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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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Abstract

Importance—Chemotherapy may result in a detrimental effect on ovarian function and fertility in premenopausal women undergoing curative treatment for early breast cancer (EBC). For this subgroup of patients, a careful consideration for techniques to minimize this risk should be given and the role of gonadotropin-releasing hormone agonists (GnRHa) for protection of ovarian function is not fully resolved.

Objective—To determine efficacy of GnRHa administered concurrently with chemotherapy for ovarian function preservation.

Data sources—The search for studies published between 1975 and March/2015 encompassed PubMed, SCOPUS and Cochrane databases, as well as ASCO Annual Meeting and San Antonio Breast Cancer Symposium abstracts.

Study selection—Prospective, randomized, controlled 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 two authors. The methodology and the risk of bias were assessment based on the description of randomization method, withdrawals and blinding process.

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Conflict of interest:
The remaining authors declare that they have no potential conflict of interest.

Main Outcomes Measures—Rate of resumption of regular menses after a minimal follow-up period of 6 months following chemotherapy was used as 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 selected, totaling 1047 randomized patients (856 evaluable patients).. The use of GnRHa was associated with a higher rate of recovery of regular menses after 6 months (OR = 2.41; 95% CI 1.40–4.15; p= 0. 002) and at least 12 months (OR 1.85; 95% CI 1.33–2.59; p = 0.0003) following last chemotherapy cycle. The use of GnRHa was also associated with a higher number of pregnancies (OR 1.85; 95% IC 1.02–3.36; p=0.04), although this outcome was not uniformly reported.

Conclusions and Relevance—GnRHa given with chemotherapy resulted in increased rates of recovery of regular menses and should be considered an option for ovarian function preservation in young women undergoing treatment for EBC. Additional outcomes related to ovarian function and fertility need to be further investigated.

Introduction

Breast cancer is among the leading causes of cancer-related mortality and the most common cancer in women worldwide (1). Significant improvements in survival have been achieved with the widespread use of adjuvant therapies in early-stage breast cancer (breast cancer that has not spread beyond the breast or the axillary lymph nodes) (EBC)(2). However, approximately 25% of the cases occur in premenopausal women, including 12% in women between the ages of 20 and 44 (3). 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 (4). In addition to complications that include osteoporosis, loss of libido, increased cardiovascular risk and atrophic vaginitis, early ovarian dysfunction may adversely impact quality of life and result in significant psychosocial burden (4, 5).

Several series suggest that the incidence of ovarian dysfunction in women undergoing systemic treatment for EBC ranges widely from 4–90% and is influenced by chemotherapies used, duration of exposure, total dose, definitions applied and patients' age (6–9). The latter represents the strongest predictor of ovarian dysfunction, with a significantly increased incidence over the age of 40 (10–12). Rates of chemotherapy-related amenorrhea and ovarian dysfunction following treatment with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) were 76%–100% in women aged 40 years and over in comparison to 21%–70% in women under 40 (8, 13–15). Increased risk results from regimens containing high cumulative doses of alkylators and anthracyclines (16). In trials investigating combinations of fluorouracil, epirubicin and cyclophosphamide (FEC), chemotherapy-induced menopause occurred in up to 60% of the patients (17), with similar incidences observed with taxane-containing regimens (16, 18, 19).

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 (20).

Pre-clinical studies suggested that hormonal suppression of the hypothalamic-pituitary-ovarian axis could minimize the impact of cytotoxic agents over ovarian function (21–23). Based on this concept, several uncontrolled trials have been conducted to evaluate the activity of luteinizing-hormone releasing-hormone (LHRH) analogs/gonadotropin-releasing hormone agonists (GnRHa) in preventing the loss of ovarian function due to exposure to cytotoxic agents (24–26). 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 a 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 (OR 10.57; 95% CI, 5.22 to 21.39). Nonetheless, statistical significance was lost when only the randomized studies were considered (OR 5.76; 95% CI, 0.47 to 71.03) (27).

These findings prompted the development of randomized, controlled trials limited to a breast cancer population (28–37). 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 (38–44). 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 POEMS trial (36).

Guidelines from the American Society of Clinical Oncology (ASCO) recently updated recommend that patients with cancer who are at reproductive ages should be advised about the potential risks of fertility impairment and additional effects of chemotherapy and preservation techniques should be considered (45). However, “evidence regarding the effectiveness of ovarian suppression” is still quoted as “insufficient”.

