Gonadotropin-Releasing Hormone Agonists for Ovarian Function Preservation in Premenopausal Women Undergoing Chemotherapy for Early-Stage Breast Cancer: A Systematic Review and Meta-analysis

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**IMPORTANCE** Chemotherapy may result in a detrimental effect on ovarian function and fertility in premenopausal women undergoing treatment for early-stage breast cancer (EBC). To minimize risk of harm to ovarian function and fertility for patients in this setting, careful considerations should be made. Gonadotropin-releasing hormone agonists (GnRHa) have been suggested as an alternative to prevent the loss of ovarian function due to exposure to cytotoxic agents, but GnRHa use for ovarian protection in EBC patients is not fully resolved.

**OBJECTIVE** To determine the effectiveness of GnRHa administered concurrently with chemotherapy for ovarian function preservation.

**DATA SOURCES** PubMed, SCOPUS, and Cochrane databases were searched for studies published between January 1975 and March 2015. The abstracts of the American Society of Clinical Oncology Annual Meeting between 1995 and 2014 and the San Antonio Breast Cancer Symposium between 2009 and 2014 were searched as well.

**STUDY SELECTION** Prospective, randomized, clinical trials addressing the role of ovarian suppression with GnRHa in preventing early ovarian dysfunction in premenopausal women undergoing treatment for EBC were selected.

**DATA EXTRACTION AND SYNTHESIS** Data extraction was performed independently by 2 authors. The methodology and the risk of bias were assessment based on the description of randomization method, withdrawals, and blinding process.

**MAIN OUTCOMES AND MEASURES** Rate of resumption of regular menses after a minimal follow-up period of 6 months following chemotherapy was used as a surrogate to assess the incidence of ovarian dysfunction. Additional secondary outcomes included hormone levels and number of pregnancies. Risk ratio estimates were calculated based on the number of evaluable patients. Analyses were conducted using a random effect model.

**RESULTS** Seven studies were included in this analysis, totaling 1047 randomized patients and 856 evaluable patients. The use of GnRHa was associated with a higher rate of recovery of regular menses after 6 months (odds ratio [OR], 2.41; 95% CI, 1.40-4.15; P = .002) and at least 12 months (OR, 1.85; 95% CI, 1.33-2.59; P < .001) following the last chemotherapy cycle. The use of GnRHa was also associated with a higher number of pregnancies (OR, 1.85; 95% CI, 1.02-3.36; P = .04), although this outcome was not uniformly reported and fertility or rate of pregnancy was not the primary outcome in any of the trials.

**CONCLUSIONS AND RELEVANCE** Gonadotropin-releasing hormone agonists given with chemotherapy was associated with increased rates of recovery of regular menses in this meta-analysis. Evidence was insufficient to assess outcomes related to GnRHa and ovarian function and fertility and needs further investigation.
Breast cancer is among the leading causes of cancer-related mortality and the most common cancer in women worldwide. Significant improvements in survival have been achieved with the widespread use of adjuvant therapies in early-stage breast cancer (EBC) (ie, breast cancer that has not spread beyond the breast or the axillary lymph nodes). However, approximately 25% of the cases occur in premenopausal women, including 12% in women between the ages of 20 and 44 years. For this subgroup of patients at reproductive age, the use of adjuvant chemotherapy with curative intent is associated with a risk of ovarian dysfunction, permanent or transient amenorrhea, infertility, and symptoms of menopause with a premature onset. In addition to complications that include osteoporosis, loss of libido, increased cardiovascular risk, and atrophic vaginitis, early ovarian dysfunction may adversely affect quality of life and result in a significant psychosocial burden.

Several series suggest that the incidence of ovarian dysfunction in women undergoing systemic treatment for EBC ranges from 4% to 90% and is influenced by chemotherapies used, duration of exposure, total doses, definitions applied, and patients’ age. Patients’ age represents the strongest predictor of ovarian dysfunction, with a significantly increased incidence after age 40 years. Rates of chemotherapy-related amenorrhea and ovarian dysfunction following treatment with cyclophosphamide, methotrexate, and fluorouracil were 76% to 100% in women 40 years and older in comparison to 21% to 70% in women younger than 40 years. Increased risk results from regimens containing high cumulative doses of alkylators and anthracyclines. In trials investigating combinations of fluorouracil, epirubicin, and cyclophosphamide, chemotherapy-induced menopause occurred in up to 60% of the patients, with similar incidences observed with taxane-containing regimens.

