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Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen (Review)

Romero SAD, Young K, Hickey M, Su HI

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[Intervention Review]

Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen

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ABSTRACT

Background

Adjuvant tamoxifen reduces the risk of breast cancer recurrence in women with oestrogen receptor-positive breast cancer. Tamoxifen also increases the risk of postmenopausal bleeding, endometrial polyps, hyperplasia, and endometrial cancer. The levonorgestrel-releasing intrauterine system (LNG-IUS) causes profound endometrial suppression. This systematic review considered the evidence that the LNG-IUS prevents the development of endometrial pathology in women taking tamoxifen as adjuvant endocrine therapy for breast cancer.

Objectives

To determine the effectiveness and safety of the levonorgestrel intrauterine system (LNG-IUS) in pre- and postmenopausal women taking adjuvant tamoxifen following breast cancer for the outcomes of endometrial and uterine pathology including abnormal vaginal bleeding or spotting, and secondary breast cancer events.

Search methods

We searched the following databases on 29 June 2020; The Cochrane Gynaecology and Fertility Group specialised register, Cochrane Central Register of Controlled Trials, MEDLINE, Embase, PsycINFO and Cumulative Index to Nursing and Allied Health Literature. We searched the Cochrane Breast Cancer Group specialised register on 4 March 2020. We also searched two trials registers, checked references for relevant trials and contacted study authors and experts in the field to identify additional studies.

Selection criteria

We included randomised controlled trials (RCTs) of women with breast cancer on adjuvant tamoxifen that compared the effectiveness of the LNG-IUS with endometrial surveillance versus endometrial surveillance alone on the incidence of endometrial pathology.

Data collection and analysis

We used standard methodological procedures recommended by Cochrane. The primary outcome measure was endometrial pathology (including polyps, endometrial hyperplasia, or endometrial cancer), diagnosed at hysteroscopy or endometrial biopsy. Secondary outcome measures included fibroids, abnormal vaginal bleeding or spotting, breast cancer recurrence, and breast cancer-related deaths. We rated the overall certainty of evidence using GRADE methods.

Main results

We included four RCTs (543 women analysed) in this review. We judged the certainty of the evidence to be moderate for all of the outcomes, due to imprecision (i.e. limited sample sizes and low event rates). In the included studies, the active treatment arm was the 20 µg/day LNG-IUS plus endometrial surveillance; the control arm was endometrial surveillance alone.

In tamoxifen users, the LNG-IUS probably reduces the incidence of endometrial polyps compared to the control group over both a 12-month period (Peto odds ratio (OR) 0.22, 95% confidence interval (CI) 0.08 to 0.64, I^2 = 0%; 2 RCTs, n = 212; moderate-certainty evidence) and over a long-term follow-up period (24 to 60 months) (Peto OR 0.22, 95% CI 0.13 to 0.39; I^2 = 0%; 4 RCTs, n = 417; moderate-certainty evidence). For long-term follow-up, this suggests that if the incidence of endometrial polyps following endometrial surveillance alone is assumed to be 23.5%, the incidence following LNG-IUS with endometrial surveillance would be between 3.8% and 10.7%.

The LNG-IUS probably slightly reduces the incidence of endometrial hyperplasia compared with controls over a long-term follow-up period (24 to 60 months) (Peto OR 0.13, 95% CI 0.03 to 0.67; I^2 = 0%; 4 RCTs, n = 417; moderate-certainty evidence). This suggests that if the chance of endometrial hyperplasia following endometrial surveillance alone is assumed to be 2.8%, the chance following LNG-IUS with endometrial surveillance would be between 0.1% and 1.9%. However, it should be noted that there were only six cases of endometrial hyperplasia.

There was insufficient evidence to reach a conclusion regarding the incidence of endometrial cancer in tamoxifen users, as no studies reported cases of endometrial cancer.

At 12 months of follow-up, the LNG-IUS probably increases abnormal vaginal bleeding or spotting compared to the control group (Peto OR 7.26, 95% CI 3.37 to 15.66; I^2 = 0%; 3 RCTs, n = 376; moderate-certainty evidence). This suggests that if the chance of abnormal vaginal bleeding or spotting following endometrial surveillance alone is assumed to be 1.7%, the chance following LNG-IUS with endometrial surveillance would be between 5.6% and 21.5%. By 24 months of follow-up, abnormal vaginal bleeding or spotting occurs less frequently than at 12 months of follow-up, but is still more common in the LNG-IUS group than the control group (Peto OR 2.72, 95% CI 1.04 to 7.10; I^2 = 0%; 2 RCTs, n = 233; moderate-certainty evidence). This suggests that if the chance of abnormal vaginal bleeding or spotting following endometrial surveillance alone is assumed to be 4.2%, the chance following LNG-IUS with endometrial surveillance would be between 4.4% and 23.9%. By 60 months of follow-up, there were no cases of abnormal vaginal bleeding or spotting in either group.