Since 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 (46) and that currently few women receiving adjuvant chemotherapy undergo active approaches to preserve fertility and ovarian function (47), this is a topic of utmost importance. We aimed to conduct a meta-analysis to determine the role of ovarian suppression with GnRHa during chemotherapy in women undergoing treatment for EBC.

Materials and 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 1975 and March/2015, as well as the ASCO and San Antonio Breast Cancer Symposium

abstracts. The following medical subject headings/specific terms were used: "*breast neoplasms*", "*menopause, premature*", *amenorrhea*", "*gonadotropin-releasing hormone*", "*goserelin*", "*triptorelin*", "leuprolide", "*fertility*", "*fertility preservation*", "*chemotherapy, adjuvant*", "antineoplastic agents", "*clinical trial, randomized*". Additional searches were performed using 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, controlled 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 and those with unclear definitions of ovarian dysfunction or follow up inferior to 6 months.

Data extraction

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

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 versus 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 chi-square-based Q statistic, with significance at a P value of less than 0.10, and expressed in I^2 index.

Statistical analyses were performed with RevMan5.1 software.

Results

Database search returned 603 entries; 592 were excluded after initial review. Primarily 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 trial corresponded to pre-planned sub-protocol of a trial addressing the antitumoral effect of GnRHa. Goserelin was administered for 2 years, with or without tamoxifen, irrespectively of the hormone receptor status; hence, the prolonged duration of treatment with tamoxifen could affect by itself the assessment of amenorrhea at 6 months and 12–24 months [31]. One trial that did not report the outcomes of interest and was also excluded (49) (Figure 1). One randomized trial had inconsistencies in the study methods and reporting of results, and was therefore excluded (50). Of the eight potentially eligible studies, one was presented in abstract form only (34) with insufficient data for the main analyses. (Figure 1). The author was contacted, but no additional information was provided.

Seven trials published in full met the predefined criteria and were included in the analysis, totaling 1047 randomized/856 evaluable patients aged between 18–49 years (28–30, 32, 35–37). Of note, long-term outcomes of the PROMISE-GIM6 study by Del Mastro et al. were presented as abstract only (51); therefore, the original publication was selected for data extraction [30] and for referencing across the manuscript. The characteristics of the studies are summarized in Table 1.

Although eligibility criteria varied, all studies required the patients to be premenopausal at enrollment, defined as prior history of cyclic menstrual bleedings/regular menses, 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 one week before the first cycle of chemotherapy and maintained until the last cycle in 6 out 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 (35). Anthracycline and cyclophosphamide-based regimens were administered to over 90% of the patients; a smaller proportion of patients also received taxanes. Treatment characteristics are summarized in Table 1.

GnRHa and recovery of menses

The administration of GnRHa (goserelin, triptorelin or leuprolide) was associated with a higher rate of recovery of regular menses after a minimum of 6 months after the last cycle of chemotherapy in premenopausal women receiving treatment for early stage breast cancer (OR = 2.41; 95% CI 1.40–4.15; p= 0.002; Figure 2A), although a high heterogeneity among trials was observed (I^2 = 58%; p= 0.03).

The rate of recovery of regular menses 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 two 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 menses resumption after a minimum interval of 12 months since 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 resumption of menses, with no heterogeneity among trials (OR 1.85; 95% CI 1.33–2.59; p = 0.0003; I^2 = 0%. Figure 2B).

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

GnRHa and hormone levels

Complete data to evaluate the impact of GnRHa on hormone serum concentrations were not consistently described and, therefore, this analysis was not performed. In the trial by Badawi et al., patients treated with GnRHa showed lower FSH (p<0.009) and higher E_2 (p<0.001) levels when compared to the control group (32). In the trial by Gerber et al., only 17/60 patients were accessible for hormone measurements (29). In the trial by Del Mastro et al. FSH/E2 measurements were not available for approximately 30% of the patients (30). In the trial by Song et al., 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<0.05) (37). No statistically significant differences in FSH and additional hormone levels were identified in two additional studies (28, 35).