The mechanism involved in ovarian damage is unclear but may be linked to apoptotic oocyte death in primordial follicles entering the differentiation stage, which is particularly vulnerable to chemotherapy effects.

Preclinical studies suggested that hormonal suppression of the hypothalamic-pituitary-ovarian axis could minimize the effect of cytotoxic agents over ovarian function. Based on this concept, several uncontrolled trials have been conducted to evaluate the activity of luteinizing hormone-releasing hormone analogs and gonadotropin-releasing hormone agonists (GnRHa) in preventing the loss of ovarian function due to exposure to cytotoxic agents. In these studies, the proportion of patients who recovered ovarian function following concurrent ovarian suppression with GnRHa and adjuvant chemotherapy ranged from 72% to 96%. Nevertheless, final conclusions are confounded by heterogeneity of treatments used, outcomes assessed, and lack of control groups. A meta-analysis of 3 randomized and 8 nonrandomized prospective controlled studies, 10 of which involved patients with diseases other than EBC, showed that GnRHa administered during chemotherapy are associated with a greater likelihood of maintaining ovarian function after treatment (odds ratio [OR], 10.57; 95% CI, 5.22-21.39). Nonetheless, statistical significance was lost when only the randomized studies were considered (OR, 5.76; 95% CI, 0.47-71.03). These findings prompted the development of randomized clinical trials limited to an EBC population. The results, however, have been conflicting, and the role of GnRHa in the prevention of ovarian failure remains a question not fully resolved. Different meta-analyses suggest a benefit from ovarian suppression during chemotherapy in premenopausal women. However, these meta-analyses did not limit the population EBC patients or did not incorporate some of the largest studies in this setting, including the recently presented Prevention of Early Menopausal Study (POEMS) trial. Recently updated Guidelines from the American Society of Clinical Oncology (ASCO) recommend that patients with cancer who are at reproductive ages should be advised about the potential risks of fertility impairment, additional adverse effects of chemotherapy, and that preservation techniques should be considered. The guidelines also recommend preservation techniques should be considered. However, evidence regarding the effectiveness of ovarian suppression is still quoted as insufficient.

Currently, few women receiving adjuvant chemotherapy undergo active approaches to preserve fertility and ovarian function, and because standard strategies for fertility maintenance, such as embryo and oocyte preservation techniques, are associated with elevated costs, a potential risk of treatment delay and low success rates, the preservation of fertility and ovarian function is a topic of utmost importance. In this study, we aimed to conduct a meta-analysis to determine the role of ovarian suppression with GnRHa during chemotherapy in women undergoing treatment for EBC.

**Methods**

**Search and Selection Criteria**
A systematic review was performed for publications encompassing the following citation indexes: PubMed, SCOPUS, and Cochrane Central Register of Controlled Trials, between January 1975 and March 2015, as well as ASCO abstracts between 1995 and 2014 and the San Antonio Breast Cancer Symposium abstracts between 2009 and 2014. The following medi-
cral subject headings and/or specific terms were used: “breast neoplasms,” “menopause, premature,” “amenorrhea,” “gonadotropin-releasing hormone,” “goserelin,” “triptorelin,” “leuproside,” “fertility,” “fertility preservation,” “chemotherapy, adjuvant,” “antineoplastic agents,” “clinical trial, randomized.” Additional searches were performed using the key phrases “breast cancer AND ovarian dysfunction” or “chemotherapy induced amenorrhea.” The reference lists of all relevant articles were also reviewed.

Publications with the following criteria were selected: prospective, randomized, clinical trials addressing the role of ovarian suppression with GnRHa in preventing early ovarian dysfunction in premenopausal women undergoing curative chemotherapy for EBC. No restrictions concerning the definition or characterization of the primary endpoints were made for the study selection. Uncontrolled studies and those using strategies other than GnRHa for preventing early menopause were excluded, as were incomplete trials, as well as those with unclear definitions of ovarian dysfunction or follow-up inferior to 6 months.

Data Extraction
Two authors (R.R.M. and A.A.L.P.) selected the studies according to the previously described criteria and extracted all data independently. In cases of discrepancies during the selection process or data extraction, consensus was achieved following discussions. An identification number was provided to each of the selected trials, allowing for a blind review. Unpublished trials and those for which additional information was not provided were allowed if adequate data extraction was possible.