The numbers of events for the following outcomes were low: fibroids (n = 13), breast cancer recurrence (n = 18), and breast cancer-related deaths (n = 16). As a result, there is probably little or no difference in these outcomes between the LNG-IUS treatment group and the control group.

Authors' conclusions

The LNG-IUS probably slightly reduces the incidence of benign endometrial polyps and endometrial hyperplasia in women with breast cancer taking tamoxifen. At 12 and 24 months of follow-up, the LNG-IUS probably increases abnormal vaginal bleeding or spotting among women in the treatment group compared to those in the control. Data were lacking on whether the LNG-IUS prevents endometrial cancer in these women. There is no clear evidence from the available RCTs that the LNG-IUS affects the risk of breast cancer recurrence or breast cancer-related deaths. Larger studies are necessary to assess the effects of the LNG-IUS on the incidence of endometrial cancer, and to determine whether the LNG-IUS might have an impact on the risk of secondary breast cancer events.

PLAIN LANGUAGE SUMMARY

Levonorgestrel intrauterine system (LNG-IUS) for endometrial protection in women with breast cancer taking tamoxifen to prevent recurrence

Review question

Cochrane authors investigated whether the levonorgestrel-releasing intrauterine system (LNG-IUS) can reduce the risk of endometrial polyps, abnormal thickening of the lining of the uterus and endometrial cancer in women taking tamoxifen following breast cancer. The review also investigated whether use of the LNG-IUS influences the risk of abnormal vaginal bleeding or spotting, fibroids, breast cancer recurrence or death in women taking tamoxifen following breast cancer.

Background

Tamoxifen is commonly used by women to reduce the risk of breast cancer recurrence. Tamoxifen can also cause abnormal changes to the lining of the uterus (endometrium), including polyps and cancer. The LNG-IUS is a uterine device that releases the synthetic hormone levonorgestrel into the endometrium and causes marked endometrial suppression. As levonorgestrel is a progestin, and many breast cancers are progesterone-sensitive, it is important to study the safety of the LNG-IUS in breast cancer survivors.

Study characteristics

We included four randomised controlled trials involving 543 women. The studies took place in the UK, Turkey, Egypt and Hong Kong, and the primary outcome in all studies was abnormal changes in the lining of the uterus. Three studies reported on the outcome of fibroids.

Three studies reported on abnormal vaginal bleeding or spotting. Two studies reported on breast cancer recurrence, and three studies reported on breast cancer-related death. The evidence is current to June 2020.

Key results

This review suggests that the LNG-IUS probably slightly reduces the risk of endometrial polyps and endometrial hyperplasia over two to five years in women taking tamoxifen following breast cancer. The evidence suggests that if the incidence of endometrial polyps following endometrial surveillance alone is assumed to be 23.5%, the incidence following LNG-IUS plus endometrial surveillance would be between 3.8% and 10.7%. Evidence also suggests that if 2.8% of women who only had endometrial surveillance developed endometrial hyperplasia, the chance following LNG-IUS plus endometrial surveillance would be between 0.1% and 1.9%.

The LNG-IUS probably increases abnormal vaginal bleeding or spotting. After one year, the evidence suggests that if the incidence of abnormal vaginal bleeding or spotting following endometrial surveillance alone is assumed to be 1.7%, the incidence following LNG-IUS plus endometrial surveillance would be between 5.6% and 21.5%. After two years, if 4.2% of women who only had endometrial surveillance experienced abnormal vaginal bleeding or spotting, between 4.4% and 23.9% of women who had both surveillance and LNG-IUS would be expected to experience this. However by five years of follow-up, no women in either group reported abnormal vaginal bleeding or spotting.

We found insufficient evidence to reach a conclusion regarding the effect on incidence of endometrial cancer (a cancer originating in glandular tissue), fibroids, breast cancer recurrence, or breast cancer-related death.

Certainty of the evidence

We judged the certainty of the evidence to be moderate because the studies only included a limited number of women and there were not many events. Larger studies are necessary to assess the effects of the LNG-IUS on the incidence of endometrial cancer, and the impact of the LNG-IUS on the risk of secondary breast cancer events.

