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[Intervention Review]

LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women

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ABSTRACT

Background

Approximately 60% of breast cancers amongst premenopausal women express the nuclear oestrogen receptor (ER+ breast cancer). Adjuvant endocrine therapy is an integral component of care for ER+ breast cancer, exerting its effect by reducing the availability of oestrogen to micrometastatic tumour cells. Endocrine strategies in premenopausal women include oestrogen receptor blockade with tamoxifen, temporary suppression of ovarian oestrogen synthesis by luteinising hormone releasing hormone (LHRH) agonists, or permanent interruption of ovarian oestrogen synthesis with oophorectomy or radiotherapy. Aromatase inhibitors are also available with concurrent suppression of ovarian oestrogen synthesis, either through LHRH agonists, surgery, or radiotherapy. Chemotherapy can also have an endocrine action in premenopausal women by interrupting ovarian oestrogen production, either temporarily or permanently. International consensus statements recommend single agent tamoxifen as the current standard adjuvant endocrine therapy for premenopausal women (often preceded by chemotherapy), and the role of LHRH agonists remains under active investigation.

Objectives

To assess LHRH agonists as adjuvant therapy for women with early breast cancer.

Search methods

The Cochrane Breast Cancer Group Specialised Register was searched on 19 February 2009. This register incorporates references from CENTRAL (*The Cochrane Library*) (to 2002), MEDLINE (1966 to July 2008), EMBASE (until 2002); and handsearches of abstracts from the San Antonio Breast Cancer Symposium, American Society of Clinical Oncology Annual Meeting, and the Clinical Oncological Society of Australia Annual Meeting. MEDLINE references (from August 2008 to 19th February 2009) were checked by the authors. The reference lists of related reviews were checked. A final check of the list of trials maintained by the Early Breast Cancer Trialists' Collaborative Group was made in January 2008.

Selection criteria

All randomised trials assessing LHRH agonists as adjuvant treatment in premenopausal women with early stage breast cancer were included. Specifically, we included trials that compared:

- (A) LHRH agonists (experimental arm) versus another treatment;
- (B) LHRH agonists + anti-oestrogen (experimental arm) versus another treatment;
- (C) LHRH agonists + chemotherapy (experimental arm) versus another treatment;

(D) LHRH agonists + anti-oestrogen + chemotherapy (experimental arm) versus another treatment.

Data collection and analysis

Data were collected from trial reports. We reported estimates for the differences between treatments on recurrence free survival, overall survival, toxicity and quality of life using data available in the reports of each trial. Meta-analyses were not performed because of variability in the reporting of the trials.

Main results

We identified 14 randomised trials that involved over 13,000 premenopausal women with operable breast cancer, most of whom were ER+. The numbers of trials making the different comparisons were:

- (A) i. LHRH versus tamoxifen (three trials),
- ii. LHRH versus chemotherapy (four trials);
- (B) i. LHRH + tamoxifen versus tamoxifen (two trials),
- ii. LHRH + tamoxifen versus LHRH (three trials),
- iii. LHRH + tamoxifen versus chemotherapy (two trials),
- iv. LHRH + aromatase inhibitor versus LHRH + tamoxifen (one trial);
- (C) i. LHRH + chemotherapy versus LHRH (one trial),
- ii. LHRH + chemotherapy versus chemotherapy (five trials);
- (D) LHRH + tamoxifen + chemotherapy versus chemotherapy (three trials).

The LHRH agonist in most of these trials was goserelin.

For most of the treatment comparisons there are too few trials, too few randomised patients, or too little follow up to draw reliable estimates of the relative effects of different treatments.

(A) *LHRH monotherapy*: results suggest that adjuvant LHRH agonist monotherapy is similar to older chemotherapy protocols (eg. CMF) in terms of recurrence-free and overall survival in ER+ patients. There are insufficient data to compare LHRH agonist monotherapy to tamoxifen alone, but available results suggest that these treatments are comparable in terms of recurrence-free survival.

(B) *LHRH + anti-oestrogen therapy*: there are insufficient data to compare the combination of an LHRH agonist plus tamoxifen to tamoxifen alone. Results suggest that the LHRH agonist plus tamoxifen combination may be superior to an LHRH agonist alone or to chemotherapy alone, but the chemotherapy protocols tested are outdated. The data comparing LHRH agonists plus aromatase inhibitors to LHRH agonists plus tamoxifen are currently inconclusive.

(C) *LHRH + chemotherapy*: there are insufficient data to compare the LHRH + chemotherapy combination to an LHRH agonist alone, although results from a single study suggest comparable efficacy in ER+ patients. There is a trend towards improved recurrence-free and overall survival in patients who received an LHRH agonist plus chemotherapy combination in comparison to chemotherapy alone.

(D) *LHRH agonist + chemotherapy + tamoxifen*: there is a trend towards improved recurrence-free and overall survival in patients who received an LHRH agonist plus tamoxifen plus chemotherapy in comparison to chemotherapy alone.

There are insufficient data to assess the effect of the addition of LHRH agonists to the current standard treatment of chemotherapy plus tamoxifen.

Endocrine therapy with LHRH agonists appears to have fewer side-effects than the forms of chemotherapy assessed. The optimal duration of LHRH therapy in the adjuvant setting is unclear.

Authors' conclusions

Overall, the data from currently published clinical trials of LHRH agonists in the adjuvant setting for premenopausal women with endocrine-sensitive breast cancer are supportive of clinical benefit. Nonetheless, definitive comparisons against current clinical standards of care that include third generation chemotherapy regimens and tamoxifen are required before their place in the adjuvant setting can be properly defined. The authors conclude that the current data strongly support the continuation of current trials that definitively compare a variety of combinations of LHRH agonists and anti-oestrogenic strategies to the current standard of five years of tamoxifen.

PLAIN LANGUAGE SUMMARY

Ovarian suppression with LHRH agonists (such as goserelin) for treating premenopausal women with early breast cancer

More than half of the premenopausal women who develop breast cancer have a type of cancer that is sensitive to hormones, termed 'oestrogen receptor positive' or ER+ disease. To slow the growth of any cancer cells that remain after surgery, hormonal therapy can be used to reduce the availability of the natural hormone oestrogen to the cells. This can be done by blocking the oestrogen receptors on the cells with drugs such as tamoxifen, by suppressing the production of oestrogen by drugs called luteinising hormone releasing hormone (LHRH) agonists, or by removing the ovaries with surgery or impairing their ability to produce hormones using radiotherapy. A new class of drugs called aromatase inhibitors work by stopping the production of oestrogen, but can only be safely used in premenopausal women if their ovarian cycling is suppressed (either by LHRH agonists, surgery, or radiotherapy). Chemotherapy, designed to kill cancer cells, can also have a hormonal action by bringing on early menopause. This review examined the role of LHRH agonists for women with early stage breast cancer. It looked at comparisons of LHRH agonists versus other types of hormonal treatment and versus chemotherapy. We also examined the role of combined LHRH agonist plus tamoxifen therapy, combined LHRH agonist plus chemotherapy, and combined LHRH agonist plus tamoxifen plus chemotherapy. A total of 14 randomised trials that involved over 13,000 women were found, but only a small number of these were relevant to each of the comparisons in this review. The LHRH agonist in the trials was usually goserelin, used for a couple of years.

We found seven trials comparing LHRH agonist therapy (alone) to other treatments. There is not enough evidence to compare LHRH agonists directly to tamoxifen. Four of the trials compared an LHRH agonist to a now superseded chemotherapy regimen. For ER+ women, these trials showed no significant differences between LHRH agonists and chemotherapy on recurrence and death, but LHRH agonists had fewer side effects.

Six trials compared LHRH agonists in combination with tamoxifen to other treatments. There is currently insufficient information to reliably compare this combination with tamoxifen alone. The LHRH agonist plus tamoxifen combination may reduce the risk of breast cancer recurrence, but not death, when compared to an LHRH agonist alone or chemotherapy alone. There is insufficient evidence to know whether an LHRH agonist plus an aromatase inhibitor is better or worse than an LHRH agonist plus tamoxifen.

Three trials compared combining an LHRH agonist plus chemotherapy plus tamoxifen to chemotherapy alone. There was a reduction in the risk of breast cancer recurrence, and possibly death, with the combination treatment.

It is important to note that the current standard of care for premenopausal women with ER+ breast cancer is five years of tamoxifen, often with chemotherapy. We found no trials of LHRH agonist-containing regimens versus this standard. The women in the trials in this review need to continue to be followed up so that the longer-term effects can be investigated, to 10 and more years after diagnosis. More research is also needed to help choose between different types of LHRH agonist, and to find out if the length of time that the drug is used makes a difference. It is also unknown whether there are important differences between the effects of LHRH agonists and ovarian ablation by surgery or radiotherapy.

BACKGROUND

Breast cancer is a major cause of morbidity and mortality. Approximately 20% of women diagnosed and treated for early breast cancer will eventually die of the disease (Jemal 2008). The aim of adjuvant therapy is to prevent recurrence and improve overall survival. In premenopausal women with early breast cancer the options for adjuvant therapy include cytotoxic chemotherapy; anti-oestrogen therapy; and ovarian ablation, either irreversibly with surgery or radiotherapy, or reversibly with luteinising hormone releasing hormone (LHRH) agonists (Gelber 1996).