Eligible endpoints to address ovarian dysfunction, our main outcome, encompassed different definitions of regular menses used across studies and included resumption of regular menses after a minimum follow-up period of 6 months and after 12 to 24 months following chemotherapy. Follie-stimulating hormone (FSH) and estradiol (E2) concentrations were also investigated. Restoration of fertility, rates of pregnancy and/or successful delivery, and sonographic description of the ovaries were not considered valid endpoints for our main analyses due to the high probability of confounding factors, but exploratory analyses were performed if data were available.

Analysis and Synthesis
Methodology and the risk of bias were evaluated using the criteria suggested by Jadad et al.48 with assessment of the randomization method, withdrawals, and blinding process.

Risk ratio estimates were calculated for the dichotomous outcomes with a 95% confidence interval for the estimation of the effect of the administration of GnRHa given concurrently with chemotherapy vs no ovarian suppression. Outcome measures were estimated according to the number of evaluable treated patients and not the intention to treat population. Analyses were conducted using a random effect model. The heterogeneity between the risk ratios for the same outcome between different studies was assessed using the χ²-based statistic, with significance at a P value of less than .10 and expressed in I² index.

Statistical analyses were performed with RevMan5.1 software (Cochrane).

Results
Database searches returned 603 entries; 592 were excluded after initial review. Excluded publications included reviews, retrospective studies, letters, trials addressing the anticancer activity of GnRHa, duplicate results, and uncontrolled trials. Among the remaining 11 studies, reasons for exclusion are as follows. One trial31 corresponded to a preplanned subprotocol of a trial addressing the antitumoral effect of GnRHa. Goserelin was administered for 2 years, with or without tamoxifen, irrespective of the hormone receptor status. The prolonged duration of treatment with tamoxifen could, by itself, affect the assessment of amenorrhea at 6 months and 12 to 24 months. One trial49 that did not report the outcomes of interest and was also excluded (Figure 1). One randomized trial50 had inconsistencies in the study methods and reporting of results and was therefore excluded. Of the 8 potentially eligible studies, one34 was presented in abstract form only with insufficient data for the main analyses (Figure 1). The author was contacted, but no additional information was provided.

Seven trials28-30,32,35-37 published in full met the predefined criteria and were included in the analysis, totaling 1047 randomized patients and 856 evaluable patients between ages 18 to 49 years. Of note, long-term outcomes of the PROMISE-GIM6 study by Del Mastro et al51 were presented as an abstract only. Therefore, the original publication was selected for data extraction30 and for referencing in this article. The characteristics of the studies are summarized in Table 1 and Table 2.

Figure 1. Study Identification Process

<table>
<thead>
<tr>
<th>Records identified through database searching and other sources</th>
<th>603</th>
</tr>
</thead>
<tbody>
<tr>
<td>Records after duplicates removed</td>
<td>490</td>
</tr>
<tr>
<td>Records screened</td>
<td>490</td>
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<tr>
<td>Records excluded</td>
<td>479</td>
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<td>Studies excluded</td>
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<td>Invalid endpoints</td>
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<tr>
<td>Unsuitable trial design</td>
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</tr>
<tr>
<td>Inconsistencies in the study methods/results</td>
<td>1</td>
</tr>
<tr>
<td>Incomplete data for analysis</td>
<td>1</td>
</tr>
<tr>
<td>Studies included in qualitative synthesis</td>
<td>7</td>
</tr>
<tr>
<td>Studies included in quantitative synthesis (meta-analysis)</td>
<td>7</td>
</tr>
</tbody>
</table>
Table 1. Selected Trial Characteristics