Summary of findings 1. The LNG-IUS with endometrial surveillance compared to endometrial surveillance alone for endometrial protection in women with breast cancer on adjuvant tamoxifen

The LNG-IUS with endometrial surveillance compared to endometrial surveillance alone for endometrial protection in women with breast cancer on adjuvant tamoxifen

Patient or population: women with breast cancer on adjuvant tamoxifen
Setting: hospital, outpatient clinic
Intervention: LNG-IUS with endometrial surveillance
Comparison: endometrial surveillance alone

Outcomes		Illustrated comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Assumed Risk	Corresponding Risk				
		Endometrial surveillance alone	LNG-IUS with endometrial surveillance				
Endometrial polyps follow-up: range 24 months to 60 months		235 per 1000	63 per 1000 (38 to 107)	OR 0.22 (0.13 to 0.39)	417 (4 RCTs)	⊕⊕⊕⊖ MODERATE[a]	—
Endometrial hyperplasia follow-up: range 24 months to 60 months		28 per 1000	4 per 1000 (1 to 19)	OR 0.13 (0.03 to 0.67)	417 (4 RCTs)	⊕⊕⊕⊖ MODERATE[a]	—
Endometrial cancer follow-up: range 24 months to 60 months		0 per 1000	0 per 1000 (0 to 0)	not estimable	154 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a]	—
Fibroids follow-up: range 12 months to 24 months		58 per 1000	29 per 1000 (10 to 82)	OR 0.48 (0.16 to 1.46)	314 (3 RCTs)	⊕⊕⊕⊖ MODERATE[a]	—
Abnormal vaginal bleeding or spotting	follow-up: 12 months	17 per 1000	113 per 1000 (56 to 215)	OR 7.26 (3.37 to 15.66)	376 (3 RCTs)	⊕⊕⊕⊖ MODERATE[a]	—
	follow-up: 24 months	42 per 1000	107 per 1000 (44 to 239)	OR 2.72 (1.04 to 7.10)	233 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a]	—
	follow-up: 60 months	0 per 1000	0 per 1000 (0 to 0)	not estimable	94 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]	—

Breast cancer recurrence follow-up: range 24 months to 60 months	80 per 1000	131 per 1000 (53 to 291)	OR 1.74 (0.64 to 4.74)	154 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a]	—
Breast cancer-related death follow-up: range 12 months to 60 months	69 per 1000	70 per 1000 (26 to 174)	OR 1.02 (0.36 to 2.84)	277 (3 RCTs)	⊕⊕⊕⊖ MODERATE[a]	—

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **LNG-IUS:** levonorgestrel intrauterine system; **OR:** odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level for imprecision due to limited sample size and low event rate.

BACKGROUND

Description of the condition

Breast cancer is the most common cancer in women, affecting up to one in eight women in developed countries (ACS 2020). Most of these cancers express the oestrogen receptor (ER) and progesterone receptor (PR). Adjuvant treatment in most cases includes anti-oestrogen therapy. For most premenopausal and many postmenopausal women, this is with the selective ER modulator tamoxifen. Five-year treatment with tamoxifen is associated with a 50% relative reduction in the annual risk of recurrence during the first four years, and a 33% relative reduction in the annual risk of recurrence during years five to nine among women with ER-positive breast cancer (EBCTCG 2011). Additionally, five-year treatment with tamoxifen is associated with a 33% relative reduction in the annual risk of death among women with ER-positive breast cancer (EBCTCG 2011). Ten-year treatment with tamoxifen is associated with significant reductions in the risk of breast cancer recurrence, breast cancer mortality and overall mortality in women with ER-positive breast cancer (Davies 2013).

Tamoxifen is a selective ER modulator (SERM), which inhibits growth of breast cancer by competitive antagonism at the ER level. However, it has partial agonist effects on the skeletal system, lipid metabolism, the vagina, and the uterus. This oestrogenic effect in the uterus may promote benign and malignant uterine pathology in tamoxifen users, such as uterine fibroids, endometrial hyperplasia, and endometrial polyps, which is a significant clinical problem. These effects appear to be largely confined to postmenopausal women. For example, among postmenopausal women, tamoxifen use has been associated with an increased incidence of between 8 and 36% of endometrial polyps compared to 0 to 10% in non-users (Polin 2008). Tamoxifen use has also been associated with an increased incidence of between 1.3 and 20% of endometrial hyperplasia in postmenopausal women compared to 0 to 10% in postmenopausal women not taking tamoxifen (Polin 2008). Further, tamoxifen use has been shown to be associated with a 1.3 to 7.5 increase in the relative risk of endometrial cancer (Polin 2008). Specifically, among women with breast cancer aged 50 or older, the risk ratio was 4.0 (95% confidence interval 1.7 to 10.9) for those taking tamoxifen compared to those taking placebo (ACOG 2014; Fisher 1998). Premenopausal women do not appear to have an increased risk of endometrial cancer while taking tamoxifen (ACOG 2014; Davies 2013). Despite this adverse endometrial profile for tamoxifen users, the benefits of taking tamoxifen for 5 to 10 years outweigh the risks for most women with breast cancer (ACOG 2014; Davies 2013; NCCN 2020).