Approximately 60% of tumours in premenopausal women are hormone sensitive and these patients may be suitable for hormonal treatment (Pujol 1998; Williams 2006). The goal of hormonal therapy is to reduce the availability of oestrogen to the cancer cells. This can be achieved by blocking oestrogen receptors with drugs such as tamoxifen, suppression of oestrogen synthesis by LHRH agonists, or ovarian ablation either surgically or by radiotherapy. Aromatase inhibitors (used in postmenopausal women with no ovarian oestrogen synthesis) prevent the synthesis of oestrogen from androgens, and can be used safely in premenopausal patients if there is concurrent suppression of ovarian oestrogen synthesis (by LHRH agonists, or through surgery or radiotherapy) (Forward 2004). Chemotherapy has been shown to induce amenorrhoea in 60% to 80% of premenopausal women who receive adjuvant treatment (Bines 1996; Walshe 2006). It is clear that, particularly in the case of hormone sensitive disease, patients who become amenorrhoeic following chemotherapy have a better disease-free survival than those who do not (Pagani 1998; Davidson 2003; Walshe 2006). This suggests that at least some of the beneficial effect of chemotherapy in premenopausal women is mediated via its toxic effect on the ovaries, resulting in ovarian ablation or suppression. The value of ovarian ablation by either oophorectomy or radiotherapy is clearly demonstrated by a meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG 1996; EBCTCG 2003; EBCTCG 2005), which focused on women under the age of 50 years, most of whom were likely to be premenopausal. For women who underwent ovarian ablation in the absence of chemotherapy there was a 25% reduction in the annual odds of recurrence and a 24% reduction in the annual odds of death. The benefit was seen in both node-positive and node-negative women. In women randomised to ovarian ablation following chemotherapy the benefit of ablation appeared smaller and was not statistically significant (reduction in the annual odds of recurrence was 10% with a standard error (SE) of 9%; reduction in the annual odds of death was 8%, SE 10%). These results were further supported by two other trials, which compared adjuvant ovarian ablation to chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) (SCTBG and ICRF 1993; Ejlersen 1999). Both these trials concluded that chemotherapy and oophorectomy have similar effects on disease-free survival (DFS) and overall survival (OS) for premenopausal women with node-positive disease. However, a retrospective subanalysis of the Scottish/ICRF trial suggested that oophorectomy had a survival benefit over chemotherapy in those women whose tumours were ER positive, whereas oral CMF had a benefit over oophorectomy in women with ER negative tumours (SCTBG and ICRF 1993).

LHRH agonists provide effective ovarian suppression in premenopausal women and are an effective alternative to oophorectomy or pelvic radiotherapy. These agents induce a

menopausal status that is usually reversible on cessation of therapy. LHRH agonists act by binding to pituitary LHRH receptors, resulting in down regulation of receptors and subsequent suppression of luteinising hormone and oestradiol (Furr 1989). The most commonly prescribed LHRH agonist is goserelin. The major side effects of these drugs are fertility impairment, decreased libido, hot flushes, sweating, headache, blood pressure changes, loss of bone density, transient increased pain in bony metastases, hypercalcaemia, and a number of other rare complications. A number of clinical trials have shown goserelin to be effective in the treatment of advanced breast cancer in premenopausal women (Klijn 2001), with a response similar to that seen with surgical oophorectomy or ovarian suppression (Taylor 1998). The aim of this review is to clarify the effect of LHRH agonists in the adjuvant treatment of ER positive breast cancer in premenopausal women, by performing a systematic review of the available randomised trials. An earlier version of this review has been published (Sharma 2005); a number of the trials have since been reported in full, and a new trial has been reported.

OBJECTIVES

To review randomised trials that assessed the use of LHRH agonists in adjuvant therapy for women with early breast cancer.

The specific objectives of the review are as follows.

1. To summarise the available data that compares:
 - (A) LHRH agonists (experimental arm) versus another systemic treatment;
 - (B) LHRH agonists + anti-oestrogen (experimental arm) versus another systemic treatment;
 - (C) LHRH agonists + chemotherapy (experimental arm) versus another systemic treatment;
 - (D) LHRH agonists + anti-oestrogen + chemotherapy (experimental arm) versus another systemic treatment.
2. To describe the best available evidence pertaining to the optimum duration of LHRH treatment.
3. To describe the impact of the treatments on amenorrhoea in the long term.
4. To describe the role of LHRH agonists in relation to:
 - a. restoration of fertility following ovarian suppression;
 - b. women who are ER+ and have HER-2 or neu gene amplification or HER-2 protein overexpression;
 - c. women with familial breast cancer syndromes.

METHODS

Criteria for considering studies for this review

Types of studies

Properly randomised controlled trials as defined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Quasi-randomised trials were not eligible. Trials published in full or as conference abstracts were considered.

Types of participants

Inclusion criteria

Premenopausal women with a histological diagnosis of early breast cancer. Early breast cancer is defined as operable breast cancer (TNM stage 1 and stage 2) and premenopausal is defined as women less than 50 years of age.

Exclusion criteria

Women with locally advanced or metastatic disease.

Types of interventions

Intervention being assessed: LHRH agonists (buserelin, goserelin, leuprolide, nafarelin, and triptorelin)

Comparisons:

- (A) i. LHRH versus tamoxifen,
- ii. LHRH versus chemotherapy;
- (B) i. LHRH + tamoxifen versus tamoxifen,
- ii. LHRH + tamoxifen versus LHRH,
- iii. LHRH + tamoxifen versus chemotherapy,
- iv. LHRH + aromatase inhibitor versus LHRH + tamoxifen;
- (C) i. LHRH + chemotherapy versus LHRH,
- ii. LHRH + chemotherapy versus chemotherapy;
- (D) i. LHRH + tamoxifen + chemotherapy versus chemotherapy.

Types of outcome measures

1. Overall survival
2. Disease-free survival
3. Quality of life
4. Toxicity

For the purpose of this review, the following outcome definitions apply.

1. Overall survival: time from date randomised to date of death due to any cause.
2. Disease-free survival: time from date randomised to first recurrence, or death.

Search methods for identification of studies

The Cochrane Breast Cancer Group Specialised Register was searched (most recently on 19 February 2009). The search strategy applied by the Group to create the register and the procedure used to code references, are described in the Group's module in *The Cochrane Library*. Studies coded as "early breast cancer" and "endocrine therapy" on the specialised register were extracted for consideration. In addition, the reference lists of related reviews were checked. The list of trials maintained by the Early Breast Cancer Trialists' Collaborative Group was checked (most recently in January 2008). Furthermore, the proceedings of the annual meetings of the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium (2005 to 2008) were handsearched. A copy of the full article for each reference reporting a potentially eligible trial was obtained.

Data collection and analysis

Selection of studies

The eligibility criteria were applied to each of the potentially eligible trials identified. In the first instance, trial publications were used to assess each trial's eligibility. If a trial had not been published, the necessary information was sought from the trial protocol or from the principal investigator of the trial. Two review authors independently assessed each potentially eligible trial and differences were resolved by a third author.

Data extraction and management

A single author extracted data describing the trial and patients' baseline characteristics. Two independent review authors extracted data on outcomes (including follow-up times). The most complete data set feasible was assembled from the published reports of the trials.

Assessment of risk of bias in included studies

Two independent review authors appraised the design and conduct of each trial to assess its susceptibility to bias. Where the two authors differed in their quality assessment, arbitration from a third review author was sought. Methodological quality was assessed using a modified subset of the Methods for Evaluating Research and Guideline Evidence (MERGE) criteria (Liddle 1996). The following aspects of each trial were considered:

- a. concealment of treatment allocation;
- b. generation of the allocation sequence;
- c. comparability between groups at baseline;
- d. inclusion of all randomised participants in the analysis;
- e. withdrawals from the trial;
- f. valid assessment of endpoints.

Where possible (that is a full report in English was available) a global quality score was assigned to each trial as follows.

A: all or most the evaluation criteria from the MERGE checklist were fulfilled. Where evaluation criteria are not fulfilled, the conclusions of the study are thought very unlikely to alter.

B1: some evaluation criteria from the MERGE checklist were fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study are thought unlikely to alter.

B2: some evaluation criteria from the MERGE checklist were fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study are thought likely to alter.

C: few or no evaluation criteria were fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study are thought very likely to alter.

Data synthesis

Results of included studies have not been combined in a meta-analysis because this was not judged appropriate or possible at this time. The aim for all analyses was to use the intention-to-treat principle, which would be dependent upon the quality of the trial reporting. Our aim was to perform time-to-event analyses using the time to death (censoring at last known follow up) and time to first recurrence, and to combine the time-to-event data to obtain a pooled hazard rate (HR) using the fixed-effect model (Yusuf 1985). However, because of the limited amount of data available we chose instead to present the results of the included studies in accordance

with how they had been published, using the maximum amount of information available. A future update of this review, when the included and ongoing studies are sufficiently mature, should allow for a more robust analysis.

Our analyses rely on the summary data reported for each trial, which are dependent upon the trialists' definitions of outcomes and the detail in their reports. For this version of this review we have not extracted data from published survival curves (Parmar 1998).

In our protocol, we wrote that decisions regarding the combination of quality of life outcomes would be made depending on the availability of this information from the included studies. The information available on these outcomes varied so widely among the trials that meta-analyses were not done but where information was available this is described for each trial in the Results section below.

Sensitivity analyses (for example including trials of borderline quality) and subgroup analyses were to be performed, if appropriate and possible.

RESULTS

Description of studies

Results of the search

Following application of the eligibility criteria, 14 eligible randomised trials were identified that addressed the role of LHRH agonists in the adjuvant treatment of premenopausal women with ER+ early breast cancer. Four relevant, ongoing trials were identified and these are described in the table 'Characteristics of ongoing studies'. Four further studies were identified and excluded for the reasons given below.

Included studies

In summary, the included trials addressed the predefined therapeutic questions as outlined below.

Following application of the eligibility criteria, 14 eligible randomised trials were identified that addressed the role of LHRH agonists in the adjuvant treatment of premenopausal women with ER+ early breast cancer. These contributed a total of 24 comparisons to this review. A description of each trial is in the table 'Characteristics of included studies'. In summary, the included trials addressed the predefined therapeutic questions as outlined below.

Comparisons of LHRH agonists (experimental arm) versus another treatment

Seven trials provided seven comparisons (Table 1):

- three trials compared an LHRH agonist versus tamoxifen (Soreide 2002; ZBCSG Trial B; ZIPP);
- four trials compared an LHRH agonist versus CMF chemotherapy (GABG IV-A-93; IBCSG VIII; TABLE; ZEBRA);
- no trials comparing an LHRH agonist to a non-CMF chemotherapy regimen were identified.