GnRHa and pregnancies

The use of GnRHa was also associated with a higher number of pregnancies (OR 1.85; 95% IC 1.02–3.36; p=0.04). However, pregnancy outcomes and the total number of attempted pregnancies was not uniformly reported across trials and fertility/rate of pregnancies were not the primary endpoint in any of the studies. In addition, in the trial by Moore et al, patients with incomplete data and therefore not evaluable for the primary endpoint were still included in pregnancy outcomes (total number of evaluable patients for pregnancies: 113 in the control arm/105 in the GnRHa arm) (36).

Discussion

Chemotherapy-induced early menopause and its impact on quality of life is a pragmatic and clinically important topic that often arises during the treatment with curative intent of premenopausal patients with EBC. The present meta-analysis of RCT 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 young women with EBC.

Alternative methods for preserving fertility, including embryo/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, our findings suggest that goserelin, triptorelin or leuprolide are effective in preventing chemotherapy-induced premature menopause in young women with EBC (OR 1.85; p = 0.0003).

Major concerns when evaluating effects of chemotherapy on fertility and menopause are the discrepant definitions of ovarian dysfunction used. This heterogeneous characterization of outcomes is, in part, responsible for the wide variability in the incidence of ovarian dysfunction (8, 16, 52–54). Resumption 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 Inhibin and anti-Müllerian hormone, are of clinical interest.

In our meta-analysis, high heterogeneity among trials (I^2=65%) was observed after first efficacy analysis after a minimal follow up of 6 months, which could be attributable to two determinant aspects: age of the patients and time to outcome measurement. Age independently has an impact on the risk of permanent menopause and could be associated with efficacy of GnRHa (16, 54). The trial by Badawy et al included patients aged 40 or less, with a median age of 30 years, versus 37–39 years 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 GnRHa could have only a marginal effect in older patients. However, the cut-off to select patients for whom ovarian suppression is of clinical relevance is still unknown.

GnRHa were given concurrently with the standard regimens recommended for the neo-/adjuvant treatment of EBC. Noteworthy, more than 90% of the included patients received anthracycline-based combinations and a significant proportion received taxanes. Therefore, it is unlikely that the conflicting efficacy 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 impact 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 (55) and this was also suggested by other authors (56, 57). In fact, some of the trials included in this meta-analysis excluded patients with positive expression of estrogen (ER) and progesterone receptors (PR) (29, 35, 36). However, the true impact of amenorrhea as an independent prognostic factor and the benefits of re-introducing GnRHa in this subgroup of patients is still under investigation. Moreover, breast cancer in younger patients has different

clinicopathological characteristics, with a high incidence of hormone-receptor negative tumors (58), for whom the restoration of ovarian function could have little, if any, impact on survival. In fact, concurrent administration of GnRHa resulted in longer disease-free survival and overall survival in the POEMS trial, restricted to patients with ER/PR-negative tumors (HR=0.49, p=0.04; HR=0.43, p=0.05, respectively)(36). Furthermore, long-term results of the PROMISE-GIM6 trial support the safety of GnRHa even in hormone-sensitive patients, in which 81% of the patients had ER/PR-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 versus 80.5% in CT plus GnRHa; p=0.519) (51).

Several limitations should be highlighted. Despite the extensive search, only seven studies met the predefined criteria, leading to a limited number of patients, 44% of which were derived from two studies (30)(37). The data extracted for the analysis were retrieved from published articles and abstracts; 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 1. Furthermore, the effect of additional confounding factors affecting the ovarian function and efficacy of GnRHa (examples include body mass index, concurrent endocrine/auto-immune diseases, specific age groups etc.) could not be assessed. Some of the included trials were discontinued prematurely and had incomplete analyses of outcomes relevant for a thorough assessment of ovarian function, including hormone levels, restoration of ovulation, rates of pregnancies etc. Another limitation was the lack of detailed survival outcomes, which led this meta-analysis not to address a possible interaction between GnRHa and long-term results. In addition, although a higher number of pregnancies was also observed in the intervention arm, this was not statistically significant and it’s 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, and the true impact of GnRHa in fertility remains unclear. Although similar meta-analyses have been published (38–44), this is the first to encompass the largest and most recent trials reported to date, consequently including a larger number of individuals and providing more robust estimates of the benefit of GnRHa specifically for patients undergoing treatment for EBC.