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Randomized (Control/Intervention)</th>
<th>Evaluative Points (Control/Intervention)</th>
<th>Age, Mean (Range), y</th>
<th>HR Status (+/-)</th>
<th>Chemotherapy Regimen</th>
<th>No. of Patients</th>
<th>Anthracyclines (Control/Intervention)</th>
<th>Cyclophosphamide (Control/Intervention)</th>
<th>Taxanes (Control/Intervention)</th>
<th>Tamoxifen (Control/Intervention)</th>
<th>Use of Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore et al, 2015 (POEMS)</td>
<td>416</td>
<td>257 (131/126)</td>
<td>135 (69/66)</td>
<td>38 (25-49)</td>
<td>0/135</td>
<td>Cyclophosphamide-based</td>
<td>62/61</td>
<td>69/66</td>
<td>NI</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Song et al, 2013</td>
<td>62</td>
<td>220 (110/110)</td>
<td>183 (94/89)</td>
<td>41 (26-45)</td>
<td>150/33</td>
<td>AC +/- taxane</td>
<td>94/89</td>
<td>94/89</td>
<td>25/32</td>
<td>74/76</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Elgindy et al, 2013</td>
<td>50</td>
<td>100 (50/50)</td>
<td>93 (47/46)</td>
<td>33 (18-40)</td>
<td>0/93</td>
<td>FAC</td>
<td>47/46</td>
<td>47/46</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Munster et al, 2012</td>
<td>124</td>
<td>49 (22/27)</td>
<td>47 (21/26)</td>
<td>39 (21-44)</td>
<td>36/28</td>
<td>AC, AC-taxane, FAC/FEC</td>
<td>21/26</td>
<td>21/26</td>
<td>5/8</td>
<td>16/20</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Del Mastro et al, 2011 (PROMISE/GIM6)</td>
<td>280</td>
<td>281 (133/148)</td>
<td>260 (121/139)</td>
<td>39 (24-45)</td>
<td>226/51</td>
<td>CMF, anthracycline-based, with or without taxanes</td>
<td>119/142</td>
<td>119/135</td>
<td>62/86</td>
<td>96/100</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Gerber et al, 2011 (ZORO)</td>
<td>62</td>
<td>61 (31/30)</td>
<td>60 (30/30)</td>
<td>37 (26-47)</td>
<td>0/61</td>
<td>FEC-taxane, EC-taxane, FAC, FAC, TAC</td>
<td>30/30</td>
<td>30/30</td>
<td>16/15</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Badawy et al, 2009</td>
<td>48</td>
<td>80 (40/40)</td>
<td>78 (39/39)</td>
<td>30 (18-40)</td>
<td>NI</td>
<td>FAC</td>
<td>39/39</td>
<td>39/39</td>
<td>0</td>
<td>NI</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil; FAC, fluorouracil, doxorubicin, and cyclophosphamide; FEC, fluorouracil, epirubicin, and cyclophosphamide; GnRHa, gonadotropin-releasing hormone agonists; HR, hormone receptor; NA, not applicable; NI, not informed; TAC, docetaxel, doxorubicin, and cyclophosphamide. +, positive; −, negative.

a Among the 281 patients initially randomized and not limited to evaluable patients.
Although eligibility criteria varied, all studies required that patients be premenopausal at enrollment, defined as prior history of cyclic menstrual bleedings and/or regular menses, with or without premenopausal hormone levels at baseline. Ovarian suppression was induced with goserelin, triptorelin, or leuprolide, beginning at least 1 week before the first cycle of chemotherapy and maintained until the last cycle in 6-24 months of 7 trials. In the trial by Elgindy et al, simultaneous commencement of the GnRHa and chemotherapy was allowed, but patients received concurrent GnRH antagonist (cetrorelix acetate) until suppression of estradiol levels. Anthracycline- and cyclophosphamide-based regimens were administered to over 90% of the patients; a smaller proportion of patients also received taxanes.

GnRHa and Recovery of Menses
The administration of GnRHa (goserelin, triptorelin, or leuprolide) was associated with a higher rate of recovery of regular menstruations after a minimum of 6 months after the last cycle of chemotherapy in premenopausal women receiving treatment for EBC with 28,29,32,36,37 or without 30,35 premenopausal hormone levels at baseline. Ovarian suppression was induced with goserelin, triptorelin, or leuprolide, beginning at least 1 week before the first cycle of chemotherapy and maintained until the last cycle in 6-24 months of 7 trials. In the trial by Elgindy et al, simultaneous commencement of the GnRHa and chemotherapy was allowed, but patients received concurrent GnRH antagonist (cetrorelix acetate) until suppression of estradiol levels. Anthracycline- and cyclophosphamide-based regimens were administered to over 90% of the patients; a smaller proportion of patients also received taxanes.

The rate of recovery of regular menstruations in the control groups increased uniformly with time and this endpoint was reached after a median of 5 to 6.1 months in at least 2 of the included trials. 28,29 As a result, we hypothesized that measuring the outcomes at 6 months could be inadequate. Therefore, an additional analysis was performed, including only the rates of menstruation resumption after a minimum interval of 12 months since the last chemotherapy cycle. When the analysis was limited to trials with a minimum follow-up of 12 months, GnRHa resulted in a statistically significant improvement in the rate of menstruation resumption with no heterogeneity among trials (OR, 1.85; 95% CI, 1.33-2.59; P = .002; I² = 0%) (Figure 2B).