Comparisons of LHRH agonists + anti-oestrogen (experimental arm) versus another treatment

Six trials provided eight comparisons (Table 2):

- two trials compared combined LHRH agonist and tamoxifen versus tamoxifen (ZBCSG Trial B; ZIPP);
- three trials compared an LHRH agonist and tamoxifen versus an LHRH agonist (ECOG 5188 INT-0101; ZBCSG Trial B; ZIPP);
- one trial compared combined LHRH agonist and tamoxifen versus CMF chemotherapy (ABCSG 5) and one trial compared combined LHRH agonist and tamoxifen versus an anthracycline-based chemotherapy regimen (FASG 06);
- one trial compared an LHRH agonist plus tamoxifen versus an LHRH agonist plus an aromatase inhibitor (ABCSG-12).

Comparisons of LHRH agonists + chemotherapy (experimental arm) versus another treatment

Five trials provided six comparisons (Table 3):

- one trial compared an LHRH agonist and chemotherapy versus an LHRH agonist (IBCSG VIII);
- five trials compared an LHRH agonist plus chemotherapy versus chemotherapy (ECOG 5188 INT-0101; GABG IV-B-93; IBCSG VIII; Pretoria; ZIPP).

Comparisons of LHRH agonists + tamoxifen + chemotherapy versus another treatment

Three trials provided one comparison (Table 4):

- Three trials compared chemotherapy followed by combined LHRH agonist and tamoxifen versus chemotherapy (ECOG 5188 INT-0101; MAM 01 GOCSI; ZIPP).

Excluded studies

We identified two trials in which women were randomised to chemotherapy with or without ovarian ablation or suppression. The choice of ovarian ablation was not randomised and it was achieved by surgery, irradiation, or LHRH agonist (Arriagada 2005; Grota 02). It was not possible to separate the results for women allocated to the LHRH agonist from those allocated to ovarian ablation by surgery or irradiation in these trials. In another trial women receiving tamoxifen (with or without chemotherapy) were randomised to ovarian suppression or no ovarian suppression, but again the methods of ovarian suppression were not randomised and included surgery, radiation, and LHRH agonists (ABCTCG study). A fourth study randomised women to tamoxifen or ovarian ablation (without chemotherapy) but again the method of ovarian ablation varied between surgery, radiotherapy, and a LHRH agonist (INT 0142).

Risk of bias in included studies

Where it was possible to assess this, the included studies had high ratings for trial quality. Most of the trials were multicentre studies and those that included information on how the randomisation was done reported that this was by contact with a central trial office. Where a global quality score could be assigned, this is given in the table 'Characteristics of included studies'.

Effects of interventions

The results from the trials included in this review are presented below, in accordance with the predefined treatment questions. The numbers of events in each treatment group in each trial have not been entered into the relevant forest plots because of inconsistencies in how these data were reported by the trialists.

These inconsistencies include the duration of follow up, the presentation of absolute numbers of events or percentages, and the presentation of subgroups on the basis of ER status. The main presentation of the results is by a narrative summary of the results of each trial in each therapeutic question.

A. LHRH agonists (experimental arm) versus other treatments

Seven trials were identified that addressed the comparison of LHRH agonists (as an experimental treatment) to another treatment (Table 1). Three trials addressed the effects of an LHRH agonist compared to tamoxifen (Soreide 2002; ZBCSG Trial B; ZIPP) in a total of approximately 1400 women. In each of these trials, the LHRH agonist was goserelin given as a 3.6 mg depot every 28 days for two years. Tamoxifen was given at 20 mg per day orally for two years in these trials (40mg for some patients in the ZIPP trial). Another four trials (GABG IV-A-93; IBCSG VIII; TABLE; ZEBRA) addressed the effects of an LHRH agonist compared to chemotherapy.

i. LHRH agonist versus tamoxifen

The largest of the trials assessing the integration of LHRH agonists into hormonal therapy was the ZIPP trial (ZIPP). This was an international collaboration between four breast cancer research groups who adopted similar protocols with the intention of combining their results in a meta-analysis. The trial used a 2 x 2 factorial design. The main randomisation was goserelin versus control (all 2710 patients) and a second randomisation of tamoxifen versus control was done for 1800 women. A further 860 women in the randomisation of goserelin versus no goserelin were given tamoxifen electively. Only 68% of the 2032 patients with known ER status in the ZIPP trial were ER+. The ZIPP results have not been reported separately for patients who underwent both randomisations (apart from in relation to major reported side effects (Baum 2006)). The reporting of recurrence and survival data for these women would provide a direct comparison of goserelin (444 patients) versus tamoxifen (448). The proportion of patients who experienced at least one side effect was 56% among patients allocated goserelin alone and 41% among patients receiving tamoxifen alone. The most common side effect was hot flushes (26% versus 17%). The only other side effect reported by more than 10 patients in either group was weight gain (4% versus 7%) (Baum 2006).

The other two trials identified, the Soreide trial and the Zoladex Breast Cancer Study Group trial from Japan, have reported the direct randomised comparison of goserelin versus tamoxifen, but in much smaller numbers of patients. The Soreide trial randomised 320 premenopausal patients who were not known to be ER- to goserelin versus tamoxifen. After a median follow up of 88 months, patients randomised to goserelin were not statistically different to those allocated to tamoxifen in their risk of recurrence (RR 1.10, 95% CI 0.81 to 1.48, $P = 0.56$) or death (RR 1.16, 95% CI 0.80 to 1.69, $P = 0.42$) (Soreide 2002). In the Japanese trial, 187 patients were randomised to goserelin versus tamoxifen. There was no statistically significant difference for patients allocated goserelin in recurrence-free survival (HR 0.87, 95% CI 0.47 to 1.63) or overall survival (HR 2.10, 95% CI 0.38 to 11.49), for which there were only four deaths (ZBCSG Trial B).

ii. LHRH agonist versus chemotherapy

Four studies were identified that compared an LHRH agonist versus chemotherapy, including a total of more than 3000 women. All four

trials used CMF: three as six cycles each of 28 days (IBCSG VIII; TABLE; ZEBRA) and one using three cycles (GABG IV-A-93). Two trials used classical CMF with cyclophosphamide given orally on each of the first 14 days of the cycle (IBCSG VIII; TABLE). The ZEBRA trial allowed either classical CMF with oral cyclophosphamide or CMF with intravenous cyclophosphamide (ZEBRA). The GABG trial used intravenous cyclophosphamide (GABG IV-A-93). There was also variability in the hormonal therapy used in these three trials. Goserelin (3.6 mg depot every 28 days) was used in IBCSG VIII, for two years in the absence of chemotherapy or for 18 months when following six months of chemotherapy. It was used for two years in the GABG and ZEBRA trials. In the TABLE trial, the LHRH agonist was leuporelin acetate (11.5 mg every 3 months) for two years.

The largest of these four trials was the ZEBRA trial, in which three quarters of the women were ER+ (1189 of 1614, 73.7%), 304 (18.8%) were ER-, and 121 (7.5%) had unknown ER status (ZEBRA). Overall, with a median follow up of 87 months, patients randomised to goserelin had significantly worse recurrence-free survival (49.8%) than those allocated to chemotherapy (56.2%) (HR 1.22, 95% CI 1.05 to 1.40, $P = 0.007$), and a non-significantly worse overall survival (HR 1.15, 95% CI 0.96 to 1.39, $P = 0.14$). However, a highly significant interaction was found between treatment and ER status ($P = 0.0016$) for recurrence-free survival. Patients who were ER+ had similar recurrence-free survival and overall survival in both treatment groups (HR for recurrence-free survival for goserelin versus CMF 1.05, 95% CI 0.88 to 1.24, $P = 0.60$; HR for overall survival 0.94, 95% CI 0.75 to 1.18, $P = 0.62$) with the worse outcome for goserelin-treated patients being due to the effect in the ER- patients (HR for recurrence-free survival 1.64, 95% CI 1.13 to 2.39, $P = 0.0009$; HR for overall survival 1.83, 95% CI 1.33 to 2.52, $P = 0.001$) and ER-unknown patients (HR for recurrence-free survival 2.00, 95% CI 1.07 to 3.75, $P = 0.026$; HR for overall survival 1.81, 95% CI 0.81 to 4.05, $P = 0.14$). After six months of treatment in ZEBRA, amenorrhoea was more common in patients treated with goserelin (95%) than with chemotherapy (59%). However, after three years, 23% of patients who had received goserelin remained amenorrhoeic compared with 77% of patients treated with chemotherapy. The incidence of adverse reactions, including menopausal side effects, hot flushes, vaginal discharge and vaginal soreness, was similar in both groups (in total, goserelin: 42.6%; chemotherapy: 48.0%). These side effects tended to resolve within a year after stopping goserelin but persisted in the chemotherapy group for the 30 months under investigation. A special assessment of quality of life was done in 86 of the 102 centres, involving 1010 of the randomised patients. Early benefits were noted during months three to six of treatment for women in the goserelin group. However, at one, two, and three years there were no significant differences between the two treatment groups (de Haes 2003).

The IBCSG VIII trial randomised just over 1000 patients to CMF alone versus CMF followed by goserelin versus goserelin alone (IBCSG VIII). A fourth option of no adjuvant therapy was closed two years into the trial, when a total of 205 patients had been randomised to the trial as a whole. Two thirds of the women in the trial were ER+ (720 of 1111, 68%); 315 (30%) were ER-; and 28 (3%) had unknown ER status. Overall, with a median follow up of 84 months, there were no significant differences between the treatment groups in disease-free survival or overall survival. The five-year disease-free survival was 79% (95% CI 75% to 84%) for goserelin alone and 82% (95% CI 78% to 86%) for chemotherapy alone. In the comparison of goserelin versus chemotherapy, the

relative risk for disease free survival was 1.13 (95% CI 0.83 to 1.53, $P = 0.44$). However, an interaction was found between treatment and ER status. ER+ patients in both the goserelin group and the chemotherapy group had similar disease-free survival (5-year DFS 81%, 95% CI 76% to 87% in both groups; RR 0.97, 95% CI 0.66 to 1.42, $P = 0.86$). In contrast, ER- patients had worse disease-free recurrence in the goserelin group (73%, 95% CI 64% to 81%) compared to the chemotherapy group (84%, 95% CI 77% to 91%) (RR 1.52, 95% CI 0.89 to 2.58, $P = 0.12$). Toxicities of grade 3 or worse were experienced by 4.7% of patients allocated to goserelin alone (mostly weight gain) and by 18.8% of patients during chemotherapy (mostly leucopenia, neutropenia, and nausea or vomiting).