Description of the intervention

The levonorgestrel intrauterine system (LNG-IUS) releases 20 µg of levonorgestrel daily from a central core. Systemic concentrations of levonorgestrel are low and most of the progestogen is delivered to the endometrial cavity (Xiao 1990), where it causes profound suppression and decidualisation of the endometrium (i.e., morphological and functional cellular changes to the endometrium in preparation for and during pregnancy) (Philip 2019), and glandular atrophy (Scommegna 1970).

How the intervention might work

Because of its profound anti-proliferative effect, the LNG-IUS is thought to reduce the risk of endometrial hyperplasia and endometrial cancer, and has been shown to be effective in treating established endometrial hyperplasia (Mittermeier 2020). The LNG-IUS has been used in women with breast cancer taking tamoxifen as a way of preventing endometrial proliferation. However, the safety of the LNG-IUS following oestrogen or progesterone receptor-positive breast cancer is unclear (Gizzo 2014). A case control study from Finland suggested that the LNG-IUS is associated with an increased risk for developing breast cancer (Lyytinen 2009). Small observational studies suggest that the LNG-IUS does not adversely impact breast cancer prognosis (Trinh 2008).

Why it is important to do this review

This systematic review evaluated all available data from randomised controlled trials to assess the effectiveness of the LNG-IUS in preventing the development of endometrial pathology (polyps, hyperplasia, and cancer) in pre- and postmenopausal women taking adjuvant tamoxifen following breast cancer. Additionally, it is important to determine the safety of the LNG-IUS in regards to developing fibroids, abnormal vaginal bleeding or spotting and secondary breast cancer events. This is an update of a previously published review (Chin 2009b; Dominick 2015).

OBJECTIVES

To determine the effectiveness and safety of the levonorgestrel intrauterine system (LNG-IUS) in pre- and postmenopausal women taking adjuvant tamoxifen following breast cancer for the outcomes of endometrial and uterine pathology including abnormal vaginal bleeding or spotting, and secondary breast cancer events.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were eligible for inclusion. We excluded quasi-randomised and non-randomised studies.

Types of participants

Pre- and postmenopausal women with breast cancer on adjuvant tamoxifen were eligible for inclusion. We excluded women if they had any of the following conditions: contraindications to the LNG-IUS, evidence of recurrent breast cancer prior to LNG-IUS insertion, or history of malignant disease other than breast cancer.

Types of interventions

We included trials that compared the LNG-IUS combined with endometrial surveillance (experimental condition) versus endometrial surveillance alone (control condition).

Types of outcome measures

Primary outcomes

1. Endometrial polyps

2. Endometrial hyperplasia

3. Endometrial cancer

Secondary outcomes

4. Fibroids

5. Abnormal vaginal bleeding or spotting

6. Breast cancer recurrence

7. Breast cancer-related death

Search methods for identification of studies

Using a search strategy developed in consultation with the Information Specialist for the Cochrane Gynaecology and Fertility Group (CGFG), we searched the following databases for all published and unpublished RCTs that compared the LNG-IUS with endometrial surveillance versus endometrial surveillance alone, without language or date restrictions.

Electronic searches

We searched the following databases:

- the Cochrane Gynaecology and Fertility Specialised Register (CGFG), PROCITE platform (searched 29 June 2020) (Appendix 1);
- the Cochrane Breast Cancer Group Specialised Register (CBCG; searched 4 March 2020) (Appendix 2);
- Cochrane Central Register of Controlled Trials (CENTRAL), via The Cochrane Register of Studies Online (CRSO) web platform (searched 29 June 2020) (Appendix 3);
- MEDLINE, searched from 1946 to 29 June 2020, OVID platform (Appendix 4);
- Embase, searched from 1980 to 29 June 2020, OVID platform (Appendix 5);
- PsycINFO, searched from 1806 to 29 June 2020, OVID platform (Appendix 6);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature), searched from 1961 to 29 June 2020, OVID platform (Appendix 7).

Searching other resources

We searched 'ClinicalTrials.gov', a service of the US National Institutes of Health (www.clinicaltrials.gov), and the World Health Organization International Trials Registry Platform search portal (www.who.int/trialsearch), on 29 June 2020 to identify ongoing and registered trials.