Even though this was not the scope of the present study, side effects associated with GnRHa must also be weighted, and include hot flashes, vaginal dryness, headache and, rarely, thromboembolic events. Although not uniformly reported, side effects resulting from GnRHa were tolerable and had little impact in the overall toxicity. For example, only 7% of the patients in the trial by Moore et al. experienced grade 3/4 adverse events in the group treated with goserelin, versus 5% in the control arm (36). In the trial by Del Mastro et al., rates of hot flushes, 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., adverse events attributed to leuprolide were of grade 1 or 2 only (37).

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 are effective tools to prevent early

menopause and this strategy could be incorporated into clinical practice. Nevertheless, additional outcomes related to ovarian function and fertility need to be further investigated.

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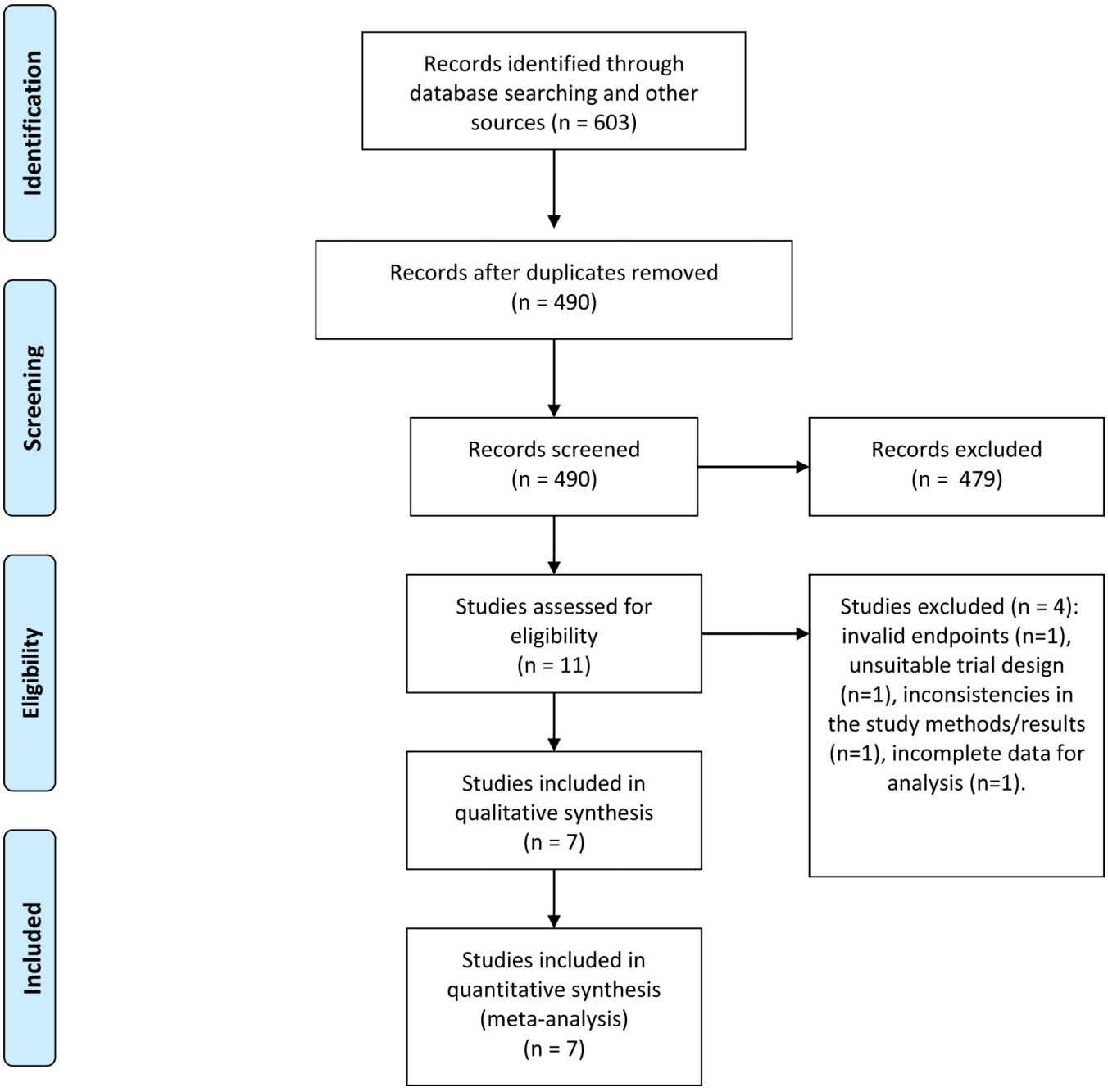