In younger women under the age of 40 years receiving chemotherapy, amenorrhoea occurred later, being observed in 50% of these patients by the end of six cycles of CMF. In women who received goserelin after chemotherapy, 90% became amenorrhoeic a few months after starting goserelin. Whilst menses resumed for many women on cessation of goserelin, menses was still absent for 35% to 40% of women in this group at month 36.

Among women aged 40 years and older, amenorrhoea due to chemotherapy was observed sooner than among the younger women, affecting 80% to 90% of these patients by the end of six cycles of CMF. In these older women who started goserelin after six months of chemotherapy, amenorrhoea was induced in more than 90% within three months of starting this drug, and remained so at month 36.

Quality of life has been reported in detail for 874 patients in the IBCSG VIII trial, based on an assessment at 36 months for 746 of these 874 patients (Bernhard 2007). Patients in the goserelin alone group showed a marked improvement or less deterioration in various quality of life indicators during the first six months compared to those receiving chemotherapy. But, there was no significant difference in quality of life at 36 months between the groups allocated chemotherapy followed by goserelin versus goserelin alone.

The TABLE study recruited 599 premenopausal patients who were not known to be ER- (TABLE). The inclusion criteria were amended part way through the trial, so that only ER+ patients were randomised. Although 599 patients were recruited, results for the 589 patients in the intention-to-treat population have been published, with a median follow up of 69 months. No significant differences were found between the treatments on either recurrence-free survival or overall survival. The 5-year disease-free survival was 63.9% for women allocated leuporelin compared to 63.4% for women allocated chemotherapy. Over 95% of women in the leuporelin group became amenorrhoeic during treatment, compared to 62.1% of women treated with chemotherapy. The most common adverse events were low-grade hot flushes, oedema, and fatigue among the leuporelin patients; and alopecia, nausea and vomiting, and fatigue among the chemotherapy patients. The overall assessment of tolerability by patients was markedly better during the first six months of treatment in the leuporelin group, but there was no significant difference between the two groups at two years.

The GABG study recruited 771 node-negative premenopausal patients with hormone receptor positive breast cancer (GABG IV-A-93). No significant differences were found between the treatments on local recurrence, distant recurrence, event-free

survival, or death without recurrence. The 5-year event-free survival was 85.0% for women allocated goserelin compared to 81.0% for women allocated chemotherapy. The estimated hazard ratio using an intention-to-treat analysis for goserelin versus CMF was 0.81 (95% CI 0.56 to 1.17, $P = 0.25$).

B. LHRH agonists + anti-oestrogen (experimental arm) versus other treatments

Six trials were identified that addressed the combination of an LHRH-agonist plus an anti-oestrogen versus another treatment (Table 2). Two of these compared an LHRH agonist plus tamoxifen to tamoxifen alone (ZBCSG Trial B; ZIPP). Three trials (ZBCSG Trial B; ZIPP; ECOG 5188 INT-0101) compared an LHRH agonist plus tamoxifen versus an LHRH agonist alone. In two studies, the LHRH agonist plus tamoxifen was compared against chemotherapy (FASG 06; ABCSG 5) and in a final study, the combination of an LHRH agonist plus tamoxifen was compared against an LHRH agonist plus an aromatase inhibitor (ABCSG-12). Most trials used goserelin 3.6 mg depot every 28 days. Goserelin was given for two years in ZBCSG Trial B and ZIPP, for three years in ABCSG 5 and ABCSG-12, and for five years in ECOG 5188 INT-0101. The FASG 06 trial used triptorelin 3.75 mg IM every 28 days for three years. Tamoxifen was given at a dose of 20 mg in all studies except for ZIPP (some patients received 40 mg) and FASG 06 (30 mg). Tamoxifen was used for two years in ZBCSG Trial B and ZIPP, three years in FASG 06 and ABCSG-12, and five years in ECOG 5188 INT-0101 and ABCSG 5. Anastrozole was given at 1 mg daily for three years in ABCSG-12.

i. LHRH agonist and tamoxifen versus tamoxifen

All women in the ZIPP trial were randomised to goserelin versus the same treatment but without goserelin, which included comparisons of women receiving tamoxifen with and without goserelin, and women who did not receive tamoxifen and were randomised to goserelin or not (ZIPP). Among the 2710 women in this trial, 905 women were randomised to receive tamoxifen and 860 received tamoxifen electively. However, the main analyses for the trial have been reported on the basis of goserelin versus no goserelin, not separately in the presence and absence of tamoxifen. After a median follow up of 66 months, patients randomised to goserelin had significantly better recurrence-free survival (73%) and overall survival (86%) than those allocated to no goserelin (68% and 83%, respectively). The hazard ratio was 0.80 (95% CI 0.69 to 0.82, $P = 0.002$) for recurrence-free survival and 0.81 (95% CI 0.67 to 0.99, $P = 0.038$) for overall survival. These overall effects of goserelin versus no goserelin were reported to be similar in women who received tamoxifen, either electively or by randomisation. Subgroup analyses have also been reported on the basis of ER status, with benefits for goserelin compared to no goserelin in recurrence-free survival and overall survival for women in each of the three subgroups (ER-, ER+, or ER unknown). However, these subgroup analyses have less statistical power than the overall results; most are not statistically significant and there is insufficient evidence from the ZIPP trial to assess differences in effect among ER subgroups in the presence of tamoxifen. The proportion of patients who experienced at least one side effect in the ZIPP trial was 65% among patients randomised to tamoxifen and goserelin and 41% among patients allocated to tamoxifen alone. The most common side effects were hot flushes (44% versus 17%) and weight gain (11% versus 7%) (Baum 2006).

As noted above, the goserelin and tamoxifen treatment group was closed early in the Japanese trial, with only 20 patients allocated to this group, because of slow accrual ([ZBCSG Trial B](#)). The results for the comparison of goserelin and tamoxifen versus tamoxifen alone have not been reported.

ii. LHRH agonist and tamoxifen versus LHRH agonist

The ZIPP trial randomised 1800 women to tamoxifen versus no tamoxifen, of whom 901 had been randomised to goserelin ([ZIPP](#)). This led to a randomised comparison of goserelin (444 patients) versus goserelin and tamoxifen (457). However, the effects on event-free survival and overall survival within this comparison have not been reported. Overall, after a median follow up of 66 months, patients randomised to tamoxifen (which included those randomised to no goserelin) had statistically significantly better event-free survival (HR 0.79, 95% CI 0.68 to 0.92) compared to those randomised to no tamoxifen, but the difference on overall survival was not statistically significant (HR 0.83, 95% CI 0.68 to 1.02). As with the goserelin versus tamoxifen randomisation, data have been published on major reported side effects. These were experienced by 56% of patients allocated goserelin alone and by 65% of patients allocated goserelin and tamoxifen. The most common side effect was hot flushes (26% versus 44%), followed by weight gain (4% versus 11%) ([Baum 2006](#)).

The US Intergroup trial recruited women treated with CAF chemotherapy and randomised them to three groups: goserelin and tamoxifen versus goserelin versus no hormonal therapy ([ECOG 5188 INT-0101](#)). This trial recruited premenopausal women who had node-positive breast cancer and were ER+. After a median follow up of 115 months, recurrence-free survival was significantly better for patients randomised to tamoxifen, chemotherapy and goserelin (68%) versus chemotherapy and goserelin alone (60%) (HR 0.73, $P < 0.01$). There was no significant difference for overall survival (76% versus 73%, HR 0.91, $P = 0.21$).

In the Japanese trial, the comparison of goserelin versus goserelin and tamoxifen has not been reported because the goserelin and tamoxifen option was closed early due to slow accrual, when only 20 patients had been allocated to this group ([ZBCSG Trial B](#)).

iii. LHRH agonist and tamoxifen versus chemotherapy

Two trials compared the effects of a combination of an LHRH agonist and tamoxifen versus chemotherapy ([ABCSG 5](#), [FASG 06](#)), recruiting a total of 1367 women to this comparison. One of these trials used CMF in six cycles each taking 28 days ([ABCSG 5](#)), and the other used an anthracycline-containing regimen, FEC50 ([FASG 06](#)). The ABCSG 05 trial used intravenous cyclophosphamide on days 1 and 8 ([ABCSG 5](#)), and goserelin (3.6 mg depot) every 28 days for three years with tamoxifen (20 mg daily) for five years. In the FASG 06 trial, triptorelin (3.75 mg im every month) and tamoxifen (30mg daily) were used for three years.

The largest trial, ABCSG 5, randomised just over a 1000 premenopausal women to goserelin (3.6 mg depot every 28 days) for three years combined with tamoxifen (20 mg daily) for five years versus CMF every 28 days for six cycles ([ABCSG 5](#)). Most of the women were ER+. After a median follow up of 60 months, patients randomised to goserelin and tamoxifen had significantly better recurrence-free survival (81%) than those allocated to chemotherapy (76%) ($P = 0.037$). There was no statistically significant difference in overall survival between the

hormonal therapy group (92%) and the chemotherapy group (90%) ($P = 0.195$). Hot flushes were the main side effect for patients in the goserelin and tamoxifen group: 91% of patients experienced at least one. The side effects of chemotherapy were typical of CMF: nausea (81%), alopecia (55%), and hot flushes (54%).

