analog addition.^{6,53,54} In two of these meta-analyses, separate analysis of randomized studies failed to prove protective effects of an analog.^{6,53}

Bedaiwy et al⁵ reported a potential benefit of agonist cotreatment but with major limitations for this met-analysis. First, it included 6 months follow-up of the ZOladox Rescue of Ovarian function (ZORO) trial.²⁶ Currently, inclusion of follow-up data at 24 months in the ZORO trial is available with no difference in cycle resumption between agonist and control. Second, one of the largest included studies²⁷ had significant methodologic flaws, such as:

1. Inconsistencies in hormonal levels existed before and after the end of chemotherapy. Oktay and Sönmezer, in a letter to the editor (Oktay K, Sonmezer M. Questioning GnRH analogs for gonadal protection in cancer patients [letter]. *Fertil Steril* 2009;92:e32), emphasize the presence of elevated basal E₂ and progesterone levels, which suggest that all patients were in the luteal phase.

Table 3. Comparison Between Gonadotropin-Releasing Hormone Plus Chemotherapy Compared With Chemotherapy Alone Regarding Secondary Outcomes

Outcome	Effect Measure (95% CI)	P	I ² [% (95% CI)]
Serum FSH	−2.63 (−7.33 to 2.07)*	.27	0.0 (0–28)
Serum antimüllerian hormone	0.31 (−0.41 to 1.03)*	.40	96
Antral follicle count	1.66 (−0.69 to 4.01)*	.17	79
Spontaneous pregnancy	1.63 (0.94–2.82) [†]	.08	0.0 (0–33)

CI, confidence interval; FSH, follicle-stimulating hormone.

* Mean difference.

[†] Risk ratio.



This is not probable if patients were properly randomly selected (Oktay et al. *Fertil Steril*).

2. The study²⁷ did not mention using tamoxifen for estrogen receptor–positive tumors in study arms.
3. The longest follow-up period was 8 months.
4. Although this study included young women younger than 40 years, there was markedly low resumption of menstruation in control (33.3%) compared with agonist users (89.6%). This is mostly attributed to previously stated methodological flaws.

Balkenende et al⁵⁵ performed a new meta-analysis, which included studies in Bedaiwy's meta-analysis excluding the controversial study²⁷ and including the completed ZORO trial results.²⁶ There was no benefit of agonist cotreatment.⁵⁵ In our meta-analysis, we excluded this controversial study in addition to including the completed ZORO trial as well as including a number of recently completed RCTs^{22–25,32} so as to reach reliable evidence. According to our results, a RCT including at least 819 participants in each arm is needed to proof a beneficial effect of GnRH analogs in preventing ovarian toxicity.

Limitations also exist in other meta-analyses. Wang et al⁵⁶ included two Chinese-language studies in their meta-analysis without clear explanation how they got an accurate English translation to critically appraise the studies. A recent meta-analysis reported a beneficial effect of analog coadministration.⁵⁷ The aforementioned controversial study was included²⁷ and investigators reported doing sensitivity analysis with satisfactory stability. However, there was significant heterogeneity (P 55.8%; $P=.01$) and excluding this study made a marked decrease in heterogeneity extent (P 25.7%; $P=.2$). Excluding any of remaining studies did not change heterogeneity significantly ($P>50\%$, $P<.05$). This underscores the bias of including this study and enforces our rationale in its exclusion. Preliminary data of 87 women younger than 40 years in the Ovarian Protection Trial In Oestrogen Negative trial were presented at the 46th annual meeting of the American Society of Clinical Oncology.⁵⁸ Amenorrhea was comparable between agonist (34.7%) and control (15.7) arms. There is rising evidence against the protective effect of analog cotreatment.

The American Society of Clinical Oncology does not recommend analog coadministration as a standard method for fertility preservation; still its use causes menstrual suppression and protection from thrombocytopenia. Therefore, it can be beneficial, but not for fertility-sparing. Depending on this approach for fertility preservation raises ethical issues.