We also aimed to perform a time-to-event analysis comparing the mean time to recovery of menstruations in patients treated with GnRHa and controls. However, this comparison was hampered by incomplete data.

GnRHa and Hormone Levels
Complete data to evaluate the effect of GnRHa on hormone serum concentrations were not consistently described and, therefore, this analysis was not performed. In the trial by Badawi et al, 32 patients treated with GnRHa showed lower FSH (P < .009) and higher E2 (P = .001) levels compared to the control group.

Table 2. Outcomes, Interventions, and Risk of Bias

<table>
<thead>
<tr>
<th>Source</th>
<th>Outcome Primary</th>
<th>Secondary</th>
<th>Interval for Primary Outcome Measurement After Chemotherapy, mo</th>
<th>GnRHa</th>
<th>Dose (mg/dL) / Interval (d)</th>
<th>Start of Suppression</th>
<th>Randomization Process</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore et al, 2015 (POEMS)</td>
<td>Rate of ovarian failure (amenorrhea for 1 mo and postmenopausal FSH levels at 24 mo)</td>
<td>Amenorrhea and FSH/E2 levels, inhibin B levels at 12 and 24 mo, rate of pregnancy, survival</td>
<td>24</td>
<td>Goserelin</td>
<td>3.6/28</td>
<td>1 Week before chemotherapy</td>
<td>Adequate</td>
<td>Low</td>
</tr>
<tr>
<td>Song et al, 2013</td>
<td>Rate of early menopause (amenorrhea and postmenopausal hormone levels)</td>
<td>Amenorrhea, FSH or E2 levels</td>
<td>12</td>
<td>Leuprolide</td>
<td>3.75/28</td>
<td>Before chemotherapy</td>
<td>Not described</td>
<td>High</td>
</tr>
<tr>
<td>Elgindy et al, 2013</td>
<td>Rate of resumption of regular menses (3 consecutive menses within 21-35 d each)</td>
<td>Rate of resumption of regular menses after 12 mo</td>
<td>12</td>
<td>Triptorelin</td>
<td>3.75/28</td>
<td>10 Days to concurrently with chemotherapy</td>
<td>Adequate</td>
<td>Low</td>
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<tr>
<td>Munsteret al, 2012</td>
<td>Rate of resumption of regular menses (3 menses in a 6-mo interval)</td>
<td>FSH, Inhibin A or B levels</td>
<td>24</td>
<td>Triptorelin</td>
<td>3.75/28-30</td>
<td>1 to 4 Weeks before chemotherapy</td>
<td>Adequate</td>
<td>Low</td>
</tr>
<tr>
<td>Del Mastro et al, 2011 (PROMISE/GIM6)</td>
<td>Rate of menopause (amenorrhea + postmenopausal hormone levels for a 12-mo interval)</td>
<td>None</td>
<td>12</td>
<td>Triptorelin</td>
<td>3.75/28</td>
<td>&gt;1 Week before chemotherapy</td>
<td>Adequate</td>
<td>Low</td>
</tr>
<tr>
<td>Gerber et al, 2011 (ZORO)</td>
<td>Rate of resumption of regular menses (2 menstrual periods within 21-35 d in 5-8 mo)</td>
<td>Time to recovery of menses, hormone levels, ovarian reserve, follicle count, rate of pregnancy, toxicity, compliance</td>
<td>5-8</td>
<td>Goserelin</td>
<td>3.6/28</td>
<td>&gt;2 Weeks before chemotherapy</td>
<td>Not described</td>
<td>High</td>
</tr>
<tr>
<td>Badawy et al, 2009</td>
<td>Rate of resumption of regular menses and ovulation</td>
<td>Hormone levels</td>
<td>6-8</td>
<td>Goserelin</td>
<td>3.6/28</td>
<td>2 Weeks before chemotherapy</td>
<td>Adequate</td>
<td>Low</td>
</tr>
</tbody>
</table>