An anthracycline-containing regimen, rather than CMF, was used as the chemotherapy in the FASG 06 trial ([FASG 06](#)); 333 premenopausal women with hormone responsive breast cancer were randomised to triptorelin (3.75 mg im every month) and tamoxifen (30 mg daily) for three years versus FEC50. After a median follow up of 83 months, recurrence-free survival was 76% in the hormonal therapy group and 72% in the chemotherapy group. This difference was non-significant ($P = 0.13$). There was also no significant difference for overall survival ($P = 0.20$): 91% and 88%, respectively. All women treated with triptorelin became amenorrhoeic during treatment compared to 64% in the chemotherapy group.

iv. LHRH agonist and aromatase inhibitor versus LHRH agonist and tamoxifen

The Austrian Breast Cancer Study Group-12 trial recruited 1803 premenopausal women with stage 1 or stage 2 hormone receptor positive breast cancer ([ABCSG-12](#)), and randomised them using a two-by-two factorial design. The first randomisation (relevant to this review) was to either goserelin plus tamoxifen or goserelin plus anastrozole (all for three years). The second randomisation (not relevant to this review) was to receiving concurrent intravenous zoledronic acid or not. Patients were required to have less than 10 positive axillary lymph nodes and did not receive adjuvant chemotherapy (approximately 5% received neoadjuvant chemotherapy). After median follow up of 48 months, disease-free survival (the primary endpoint) did not differ between patients receiving the two different hormonal treatments (HR 1.10, 95% CI 0.78 to 2.53, $P = 0.59$). The hazard ratio for recurrence-free survival was 1.11 (95% CI 0.80 to 1.56, $P = 0.53$) and for overall survival was 1.80 (95% CI 0.95 to 3.38, $P = 0.70$). The number of events in each arm was small (72 versus 65 disease-free survival events, 27 versus 15 deaths). Women receiving anastrozole experienced significantly more arthralgia, bone pain, and morning stiffness. More women receiving tamoxifen experienced thrombosis.

C. LHRH agonists + chemotherapy (experimental arm) versus other treatments

Five trials provided six comparisons between the combination of an LHRH agonist and chemotherapy to another treatment ([Table 3](#)). One of these addressed the comparison of LHRH agonists + chemotherapy versus LHRH agonists alone ([IBCSG VIII](#)). Five trials compared a combination of an LHRH agonist and chemotherapy versus chemotherapy alone ([ECOG 5188 INT-0101](#); [GABG IV-B-93](#); [IBCSG VIII](#); [Pretoria](#); [ZIPP](#)).

i. LHRH agonist and chemotherapy versus LHRH agonist

One trial was identified which compared an LHRH agonist versus chemotherapy followed by an LHRH agonist ([IBCSG VIII](#)). This randomised just over 1000 patients to CMF alone versus CMF followed by goserelin versus goserelin alone. Two thirds of the women in the trial were ER+ (720 of 1111, 68%), 315 (30%) were ER-, and 28 (3%) had unknown ER status. Overall, with a median follow up of 84 months, there were no significant differences between the treatment groups in disease-free survival or overall survival. The five-year disease-free survival was 87% (95% CI 83% to 91%) for

chemotherapy followed by goserelin and 79% (95% CI 75% to 84%) for goserelin alone. The relative risk for chemotherapy followed by goserelin versus goserelin alone was 0.71 (95% CI 0.52 to 0.99, $P = 0.04$). However, as noted above, an interaction was found between treatment and ER status. ER- patients appeared to derive much more benefit from the combination of chemotherapy and goserelin than ER+ patients. Among ER- patients, the disease-free recurrence was 88% (95% CI 82% to 94%) in the chemotherapy and goserelin group compared to 73% (95% CI 64% to 81%) in the goserelin alone group (RR 0.49, 95% CI 0.28 to 0.87, $P = 0.01$). Whereas, among ER+ patients, the disease-free survival was 86% (95% CI 82% to 91%) in the chemotherapy and goserelin group versus 81% (95% CI 76% to 87%) in the goserelin alone group (RR 0.86, 95% CI 0.56 to 1.26, $P = 0.40$).

ii. LHRH agonist and chemotherapy versus chemotherapy

Five eligible studies were identified that assessed the addition of an LHRH agonist to chemotherapy compared to chemotherapy alone (ECOG 5188 INT-0101; GABG IV-B-93; IBCSG VIII; Pretoria; ZIPP). These used a variety of chemotherapy regimens. The Intergroup trial used CAF; the GABG trial used CMF for patients with fewer than four positive lymph nodes, and a combination of CMF and EC for patients with four to nine positive nodes; and the IBCSG VIII and the Pretoria trials used CMF. Chemotherapy in the ZIPP trial was determined locally, with a recommendation for CMF in the trial protocol but with some centres choosing to use FEC instead. In four of the five trials, the LHRH agonist was goserelin (3.6 mg depot every 28 days), lasting five years in the INT-0101 trial, three years in the GABG trial, two years in ZIPP, and eighteen months in the IBCSG trial. Depot buserelin (6.6 mg monthly) was used in the Pretoria trial.

The ZIPP trial is the largest study in this review (ZIPP). After a median follow up of 66 months, the primary analyses of goserelin versus no goserelin (regardless of the presence or absence of chemotherapy) showed that patients randomised to goserelin had significantly better recurrence free survival (73%) and overall survival (86%) than those allocated to no goserelin (68% and 83%, respectively). These correspond to a hazard ratio of 0.80 (95% CI 0.69 to 0.82, $P = 0.002$) for recurrence-free survival and 0.81 (95% CI 0.67 to 0.99, $P = 0.038$) for overall survival. Despite this, data comparing goserelin versus no goserelin in the (non-randomised) subgroup of patients who all received chemotherapy has not been published.

The next largest trial is the US Intergroup trial of CAF chemotherapy followed by a three-way randomisation to goserelin and tamoxifen versus goserelin versus no hormonal therapy (ECOG 5188 INT-0101). This trial recruited 1503 premenopausal women who had node-positive breast cancer and were ER+. After a median follow up of 115 months, there was no statistically significant difference in recurrence-free survival (60% versus 57%, HR 0.93, $P = 0.22$) or overall survival (73% versus 70%, HR 0.88, $P = 0.14$) in patients randomised to the addition of goserelin to chemotherapy and those allocated to chemotherapy alone.

The IBCSG VIII trial randomised just over 1000 patients to CMF alone versus CMF followed by goserelin versus goserelin alone (IBCSG VIII). Two thirds of the women were ER+ (720 of 1111, 68%), 315 (30%) were ER-, and 28 (3%) had unknown ER status. Overall, with a median follow up of 84 months, there were no significant differences between the treatment groups in disease-

free survival or overall survival. The five-year disease-free survival was 82% (95% CI 78% to 86%) for chemotherapy alone, and 87% (95% CI 83% to 91%) for chemotherapy followed by goserelin. In the comparison of the combination of chemotherapy and goserelin versus chemotherapy, the relative risk for disease-free survival was 0.80 (95% CI 0.57 to 1.11, $P = 0.17$). This was similar in both the ER+ and ER- subgroups (RR 0.80, 95% CI 0.54 to 1.19, $P = 0.26$; and RR 0.75, 95% CI 0.40 to 1.39, $P = 0.35$, respectively).

The GABG-IV-B-93 trial was initially restricted to patients who were known to be hormone receptor negative, and 60% of the 776 women in the trial were ER- (GABG IV-B-93). ER+ patients were subsequently included. Median follow up at time of last reporting was 66 months in ER- patients and 48 months in ER+ patients. Amongst all patients, the 5-year recurrence-free survival was 71% for goserelin and 68% for no goserelin (HR 0.92, 0.70 to 1.21, $P = 0.54$). Overall survival was also similar between groups (86% versus 85%, respectively). In the ER- patients, there was again no difference in recurrence-free survival noted (HR 1.01, 0.72 to 1.42, $P = 0.97$) and, in the ER+ patients, there was also no difference in recurrence-free survival (HR for goserelin versus no goserelin 0.77, 0.47 to 1.24, $P = 0.27$).

The Pretoria trial randomised 148 premenopausal women to CMF or CMF followed by depot buserelin (Pretoria). The differences between the treatments on disease-free survival and overall survival were not statistically significant in this relatively small trial, with a disease-free interval of 6.8 years for women in the combination therapy group compared to 6.2 years for women in the chemotherapy alone group.

D. LHRH agonists + tamoxifen + chemotherapy (experimental arm) versus other treatments

Three trials compared the combination of LHRH agonist, tamoxifen and chemotherapy versus chemotherapy alone (ECOG 5188 INT-0101; MAM 01 GOCSI; ZIPP) (Table 4).

Chemotherapy and LHRH agonist and tamoxifen versus chemotherapy

Two studies also included a randomisation in which the combination of goserelin and tamoxifen added to chemotherapy were compared with chemotherapy alone (ECOG 5188 INT-0101; ZIPP). The tamoxifen was for five years in INT-0101 and two years in ZIPP. Furthermore, the MAM 01 trial used a 2 x 2 factorial design to randomise women to CMF versus A-CMF, and goserelin and tamoxifen for two years versus no hormonal therapy (MAM 01 GOCSI).

As described above, the results for the ZIPP trial have not been published separately for women randomised to goserelin plus tamoxifen versus control, neither overall nor in the presence of chemotherapy. Although the results were available for a group of women in ZIPP who received chemotherapy, LHRH agonist and tamoxifen and for another group who received chemotherapy alone, the former included some women who were electively given tamoxifen and the latter included some women who were electively not given this drug (Baum 2006). Thus, the analyses available for the ZIPP trial come, in part, from a non-randomised comparison and are not presented here.

The INT-0101 trial had a 3-arm randomisation for women after CAF chemotherapy to goserelin and tamoxifen versus goserelin

versus no hormonal therapy (ECOG 5188 INT-0101). This trial recruited 1503 premenopausal women who had node-positive breast cancer and were ER+. After a median follow up of 115 months, patients randomised to the addition of goserelin and tamoxifen to chemotherapy appeared to have better recurrence free survival (68%) than those allocated chemotherapy alone (57%) and better overall survival (76% versus 70%). However, the associated hazard ratios and significance tests for this comparison have not been published.