Although our review included only the highest quality RCTs, variation in defining gonadal toxicity and nonuniform follow-up periods are obvious limitations.

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics, 2010. *CA Cancer J Clin* 2010;60:277–300.
2. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol* 1999;17:2365–70.
3. Oktem O, Oktay K. A novel ovarian xenografting model to characterize the impact of chemotherapy agents on human primordial follicle reserve. *Cancer Res* 2007;67:10159–62.
4. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006;24:2917–31.
5. Bedaiwy MA, Abou-Setta AM, Desai N, Hurd W, Starks D, El-Nashar SA, et al. Gonadotropin-releasing hormone analog co-treatment for preservation of ovarian function during gonadotoxic chemotherapy: a systematic review and meta-analysis. *Fertil Steril* 2011;95:906–14.e1–4.
6. SS Kim, Lee JR, Jee BC, Suh CS, Kim SH, Ting A, et al. Use of hormonal protection for chemotherapy-induced gonadotoxicity. *Clin Obstet Gynecol* 2010;53:740–52.
7. Wallace WH, Shalet SM, Tetlow LJ, Morris-Jones PH. Ovarian function following the treatment of childhood acute lymphoblastic leukemia. *Med Pediatr Oncol* 1993;21:333–9.
8. Sutcliffe SB. Cytotoxic chemotherapy and gonadal function in patients with Hodgkin's disease. Facts and thoughts. *JAMA* 1979;242:1898–9.
9. Blumenfeld Z. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist co-treatment in addition to cryopreservation of embryo, oocytes, or ovaries. *Oncologist* 2007;12:1044–54.
10. Lobo RA. Potential options for preservation of fertility in women. *N Engl J Med* 2005;353:64–73.
11. Oktay K, Briggs D, Gosden RG. Ontogeny of follicle-stimulating hormone receptor gene expression in isolated human ovarian follicles. *J Clin Endocrinol Metab* 1997;82:3748–51.
12. Chen H, Li J, Cui T, Hu L. Adjuvant gonadotropin-releasing hormone analogues for the prevention of chemotherapy induced premature ovarian failure in premenopausal women. *The Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No.: CD008018. DOI: 10.1002/14651858.CD008018.pub2.
13. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions*. Version 5.0.1. London (UK): The Cochrane Collaboration; 2008.
14. Churchill R, Higgins J, Chandler J, Tovey D, Lasserson T. *Methodological Expectations of Cochrane Intervention Reviews (ME-CIR)*. London (UK): The Cochrane Collaboration; 2012.
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9, W64.
16. Higgins JP, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;18:343; d5928.