Abbreviations: E2, estradiol; FSH, follicle-stimulating hormone.
* Withdrawals are described for all sources, and none of the sources were double-blind.
† Adapted from Jadad et al. 48
control group. In the trial by Gerber et al,29 only 17 of 60 patients were accessible for hormone measurements. In the trial by Del Mastro et al,30 FSH and/or E2 measurements were not available for approximately 30% of the patients. In the trial by Song et al,37 although the mean values of E2 were similar between groups at 12 months after the end of chemotherapy, significantly higher values of FSH were reported in patients treated with chemotherapy only (P < .05). No statistically significant differences in FSH and additional hormone levels were identified in 2 additional studies.28,35

### GnRHa and Pregnancies

The use of GnRHa was also associated with a higher number of pregnancies (OR, 1.85; 95% CI, 1.02-3.36; P = .04). However, pregnancy outcomes and the total number of attempted pregnancies was not uniformly reported across trials, and fertility and/or rate of pregnancies were not the primary endpoint in any of the studies. In addition, in the trial by Moore et al,36 patients with incomplete data and not evaluable for the primary endpoint were still included in pregnancy outcomes (total evaluable patients for pregnancies in the control arm, 113; GnHRa arm, 105).

### Discussion

Chemotherapy-induced early menopause and its effect on quality of life is a pragmatic and clinically important topic that often arises during the treatment of EBC with curative intent in premenopausal patients. Our meta-analysis of randomized clinical trials showed that the addition of a GnRHa during chemotherapy, given in the neoadjuvant or adjuvant setting, was associated with ovarian function preservation as assessed by the rate of recovery of regular menses in premenopausal women with EBC.

Alternative methods for preserving fertility, including embryo and/oocyte cryopreservation, ovarian transposition, and ovarian tissue transplantation can be time consuming and costly. Moreover, some of these techniques are unable to prevent negative effects of early menopause, including loss of bone density, increased cardiovascular risk, and vasomotor symptoms. In our study, the main outcome used as a surrogate for ovarian function was resumption of regular menses. Based on the current World Health Organization definition, which defines menopause as the absence of menstrual periods for 12 months, the GnRHa group had a significantly higher rate of recovery of regular menses compared with the control group (OR, 2.41; 95% CI, 1.40-4.15; P = .002).
months, our findings suggest that goserelin, triptorelin, or leuprorelin are effective in preventing chemotherapy-induced premature menopause in premenopausal women with EBC (OR, 1.85; P < .001).

There are discrepant definitions of ovarian dysfunction due to a heterogeneous characterization of outcomes, which are, in turn, responsible for the wide variability in the incidence of ovarian dysfunction and cause concern when evaluating effects of chemotherapy on fertility and menopause.\textsuperscript{8,16,52-54} Resolution of regular menses, however, is a clinically relevant and reproducible outcome. It should be noted, nevertheless, that recovery of menses does not necessarily translate into subsequent fertility restoration and that better biomarkers of ovarian function, including the Inhibin and anti-Müllerian hormone, are of clinical interest.

In our meta-analysis, high heterogeneity among trials ($I^2 = 65\%)$ was observed after the first effectiveness analysis after a minimal follow-up of 6 months, which could be attributable to 2 determinant aspects: age of the patients and time to outcome measurement. Age independently has an effect on the risk of permanent menopause and could be associated with the effectiveness of GnRH\textsubscript{a}.\textsuperscript{16,54} The trial by Badawy et al\textsuperscript{13} included patients aged 40 years or younger (median age, 30 years) vs patients 37 to 39 years of age in most of the remaining trials. This younger patient population could account for a higher likelihood of recovery of ovarian function. The fears of a negative effect over the childbearing potential is increased at younger ages, and even younger women who restore their menses will still experience premature menopause as a delayed effect. This could represent a subgroup of patients of greater interest and for whom a positive effective on ovarian protection could be associated with meaningful improvements. None of the trials evaluated the long-term ovarian reserve and the onset of premature menopause after temporary amenorrhea, and longer follow-up is necessary to address this issue. Moreover, the likelihood of resuming ovarian function decreases as a woman approaches the mean age of natural menopause, and GnRH\textsubscript{a} could have only a marginal effect in older patients. However, the cutoff to select patients for whom ovarian suppression is of clinical relevance is still unknown.

Gonadotropin-releasing hormone agonists were given concurrently with the standard regimens recommended for the neoadjuvant and adjuvant treatment of EBC. It is noteworthy that more than 90% of the included patients received anthracycline-based combinations, and a significant proportion received taxanes. Therefore, it is unlikely that the conflicting effectiveness results could be attributable to different drug combinations with distinct potential for ovarian damage.