The MAM-01 study included two randomisations for premenopausal women, 79% of whom had ER+ or ER-unknown tumours (MAM 01 GOCSI). The first randomisation was for the use, or not, of doxorubicin before CMF; and the second, of relevance to this review, was of the addition of two years of goserelin and tamoxifen versus chemotherapy alone. The trial was closed early because of slower than anticipated accrual. After a median follow up of 72 months, the estimated probability of being disease free at five years was significantly higher for the chemotherapy, goserelin and tamoxifen group (64%), compared to the chemotherapy alone group (53%), corresponding to a hazard ratio of 0.74 (95% CI 0.56 to 0.99, $P = 0.04$). The interaction between treatment effect and ER status was investigated and was not statistically significant. The estimated 5-year overall survival was 82% for the chemo-hormonal therapy group, and 80% for the women who were allocated to chemotherapy alone (HR 0.84, 95% CI 0.54 to 1.32).

DISCUSSION

This review identified 14 randomised trials relevant to the role of LHRH agonists in the treatment of women with breast cancer, involving a total of over 13,000 premenopausal women with operable breast cancer, the majority of whom were ER+. For most of the treatment comparisons assessed in this review there are too few trials, too few randomised patients, or too little follow up to obtain reliable estimates of the relative effects of different treatment options. Nonetheless, some conclusions about the general direction of the results are possible.

LHRH agonist monotherapy compared with other systemic treatments

Insufficient data have been presented to date for a meta-analysis that would reliably inform a choice between either tamoxifen or goserelin as sole adjuvant therapy. Taken together, these trials point to similar effects for LHRH agonists, compared to chemotherapy for premenopausal women with ER+ tumours, in terms of recurrence-free survival and overall survival. These results largely relate to the use of outdated chemotherapy regimens and it is uncertain how the findings from the trials would relate to the comparison of LHRH agonists with more modern chemotherapy. Additionally, the studies compare LHRH agonists to chemotherapy and not to the combination of chemotherapy and tamoxifen, which is the current standard of care. The trials also demonstrate that hormonal therapy has a more favourable toxicity profile than the forms of chemotherapy assessed.

LHRH agonists plus anti-oestrogens compared with other systemic treatments

Taken together, the trials are suggestive of, but not conclusive for, reduced rates of breast cancer recurrence for premenopausal women who take goserelin combined with tamoxifen as adjuvant

therapy compared to goserelin alone. Longer follow up of patients is needed to estimate any benefits more reliably. There are insufficient data to draw comparisons between goserelin plus tamoxifen versus tamoxifen.

The trials also suggest a reduction in breast cancer recurrence, but not death, with the use of an LHRH agonist plus tamoxifen versus (outdated) chemotherapy. The data comparing LHRH agonists plus tamoxifen versus LHRH agonists plus anastrozole are currently inconclusive given the small number of patients analysed, the short follow-up period, and the highly selected patient cohorts used in the relevant study.

LHRH agonist plus chemotherapy compared with other systemic treatments

The trials suggest no differences in recurrence or overall survival between the use of LHRH agonists alone and LHRH agonists plus chemotherapy. The relevant data only includes a small number of patients from a single study however, and thus definitive results for this comparison remain inconclusive. There is a suggestion of a reduction in recurrence demonstrated for LHRH agonists (without tamoxifen) plus chemotherapy versus chemotherapy alone.

LHRH agonists plus tamoxifen plus chemotherapy compared with other systemic treatments

Taken together, these trials demonstrate reductions in recurrence and death for premenopausal women with ER+ tumours who take LHRH agonists with tamoxifen in addition to chemotherapy versus chemotherapy alone.

Design characteristics of the available randomised trials also influence the ability to draw firm conclusions about the relevant benefits and harms of LHRH agonists and chemotherapy. As described in the Results section, the majority of trials used goserelin as the LHRH agonist of choice. While it is likely that a class effect occurs, it remains unclear if the results can be extrapolated to other LHRH agonists. The optimal duration of these drugs is also unknown. We have identified no direct randomised comparisons of different LHRH agonists or different durations of these drugs. In addition, nearly all of the trials used CMF as the chemotherapy. This has been largely superseded by anthracycline-based regimens (EBCTCG 2005), and by the use of newer agents such as taxanes and trastuzumab. It is uncertain how the findings from the CMF-based trials in this review would relate to the use of LHRH agonists with these more modern regimens.

Further follow up of the women in the included studies, and the findings of ongoing and future trials, will allow an overall estimate of the effects of these different LHRH agonist regimens and comparisons to be calculated from a meta-analysis. This would also be facilitated by the use of individual patient data and many of the trialists are currently collaborating in such projects (EBCTCG 2005; Cuzick 2006; LHRH-Agonists 2007). One of these individual patient data reviews was published in 2007 and focused on women with hormone receptor positive breast cancer (LHRH-Agonists 2007). It included many of the comparisons that are also reported in the present review, and was based on a median follow up of about seven years. The following percentage changes in hazard ratios were reported relating to overall survival and recurrence-free survival (see Description of studies) and analysed by the LHRH-Agonists Early Breast Cancer Overview Group.

LHRH agonist monotherapy versus other systemic therapy

LHRH agonist versus chemotherapy: all deaths -9.4% (95% CI -22.6 to 6.1, $P = 0.22$); recurrence or death 3.0% (95% CI -8.5 to 16.0, $P = 0.63$)

LHRH agonist plus tamoxifen versus other systemic therapy

LHRH agonist and tamoxifen versus tamoxifen: all deaths -13.7% (95% CI -38.1 to 20.3, $P = 0.39$); recurrence or death -13.9% (95% CI -31.8 to 8.7, $P = 0.21$)

LHRH agonist and tamoxifen versus chemotherapy: all deaths -12.8% (95% CI -31.6 to 11.1, $P = 0.27$); Recurrence or death -11.3% (95% CI -25.6 to 5.8, $P = 0.18$)

LHRH agonist plus chemotherapy versus other systemic therapy

Chemotherapy versus chemotherapy and an LHRH agonist: all deaths -11.5% (95% CI -24.8 to 4.2, $P = 0.14$); recurrence or death -11.0% (95% CI -22.0 to 1.5, $P = 0.08$)

LHRH agonist plus tamoxifen plus chemotherapy versus other systemic therapy

Chemotherapy versus chemotherapy and LHRH agonist and tamoxifen: all deaths -19.8% (95% CI -34.6 to -1.7, $P = 0.03$); recurrence or death -23.8% (95% CI -35.9 to -9.4, $P = 0.002$)

Currently, the standard adjuvant endocrine therapy for premenopausal women with hormone receptor positive breast cancer is single agent tamoxifen for five years. The most recent EBCTCG overview showed that five years of tamoxifen, compared to no adjuvant therapy, is associated with a 41% reduction in the annual risk of relapse and a 34% reduction in the annual risk of death among women with ER+ breast cancer. This benefit was shown to be independent of chemotherapy use (EBCTCG 2005). It is important to recognise that none of the trials included in this review contain a control arm of chemotherapy + tamoxifen, the current standard of care. It is this standard of care against which LHRH agonists need to be assessed (that is chemotherapy + tamoxifen versus chemotherapy + tamoxifen + LHRH agonists) to better establish their role in modern practice.

It has not been possible to address some of the other objectives of this Cochrane review because of a lack of available data on, for example, duration of amenorrhoea, rates of restoration of menses, HER-2 status and familial breast cancer. If results become available from the included studies, ongoing trials or future trials, these will be incorporated into updates of this review.

AUTHORS' CONCLUSIONS

Implications for practice

For premenopausal women with ER+ early breast cancer, the inclusion of an LHRH agonist as adjuvant therapy is likely to lead to a reduction in the risk of a recurrence and a delay in death. The current standard of care is single-agent tamoxifen, however, and available trials do not assess the role of LHRH agonists as an integrated addition to or substitute for this paradigm. It therefore remains difficult to assess the role of LHRH agonists in clinical practice. For cases where tamoxifen is inappropriate and the choice lies between an LHRH agonist or chemotherapy, the review does not provide evidence to choose between them on the basis of recurrence-free survival or overall survival for ER+ women. Whether this holds in the context of modern chemotherapy regimens is less certain. However, for ER- women chemotherapy is likely to lead to a reduction in the risk of recurrence and a delay in death compared to an LHRH agonist. There are fewer severe adverse effects amongst women treated with LHRH agonists in comparison to chemotherapy. The LHRH agonist for which there is most evidence is goserelin, given as a 3.6 mg depot subcutaneously every 28 days for two to three years.

Implications for research

The most pressing area of research is assessment of the role for LHRH agonists when added to standard care regimens including modern chemotherapy regimens and tamoxifen. A number of ongoing studies (see below) are examining this issue and will answer the questions of this review with greater certainty. In addition, further trials examining the use of aromatase inhibitors in conjunction with LHRH agonists are warranted, given that aromatase inhibitors have demonstrated a disease-free survival benefit in postmenopausal women when compared to tamoxifen.