Figure 1.
Search process

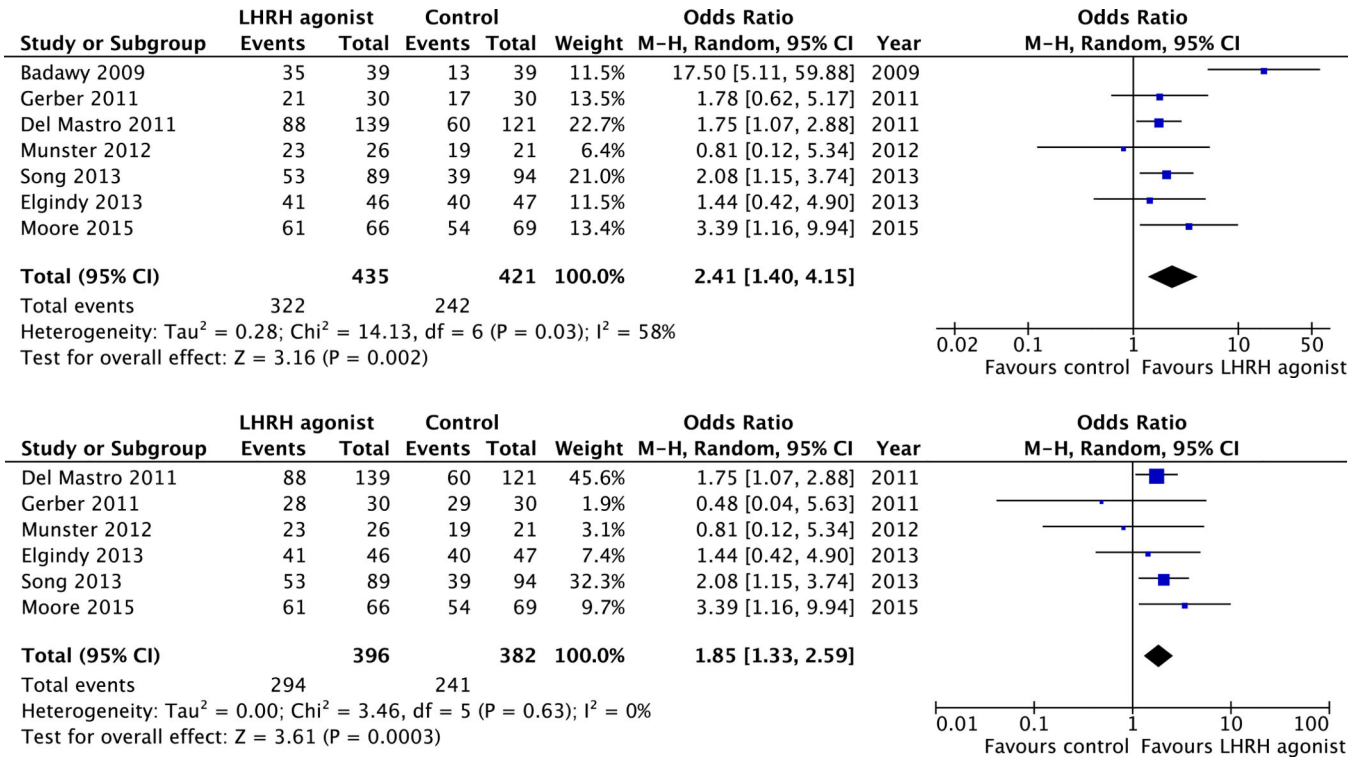

Figure 2.

Impact of GnRH – Resumption of regular menses and pregnancies.

Forest plots: (A) Menses resumption after 6 months among evaluable patients; (B) Menses resumption after 12–24 months among evaluable patients.