There has been concern that the restoration of ovarian function could negatively affect long-term outcomes of patients with EBC due to a possible stimulating effect on quiescent hormone-sensitive tumor cells. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-30 trial, women with prolonged amenorrhea showed improved disease-free survival and overall survival after adjustment for both tumor- and treatment-related variables,\textsuperscript{55} which was also suggested by other authors.\textsuperscript{56,57} In fact, some of the trials included in this meta-analysis excluded patients with positive expression of estrogen receptors and progesterone receptors.\textsuperscript{29,35,36} However, the true effect of amenorrhea as an independent prognostic factor and the benefits of reintroducing GnRH\textsubscript{a} in this subgroup of patients is still under investigation. Moreover, EBC in premenopausal patients has different clinicopathological characteristics, with a high incidence of hormone receptor-negative tumors,\textsuperscript{58} for whom the restoration of ovarian function could have little, if any, effect on survival. In fact, concurrent administration of GnRH\textsubscript{a} resulted in longer disease-free survival and overall survival in the POEMS trial restricted to patients with estrogen receptor- and/or progesterone receptor-negative tumors (hazard ratio [HR], 0.49; $P = .04$ vs HR,0.43; $P = .05$, respectively).\textsuperscript{36} Furthermore, long-term results of the PROMISE-GIM6 trial support the safety of GnRH\textsubscript{a} even in hormone-sensitive patients, in which 81% of the patients had estrogen receptor- and/or progesterone receptor-positive tumors. After a median follow-up of 7.3 years, no differences in the 5-year disease-free survival were observed (83.7% in chemotherapy alone arm vs 80.5% in chemotherapy plus GnRH\textsubscript{a}; $P = .52$).\textsuperscript{51}

Several limitations should be highlighted. Despite the extensive search, only 7 studies met the predefined criteria, leading to a limited number of patients, 44% of which were derived from 2 studies.\textsuperscript{30,37} The data extracted for the analysis were retrieved from published articles and abstracts, and we did not have access to individual patient data. Hence, the characterization of regular menses was not uniform, and the numbers used for these analyses reflect the outcomes as assessed by each investigator as detailed in Table 2. Furthermore, the effect of additional confounding factors affecting the ovarian function and the effectiveness of GnRH\textsubscript{a} (eg, body mass index, concurrent endocrine and/or autoimmune diseases, specific age groups) could not be assessed. Some of the included trials were discontinued prematurely and had incomplete analyses of outcomes (eg, hormone levels, restoration of ovulation, rates of pregnancies) relevant for a thorough assessment of ovarian function. Another limitation was the lack of detailed survival outcomes, which kept this meta-analysis from addressing a possible interaction between GnRH\textsubscript{a} and long-term results. In addition, although a higher number of pregnancies was also observed in the intervention arm, this was not statistically significant. It is important to highlight that most of the trials did not report the total number of attempted pregnancies and were not formally designed to address fertility outcomes, which could lead to significant bias associated with imbalance between treatment groups. Therefore, the true effect of GnRH\textsubscript{a} in fertility remains unclear. Although similar meta-analyses have been published,\textsuperscript{38-44} this is the first study to our knowledge to encompass the largest and most recent trials reported to date, including a larger number of individuals, and provides more robust estimates of the benefit of GnRH\textsubscript{a}, specifically for patients undergoing treatment for EBC.

Even though we did not include adverse effects in the scope of our study, they include hot flashes, vaginal dryness, headache, and, rarely, thromboembolic events and must be
taken into account. Although not uniformly reported, adverse effects resulting from GnRHa were tolerable and had little effect in the overall toxic effects. For example, only 7% of the patients in the trial by Moore et al36 experienced grade 3 or 4 adverse events in the group treated with goserelin vs 5% in the control arm.36 In the trial by Del Mastro et al,12 rates of hot flashes, headache, sweating, mood modification, and vaginal dryness were not statistically different between the treatment arms.30 In the phase II study by Song et al,37 adverse events attributed to leuprolide were grade 1 or 2 only.37

Conclusions
Currently available guidelines consider the use of GnRHa as experimental. This study provides evidence suggesting that GnRHa given concurrently with chemotherapy to premenopausal patients undergoing treatment for EBC may be used to prevent early menopause. Evidence is not sufficient to assess the effect of GnRHa on fertility or pregnancy rates. Additional outcomes related to ovarian function and fertility need to be further investigated.