The trials included in this review need to continue follow up in order to provide reliable evidence on the long-term outcomes for these different treatment strategies, as is now possible for other adjuvant treatment comparisons (EBCTCG 2005). There is also a need for randomised comparisons of different durations of LHRH agonists (for example two years versus longer). Randomised trials comparing an LHRH agonist with ovarian ablation by surgery or radiotherapy would also help to show whether there are important differences in the methods of ovarian inactivation and the effects of reversible versus irreversible suppression of ovarian function.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ABCSG 5

Methods	Multicentre Austrian trial. Patients were randomised between December 1990 and June 1999.
Participants	1099 premenopausal women were randomised. They had stage I or II disease and had undergone either mastectomy or lumpectomy, with or without radiotherapy. The analysis included 1034 of these 1099 patients. 93% of the patients had ER+ tumours and 90% had PR+ tumours.
Interventions	Patients were randomised to goserelin (3.6mg depot sc every 28 days for 3 years) and tamoxifen (20mg daily for five years) (n=511) versus CMF (cyclophosphamide 600mg/m ² iv d1 and 8, methotrexate 40mg/m ² iv d1 and 8, and 5-flourouracil 600mg/m ² iv d1 and 8) every 28 days for six cycles (n=523).
Outcomes	Primary outcomes: recurrence-free survival and overall survival.
Notes	The published analyses excluded 33 randomised patients who were found to not fulfil the eligibility criteria and 32 randomised patients who lacked basic information. Global quality rating: B1.
Risk of bias	

ABCSG 5 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

ABCSG-12

Methods	Multicentre trial. Patients were randomised between 1999 and 2006.	
Participants	1803 premenopausal women with hormone receptor positive early breast cancer (Stage 1 or 2, T1a and T4d tumours excluded, all patients < 10 axillary lymph nodes).	
Interventions	Patients were randomised to goserelin plus tamoxifen (20mg daily) for three years versus goserelin plus anastrozole (1mg daily) for three years. A second randomisation between intravenous zoledronic acid or not was also included in the study design.	
Outcomes	Primary outcome: disease-free survival. Secondary outcomes: recurrence-free survival and overall survival.	
Notes	Global quality rating: A	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

ECOG 5188 INT-0101

Methods	Multicentre trial. Patients were randomised between 1989 and 1994.	
Participants	1503 premenopausal women with node-positive, hormone receptor positive early breast cancer.	
Interventions	Patients were randomised to CAF (cyclophosphamide 100mg/m ² orally daily for 14 days, doxorubicin 30mg/m ² iv on d1 and d8, 5-fluorouracil 500mg/m ² iv on d1 and d8) every 28 days for six cycles versus CAF followed by goserelin (3.6mg sc every 28 days for five years) versus CAF followed by goserelin with tamoxifen (20mg daily for five years).	
Outcomes	Primary outcomes: Disease-free survival and overall survival.	
Notes	Toxicity data is not presented in detail for each group. Global rating: A	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

FASG 06

Methods	Multicentre French trial. Patients were randomised between 1990 and 1998.
Participants	333 premenopausal women with hormone receptor positive (either ER+ or PR+) tumours and 1, 2 or 3 positive nodes were randomised.
Interventions	Patients were randomised to triptorelin (3.75mg im every month) and tamoxifen (30mg daily) for three years (n=164) versus FEC50 (epirubicin 50mg/m ² iv d1 and 8, cyclophosphamide 500mg/m ² , and 5-fluorouracil 500mg/m ² iv d1 and 8) every 21 days for six cycles (n=169).
Outcomes	Primary outcomes: disease-free survival and overall survival.
Notes	Global quality rating: B1.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

GABG IV-A-93

Methods	Multicentre trial.
Participants	771 pre-menopausal women with hormone receptor positive tumours and no positive nodes were randomised.
Interventions	Patients were randomised to CMF (cyclophosphamide 500mg/m ² d1 and d8, methotrexate 40mg/m ² iv d1 and d8, and 5-fluorouracil 600mg/m ² iv d1 and d8) every 28 days for three cycles (n=378) versus goserelin 3.6mg every 28 days for two years (n=393).
Outcomes	Outcomes: local and distant recurrence and overall survival.
Notes	Global quality rating: A

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

GABG IV-B-93

Methods	Multicentre trial.
Participants	776 premenopausal women were randomised. Initially, patients had to be ER- or PR- but the inclusion criteria were extended to include ER+ or PR+ women with 1-9 positive lymph nodes when the ZEBRA trial closed. 60% of the patients had ER- or PR- tumours.

GABG IV-B-93 (Continued)

Interventions	Patients with 0-3 positive lymph nodes received CMF (cyclophosphamide 500mg/m ² iv d1 and 8, methotrexate 40mg/m ² iv d1 and 8, and 5-flourouracil 600mg/m ² iv d1 and 8) every 28 days for three cycles. Patients with 4-9 positive lymph nodes received EC (epirubicin 90mg/m ² iv d1, cyclophosphamide 600mg/m ² iv d1) every 22 days for four cycles followed by CMF for three cycles. Patients were then randomised to goserelin (3.6mg depot sc every 28 days for 2 years) (n=384) versus control (n=392).	
Outcomes	Outcomes: local and distant recurrence and overall survival.	
Notes	Global quality rating: A.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

IBCSG VIII

Methods	International, multicentre trial. Randomisation was done by contacting a central trials office. Patients were randomised from March 1990 to October 1999.	
Participants	1111 pre- and perimenopausal women were randomised. The main analyses exclude the 46 patients who had been allocated to no adjuvant treatment when that group was closed in April 1992 (a total of 205 patients had been randomised to the trial as a whole at that time) and two patients (one in the CMF group and one in the CMG + goserelin group) in non-compliant institutions. 720 (68%) patients were ER positive, 315 (30%) were ER negative, and 28 (3%) had unknown ER status.	
Interventions	Patients were randomised to CMF (cyclophosphamide 100mg/m ² po on d1-14, methotrexate 40mg/m ² iv d1 and d8, and 5-flourouracil 600mg/m ² iv d1 and d8) every 28 days for six cycles (n=361) versus goserelin (3.6mg sc every 28 days for two years) (n=346) versus CMF then goserelin (for 18 months) (n=358) versus no adjuvant treatment (n=46).	
Outcomes	Primary outcomes: disease-free survival and overall survival. An evaluation of quality of life in the majority of patients has been reported (Bernhard 2007).	
Notes	Global quality rating: A.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

MAM 01 GOCSI

Methods	Multicentre Italian trial with a randomised 2x2 factorial design. Randomisation was done by contacting a central trials office. Patients were randomised between September 1991 and December 1996.	
Participants	466 premenopausal women with node-positive disease. 79% of patients had ER+ or unknown tumours.	

MAM 01 GOCSI (Continued)

Interventions	Patients were randomised to CMF (cyclophosphamide 100mg/m ² on d1-14, methotrexate 40mg/m ² iv d1 and 8, and 5-flourouracil 600mg/m ² iv d1 and 8) every 28 days for six cycles (n=114) versus doxorubicin (75mg/m ²) every 3 weeks for four cycles followed by CMF for six cycles (n=119) versus CMF for six cycles followed by goserelin (3.6mg depot sc every 28 days) and tamoxifen (20mg daily) for two years (n=120) versus doxorubicin for four cycles followed by CMF for six cycles followed by goserelin and tamoxifen for two years (n=113).
Outcomes	Primary outcomes: disease-free survival and overall survival.
Notes	The trial was closed earlier than planned because of slow accrual. Analyses were performed on an intent-to-treat basis. The intended comparisons were (1) doxorubicin followed by CMF versus CMF, and (2) chemotherapy followed by goserelin and tamoxifen versus chemotherapy. Global quality rating: A.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Pretoria

Methods	Randomised trial.
Participants	148 premenopausal women with node positive breast cancer were randomised. Two postmenopausal women were randomised. 145 women were included in the disease free survival and overall survival analyses (excluding one who refused therapy and two who were lost to follow up).
Interventions	Patients were randomised to CMF (cyclophosphamide 100mg/m ² orally on d1-14, methotrexate 40mg/m ² iv d1 and d8, and 5-flourouracil 600mg/m ² iv d1 and d8) every 28 days for 6 cycles (n=75) or CMF and depo-buserelin (6.6mg implants monthly) (n=72).
Outcomes	Primary outcomes: disease-free survival and overall survival.
Notes	Global quality rating: not assigned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Soreide 2002

Methods	Multicentre trial carried out in 41 hospitals in Norway. Randomisation was done by contacting a central trials office. Patients were randomised between January 1989 and July 1994.
Participants	320 women under 50 years of age were randomised. Women who were known to be ER- were excluded. 241 (75%) women were ER+.
Interventions	Women had undergone either mastectomy (n=255) or breast conservation (n=64). 140 women received radiotherapy and 235 received peri-operative chemotherapy in accordance with local practice. Infor-

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Soreide 2002 (Continued)

mation on surgery was missing for one woman and information on peri-operative chemotherapy was missing for one woman. The peri-operative chemotherapy was vincristin 1mg iv, cyclophosphamide 400mg iv and 5-flourouracil 500mg iv on d0 followed by vincristin 1mg iv, methotrexate 50mg iv and 5-flourouracil 500mg iv on d7. Women were randomised to tamoxifen (20mg daily) for two years (n=161) versus goserelin (3.6mg sc every 28 days) for two years (n=159).

Outcomes	Primary outcome: recurrence. Other outcomes: mortality.
Notes	Global quality rating: B1.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

TABLE

Methods	Multicentre trial carried out in 71 centres in Germany and the Ukraine. Patients were randomised between 1995 and 1999.
Participants	589 pre- or perimenopausal women with node positive breast cancer, and ER+ or unknown hormone receptor status. Eligibility criteria were amended in March 1998 to include only ER+ women. Interim analysis available for 227 patients.
Interventions	Women had mastectomy (n=130) or lumpectomy (n=109). 9 women had adjuvant radiotherapy. Patients were randomised to CMF (cyclophosphamide 100mg/m ² orally d1-14, methotrexate 40mg/m ² iv d1 and d8, and 5-flourouracil 600mg/m ² iv d1 and d8) every 28 days for six cycles (n=117) versus leuprorelin acetate 11.5mg every 3 months for two years (n=110).
Outcomes	Primary outcome: recurrence-free survival.
Notes	Global quality rating: A.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

ZBCSG Trial B

Methods	Multicentre trial carried out in Japan. Patients were randomised between March 1994 and July 1998.
Participants	209 premenopausal ER+ women were randomised, but two are not included in the published analyses. 20 patients were allocated to the combination of goserelin and tamoxifen before that group was closed in June 1995.
Interventions	Patients were randomised to tamoxifen (20mg daily) for two years (n=92) versus goserelin (3.6mg sc) every 28 days for two years (n=95) versus tamoxifen and goserelin (n=20).