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Table 1

Selected trials' characteristics and risk of bias *

Study	Moore, 2015 (POEMS) (36)	Song, 2013 (37)	Elgindy, 2013 (35)	Munster, 2012 (28)	Del Mastro, 2011 (PROMISE /GIM 6) (30, 51)	Gerber, 2011 (ZORO) (29)	Badawy, 2009 (32)
N of pts planned	416	62	50	124	280	62	48
N of pts randomized (control/intervention)	257 (131/126)	220 (110/110)	100 (50/50)	49 (22/27)	281 (133/148)	61 (31/30)	80 (40/40)
Evaluable pts (control/intervention)	135 (69/66)	183 (94/89)	93 (47/46)	47 (21/26)	260 (121/139)	60 (30/30)	78 (39/39)
Age - mean (range)	38 (25–49)	41 (26–45)	33 (18–40)	39 (21–44)	39 (24–45)	37 (26–47)	30 (18–40)
HR status (pos/neg)	0/135	150/33	0/93	36/28	226/51	0/61	NI
Chemotherapy regimen	Cyclophosphamide-based	AC +/− taxane	FAC	AC, AC-taxane, FAC/FEC	CMF, anthracycline-based, with or without taxanes	FEC-taxane, EC-taxane, FEC, FAC, TAC	FAC
Use of anthracyclines (control/intervention)	62/61	94/89	47/46	21/26	119/142#	30/30	39/39
Use of cyclophosphamide (control/intervention)	69/66	94/89	47/46	21/26	119/135#	30/30	39/39
Use of taxanes (control/intervention)	Not informed	25/32	0	5/8	62/86#	16/15	0
Use of tamoxifen (control/intervention)	0	74/76	0	16/20	96/100#	0	Not informed
Use of tamoxifen	NA	Yes	NA	Yes	Yes	NA	NA
Primary outcome	Rate of ovarian failure	Rate of early menopause (amenorrhea	Rate of resumption of regular	Rate of resumption of regular	Rate of menopause (amenorrhea	Rate of resumption of regular	Rate of resumption of regular

Study	Moore, 2015 (POEMS) (36)	Song, 2013 (37)	Elgindy, 2013 (35)	Munster, 2012 (28)	Del Mastro, 2011 (PROMISE /GIM 6) (30, 51)	Gerber, 2011 (ZORO) (29)	Badawy, 2009 (32)
	(amenorrhea for 6 months and post-menopausal FSH levels at 24 months)	and post-menopausal hormone levels)	menses (three consecutive menses within 21–35 days each)	menses (three menses in a 6-month interval)	+post-menopausal hormone levels for a 12-month interval)	menses (two menstrual periods within 21–35 days in 5–8 months)	menses and ovulation
Secondary outcomes	Amenorrhea and FSH/E2 levels, inhibin B levels at 12 and 24mo, rate of pregnancy, survival	Amenorrhea, FSH/E2 levels	Rate of resumption of regular menses after 12mo	FSH, Inhibin A/B levels	None	Time to recovery of menses, hormone levels, ovarian reserve, follicle count, rate of pregnancy, toxicity, compliance	Hormone levels
Interval for primary outcome measurement after chemotherapy	24mo	12mo	12mo	24mo	12mo	5–8mo	6–8mo
GnRHa	Goserelin	Leuprolide	Triptorelin	Triptorelin	Triptorelin	Goserelin	Goserelin
Dose/Interval (days)	3.6mg / 28d	3.75mg/ 28d	3,75mg / 28d	3,75mg / 28–30d	3,75mg / 28d	3,6mg / 28d	3,6mg / 28d
Beginning of suppression	1 week before chemo	Before chemo	10 days to concurrently with chemo	1–4 weeks before chemo	>1 week before chemo	>2 weeks before chemo	2 weeks before chemo
Randomization process months	Adequate	Not described	Adequate	Adequate	Adequate	Not described	Adequate
Withdrawals	Described	Described	Described	Described	Described	Described	Described
Double-blinded	No	No	No	No	No	No	No
Risk of bias *	Low	High	Low	Low	Low	High	Low

N – number / HR – hormone receptor / GnRHa – GnRH agonist / NA – Not applicable / NI – Not informed / mo - months / AC – doxorubicin and cyclophosphamide / FAC – fluorouracil, doxorubicin and cyclophosphamide / FEC - fluorouracil, epirubicin and cyclophosphamide / CMF – cyclophosphamide, methotrexate and fluorouracil / TAC – docetaxel, doxorubicin and cyclophosphamide /

- Among the 281 patients initially randomized, not limited to evaluable patients /

* Adapted from Jadad et al. (48).