17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
20. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
22. Elgindy EA, El-Haieg DO, Khorshid OM, Ismail EI, Abdelgawad M, Sallam HN, et al. Gonadotrophin suppression to prevent chemotherapy-induced ovarian damage: a randomized controlled trial. *Obstet Gynecol* 2013;121:78–86.
23. Demeestere I, Brice P, Peccatori FA, Kentos A, Gaillard I, Zachee P, et al. Gonadotropin-releasing hormone agonist for the prevention of chemotherapy-induced ovarian failure in patients with lymphoma: 1-year follow-up of a prospective randomized trial. *J Clin Oncol* 2013;31:903–9.
24. Munster PN, Moore AP, Ismail-Khan R, Cox CE, Lacey M, Gross-King M, et al. Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2012;30:533–8.
25. Del Mastro L, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. *JAMA* 2011;306:269–76.
26. Gerber B, von Minckwitz G, Stehle H, Reimer T, Felberbaum R, Maass N, et al. Effect of luteinizing hormone releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. *J Clin Oncol* 2011;29:2334–41.
27. Badawy A, Elnashar A, El-Ashry M, Shahat M. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage; prospective randomized study. *Fertil Steril* 2009;91:694–7.
28. Sverrisdottir A, Nystedt M, Johansson H, Fornander T. Adjuvant goserelin and ovarian preservation in chemotherapy treated patients with early breast cancer results from a randomized trial. *Breast Cancer Res Treat* 2009;117:561–7.
29. Gilani MM, Hasanzadeh M, Ghaemmaghami F, Ramazanzadeh F. Ovarian preservation with gonadotropin-releasing hormone analog during chemotherapy. *Asia Pac J Clin Oncol* 2007;3:79–83.
30. Giuseppe L, Attilio G, Edoardo DN, Loredana G, Cristina L, Vincenzo L. Ovarian function after cancer treatment in young women affected by Hodgkin disease (HD). *Hematology* 2007;12:141–7.
31. Waxman JH, Ahmed R, Smith D, Wrigley PFM, Gregory W, Shalet S, et al. Failure to preserve fertility in patients with Hodgkin's disease. *Cancer Chemother Pharmacol* 1987;19:159–62.
32. Moore HC, Unger JM, Phillips KA, Boyle F, Hitre E, Porter D, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med* 2015;372:923–32.
33. Gracia CR, Sammel MD, Freeman E, Prewitt M, Carlson C, Ray A, et al. Impact of cancer therapies on ovarian reserve. *Fertil Steril* 2012;97:134–40.e1.
34. Broer SL, Mol BW, Hendriks D, Broekmans FJ. The role of antimüllerian hormone in prediction of outcome after IVF: comparison with the antral follicle count. *Fertil Steril* 2009;91:705–14.
35. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. *Hum Reprod Update* 2006;12:685–718.
36. Broer SL, van Disseldorp J, Broeze KA, Dolleman M, Opmeer BC, Bossuyt P, et al. Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: an individual patient data approach. *Hum Reprod Update* 2013;19:26–36.
37. Chemaitilly W, Mertens AC, Mitby P, Whitton J, Stovall M, Yasui Y, et al. Acute ovarian failure in the childhood cancer survivor study. *J Clin Endocrinol Metab* 2006;91:1723–8.
38. Sklar CA, Mertens AC, Mitby P, Whitton J, Stovall M, Kasper C, et al. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. *J Natl Cancer Inst* 2006;98:890–6.
39. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, et al. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2009;27:2677–85.
40. Gründker C, Emons G. Role of gonadotropin-releasing hormone (GnRH) in ovarian cancer. *Reprod Biol Endocrinol* 2003;1:65.
41. Park EJ, Shin JW, Seo YS, Kim DW, Hong SY, Park WI, et al. Gonadotropin-releasing hormone agonist induces apoptosis of human granulosa-luteal cells via caspase-8, -9 and -3, and poly-(ADP-ribose)-polymerase cleavage. *Biosci Trends* 2011;5:120–8.
42. S Zhao, Saito H, Wang X, Saito T, Kaneko T, Hiroi M. Effects of gonadotropin-releasing hormone agonist on the incidence of apoptosis in porcine and human granulosa cells. *Gynecol Obstet Invest* 2000;49:52–6.
43. Meior D, Assad G, Dor J, Rabinovici J. The GnRH antagonist cetrorelix reduces cyclophosphamide-induced ovarian follicular destruction in mice. *Hum Reprod* 2004;19:1294–9.
44. Danforth DR, Arbogast LK, Friedman CI. Acute depletion of murine primordial follicle reserve by gonadotropin-releasing hormone antagonists. *Fertil Steril* 2005;83:1333–8.
45. Azem F, Samara N, Cohen T, Ben-Yosef D, Almog B, Lessing JB, et al. Assessment of ovarian reserve following ovarian tissue banking and/or GnRH—a co-treatment prior to chemotherapy in patients with Hodgkin's disease. *J Assist Reprod Genet* 2008;25:535–8.
46. Blumenfeld Z, Avivi I, Eckman A, Epelbaum R, Rowe JM, Dann EJ. Gonadotropin-releasing hormone agonist decreases chemotherapy-induced gonadotoxicity and premature ovarian failure in young female patients with Hodgkin lymphoma. *Fertil Steril* 2008;89:166–73.
47. Huser M, Crha I, Ventruba P, Hudecek R, Zakova J, Smardova L, et al. Prevention of ovarian function damage by a GnRH analogue during chemotherapy in Hodgkin lymphoma patients. *Hum Reprod* 2008;23:863–8.
48. Castelo-Branco C, Nomdedeu B, Camus A, Mercadal S, Martínez de Osaba MJ, Balasch J. Use of gonadotropin releasing hormone agonists in patients with Hodgkin's disease for preservation of ovarian function and reduction of gonadotoxicity related to chemotherapy. *Fertil Steril* 2007;87:702–5.
49. Elis A, Tevet A, Yerushalmi R, Blickstein D, Bairy O, Dann EJ, et al. Fertility status among women treated for aggressive non-Hodgkin's lymphoma. *Leuk Lymphoma* 2006;47:623–7.
50. Dann EJ, Epelbaum R, Avivi I, Ben Shahr M, Haim N, Rowe JM, et al. Fertility and ovarian function are preserved