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ZBCSG Trial B (Continued)

Outcomes	Primary outcome: recurrence-free survival and overall survival.
Notes	Initial accrual target was 1500 patients among the three treatment groups. This was revised to 1000 patients in two treatment groups in June 1995. Entry to the trial was closed in Jly 1998 because of slow accrual. Global quality rating: not assigned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

ZEBRA

Methods	International trial carried out in 102 centres in 15 countries. Randomisation was done by contacting a central trials office. Patients were randomised from October 1990 to December 1996.
Participants	1640 pre- or perimenopausal women who were under 51 years of age with node-positive, stage II, operable disease were randomised. Data were reported for 1614 patients, having excluded 20 patients allocated to goserelin and 6 patients allocated to CMF for "major protocol violations", most of whom (10 versus 3) were postmenopausal at baseline. 1189 (73.7%) patients were ER positive, 304 (18.8%) were ER negative, and 121 (7.5%) had unknown ER status.
Interventions	Women had undergone either mastectomy (n=857, of whom 374 received radiotherapy) or lumpectomy (n=757, of whom 734 received radiotherapy). Patients were randomised to CMF (cyclophosphamide 500mg/m ² iv d1 and d8, or 100mg/m ² orally on d1-14, methotrexate 40mg/m ² iv d1 and 8, and 5-fluorouracil 600mg/m ² iv d1 and 8) every 28 days for six cycles (n=817 analysed) versus goserelin (3.6mg depot sc every 28 days) for two years (n=797 analysed).
Outcomes	Primary outcomes: disease-free survival and overall survival. A quality of life substudy was done in 86 centres, including 514 patients allocated goserelin and 496 patients allocated chemotherapy (de Haes 2003).
Notes	Global quality rating: A.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

ZIPPP

Methods	International trial with a randomised 2x2 factorial design. Randomisation was done by contacting a trials office. Patients were randomised between August 1987 and March 1999.
Participants	2710 women who were under 50 or premenopausal at randomisation, with operable stage I or II breast cancer. ER status did not need to be known. Initial treatment (surgery, radiotherapy, chemotherapy) was planned prior to randomisation according to local policies. Whether to randomise to or give tamoxifen electively was predefined by local centres. 43% of patients received chemotherapy and 56% were node negative.

ZIPP (Continued)

Interventions	Patients were randomised to control (n=1356) or goserelin (3.6mg every 28 days) for two years (n=1354). In addition, 1800 patients were also randomised to tamoxifen (20mg or 40mg daily, orally) for two years (control n=899; tamoxifen n=901), 860 patients were given tamoxifen electively, and an elective decision was made not to give tamoxifen to 50 patients.
Outcomes	Primary outcome: Recurrence-free survival. Side effects have been reported in detail (Baum 2006).
Notes	International collaboration between four trial groups: the British Cancer Research Campaign Breast Cancer Trials Group (1191 patients), the Stockholm Breast Cancer Trials Group (926 patients), the South East Sweden Breast Cancer Group (211 patients) and the Italian GIVIO collaborative group (382 patients). Each of the four groups ran similar trials, with the intention of combining them in the ZIPP meta-analysis. Analyses were performed on an intent to treat basis. Global quality rating: A.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
ABCTCG study	Women in the ovarian ablation or suppression group received either ovarian ablation by surgery or irradiation, or ovarian suppression with LHRH agonists. It was not possible to separate the results for women allocated to this LHRH agonist from those allocated to surgery or irradiation.
Arriagada 2005	Women in the ovarian ablation or suppression group received either ovarian ablation by surgery or irradiation, or ovarian suppression with triptorelin. It was not possible to separate the results for women allocated to this LHRH agonist from those allocated to surgery or irradiation.
Grocta 02	Women in the ovarian ablation or suppression group received either ovarian ablation by surgery or irradiation, or ovarian suppression with goserelin. It was not possible to separate the results for women allocated to this LHRH agonist from those allocated to surgery or irradiation.
INT 0142	Women in the ovarian ablation or suppression group received either ovarian ablation by surgery or irradiation, or ovarian suppression with an LHRH agonist. It was not possible to separate the results for women allocated to LHRH agonists from those allocated to surgery or irradiation.

Characteristics of ongoing studies [ordered by study ID]

IBCSG TEXT

Trial name or title	IBCSG TEXT
Methods	
Participants	Premenopausal women with early breast cancer.
Interventions	Patients are randomised to triptoreline + tamoxifen for 5 years or triptoreline + exemestane for 5 years.

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IBCSG TEXT (Continued)

Outcomes	Primary outcome measures: disease-free survival Secondary outcome measures: overall survival, systemic disease-free survival, quality of life, incidence of second (nonbreast) malignancies, late side effects of early menopause, causes of death without recurrence, sites of first recurrence [Designated as safety issue: No]
Starting date	August 2003
Contact information	
Notes	

PERCHE

Trial name or title	IBCSG PERCHE
Methods	
Participants	Premenopausal women with early breast cancer.
Interventions	Patients are randomised to chemotherapy and LHRH agonist and tamoxifen or exemestane versus LHRH agonist and tamoxifen or exemestane.
Outcomes	Primary outcome measures: relapse (i.e., local, regional, or distant), contralateral breast cancer, second (nonbreast) primary tumor, death Secondary outcome measures: overall survival
Starting date	August 2003
Contact information	
Notes	Completed recruitment

SOFT

Trial name or title	IBCSG SOFT
Methods	
Participants	Premenopausal women who retain menses after chemotherapy for early breast cancer.
Interventions	Patients are randomised to tamoxifen versus tamoxifen and ovarian suppression (by triptorelin or ovarian ablation by surgery or radiotherapy) versus ovarian suppression (by triptorelin or ovarian ablation by surgery or radiotherapy) and exemestane.
Outcomes	Primary outcome measures: disease-free survival at 5 years Secondary outcome measures: overall survival at 5 years, systemic disease-free survival at 5 years, quality of life as measured by presence of menopausal symptoms (e.g., hot flushes) and/or loss of sexual interest at 0, 6, 12, 18, 24, 36, 48, 60, and 72 months from randomisation
Starting date	August 2003

SOFT (Continued)

Contact information

Notes

UKCCR

Trial name or title UKCCR

Methods

Participants Premenopausal women with early breast cancer.

Interventions Patients are randomised to tamoxifen versus chemotherapy then tamoxifen versus ovarian suppression and tamoxifen.

Outcomes

Starting date

Contact information

Notes

DATA AND ANALYSES
Comparison 1. LHRH versus ovarian ablation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Recurrence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. LHRH versus tamoxifen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Recurrence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. LHRH versus tamoxifen + LHRH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Recurrence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. LHRH + tamoxifen versus tamoxifen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Recurrence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. LHRH plus tamoxifen versus LHRH plus aromatase inhibitor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Recurrence	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. LHRH versus chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Recurrence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 7. LHRH + tamoxifen versus chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Recurrence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 8. LHRH versus chemotherapy then LHRH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Recurrence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 9. Chemotherapy versus chemotherapy then LHRH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Recurrence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 10. Chemotherapy versus chemotherapy then LHRH + tamoxifen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Recurrence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

ADDITIONAL TABLES

Table 1. Studies comparing LHRH-a monotherapy versus another treatment

Comparison	LHRH-a vs Tamoxifen	LHRH-a vs chemotherapy
Study		
Soreide 2002	X	
ZBCSG Trial B	X	
ZIPP	X	
GABG IV-A-93		X
IBCSG VIII		X
TABLE		X
ZEBRA		X

Table 2. Studies comparing LHRH-a + Tamoxifen versus another treatment

Comparison Study	LHRH-a/Tamoxifen vs Tamoxifen	LHRH-a/Tamoxifen vs LHRH-a	LHRH-a/Tamoxifen vs chemotherapy	LHRH-a/Aromatase Inhibitor vs LHRH-a/Tamoxifen
ZBCSG Trial B	X	X		
ZIP	X	X		
ECOG 5188 INT-0101		X		
ABCSG 5			X (CMF)	
FASG 06			X (Anthra.)	
ABCSG-12				X

Table 3. Studies comparing LHRH-a + Chemotherapy vs another treatment

Comparison Study	LHRH-a/Chemotherapy vs LHRH-a	LHRH-a/chemotherapy vs Chemotherapy
IBCSG VIII	X	X
ECOG 5188 INT-0101		X
ZIP		X
GABG IV-B-93		X
Pretoria		X

Table 4. Studies comparing LHRH-a + Chemotherapy + Tamoxifen vs another treatment

Comparison Study	LHRH-a/Tamoxifen/Chemotherapy vs Chemotherapy
ECOG 5188 INT-0101	X
ZIP	X
MAM 01 GOCSI	X

WHAT'S NEW

Date	Event	Description
15 August 2018	Review declared as stable	Most treatment comparisons in this review have been extensively covered by an individual participant data analysis (Cuzick et al 2007, Lancet, 369: 1711-23). Therefore the scope of this review topic will be refined to reflect current practice by assessing any type of ovarian suppression with adjuvant therapy in premenopausal women.

HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 4, 2008

Date	Event	Description
5 August 2009	New search has been performed	Review update Issue 4, 2009
5 August 2009	New citation required but conclusions have not changed	Review has new lead author and has been significantly rewritten

CONTRIBUTIONS OF AUTHORS

RS designed the review and wrote the original protocol. All other authors commented on the design and content of the protocol, and the conduct of the review. SG wrote the current version of the review and approved the final review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- National Breast Cancer Centre, Australia.

External sources

- National Collaborating Centre for Cancer, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The specific objectives outlined in this review address a wider range of comparisons than those in the initial protocol (or previous versions of this review). The decision to include the comparisons listed in this version of the review was made on the basis that the general objective was to assess the role of LHRH agonists in the adjuvant therapy of premenopausal women with breast cancer in general, and not specifically in certain combinations or compared with certain therapies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Premenopause; Antineoplastic Agents, Hormonal [*therapeutic use]; Breast Neoplasms [*drug therapy] [pathology]; Chemotherapy, Adjuvant; Gonadotropin-Releasing Hormone [*agonists]; Goserelin [therapeutic use]; Ovariectomy; Randomized Controlled Trials as Topic; Survival Analysis; Tamoxifen [therapeutic use]

MeSH check words

Female; Humans