- in women treated with an intensified regimen of cyclophosphamide, adriamycin, vincristine and prednisone (Mega-CHOP) for non-Hodgkin lymphoma. *Hum Reprod* 2005;20:2247–9.
51. Somers EC, Marder W, Christman GM, Ognenovski V, McCune WJ. Use of a gonadotropin releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. *Arthritis Rheum* 2005;52:2761–7.
 52. Pereyra Pacheco B, Méndez Ribas JM, Milone G, Fernández I, Kvala R, Mila T, et al. Use of GnRH analogs for functional protection of the ovary and preservation of fertility during cancer treatment in adolescents: a preliminary report. *Gynecol Oncol* 2001;81:391–7.
 53. Ben-Aharon I, Gafer-Gvili A, Leibovici L, Stemmers SM. Pharmacological interventions for fertility preservation during chemotherapy: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2010;122:803–11.
 54. Clowse ME, Behera MA, Anders CK, Copland S, Coffman CJ, Leppert PC, et al. Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis. *J Womens Health (Larchmt)* 2009;18:311–9.
 55. Balkenende E, Dahhan T, van der Veen F, Goddijn M. Comment on GnRH analogue co-treatment with chemotherapy for preservation of ovarian function. *Fertil Steril* 2011;96:e155–6.
 56. Wang C, Chen M, Fu F, Huang M. Gonadotropin-Releasing Hormone Analog Cotreatment for the Preservation of Ovarian Function during Gonadotoxic Chemotherapy for Breast Cancer: A Meta-Analysis. *PLoS One* 2013;8:e66360.
 57. Del Mastro L, Ceppi M, Poggio F, Bighin C, Peccatori F, Demeestere I, et al. Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: systematic review and meta-analysis of randomized trials. *Cancer Treat Rev* 2014;40:675–83.
 58. Leonard RC, Adamson D, Anderson R, Ballinger R, Bertelli G, Coleman RE, et al. The OPTION trial of adjuvant ovarian protection by goserelin in adjuvant chemotherapy for early breast cancer. *J Clin Oncol* 2010;28:590.

Continuing Medical Education Credits Available for the Clinical Expert Series

Continuing medical education (CME) credits for reading the Clinical Expert Series are available through joint sponsorship with The American College of Obstetricians and Gynecologists. Visit <http://www.greenjournal.org> and click on the “CME” tab to get started.

ACCME Accreditation

The American College of Obstetricians and Gynecologists is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

AMA PRA Category 1 Credit(s)TM

The American College of Obstetricians and Gynecologists designates this enduring material for a maximum of **2 AMA PRA Category 1 CreditsTM**. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

College Cognate Credit(s)

The American College of Obstetricians and Gynecologists designates this enduring material for a maximum of 2 Category 1 College Cognate Credits. The College has a reciprocity agreement with the AMA that allows **AMA PRA Category 1 CreditsTM** to be equivalent to College Cognate Credits.

rev 2/2015