We also searched The Cochrane Database of Abstracts of Reviews of Effects (DARE); The Cochrane Library, (Appendix 8); Web of Science; OpenGrey; LILACS (Latin American and Caribbean Health Science Information database); PubMed (Appendix 9); and Google on 29 June 2020. The search strategies for databases without appendices used similar terms as the CGFG and PubMed search strategies.

We searched references of relevant systematic reviews and RCTs, and contacted experts in the field to obtain any relevant trials and additional data.

Data collection and analysis

Selection of studies

We selected studies in accordance with the described criteria. Three review authors (SADR, KY and HIS) independently, and using a standardised method, assessed eligibility of the studies retrieved from the search, see Figure 1. We resolved any disagreement by consensus.

Figure 1. Study flow diagram

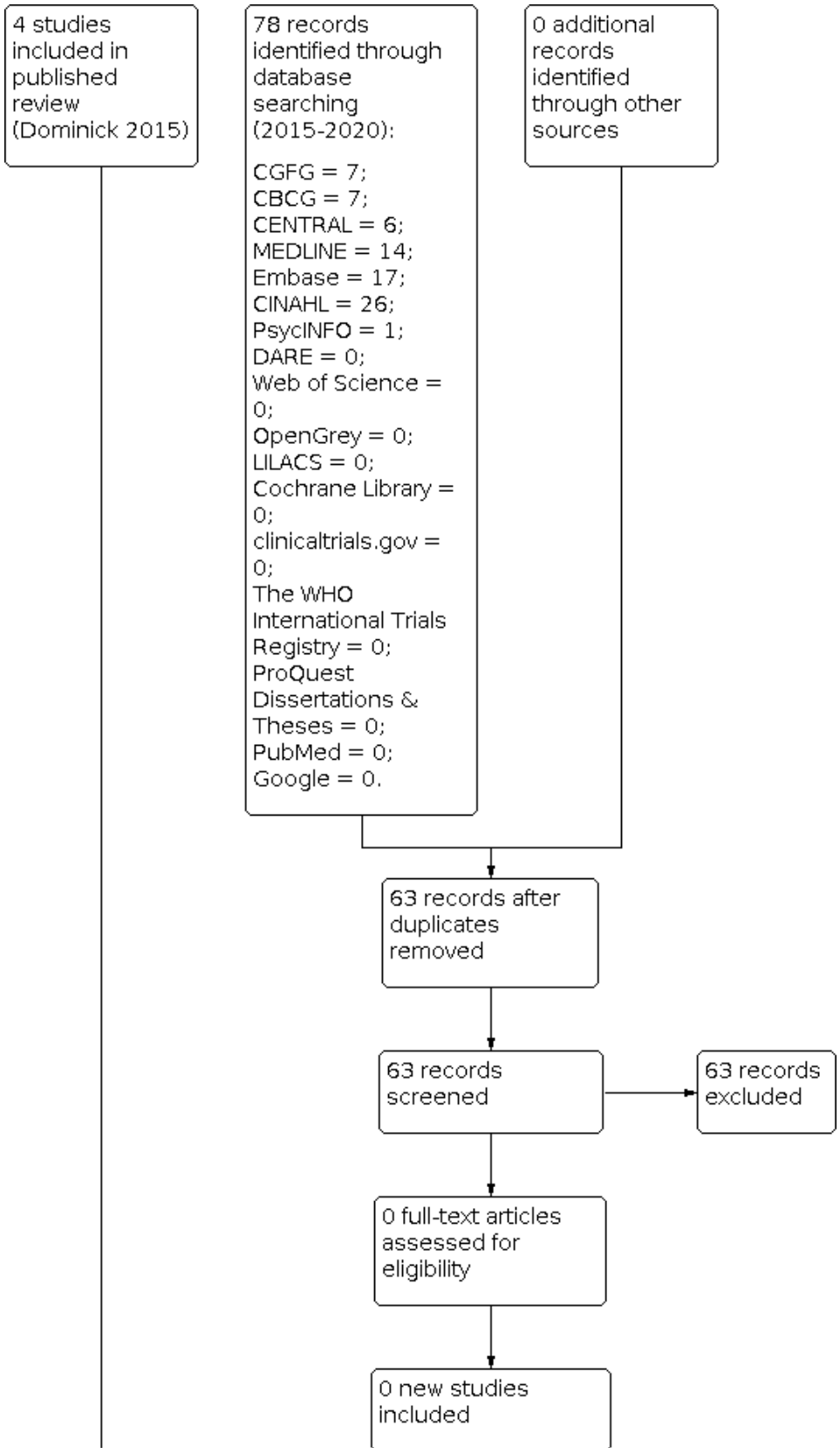
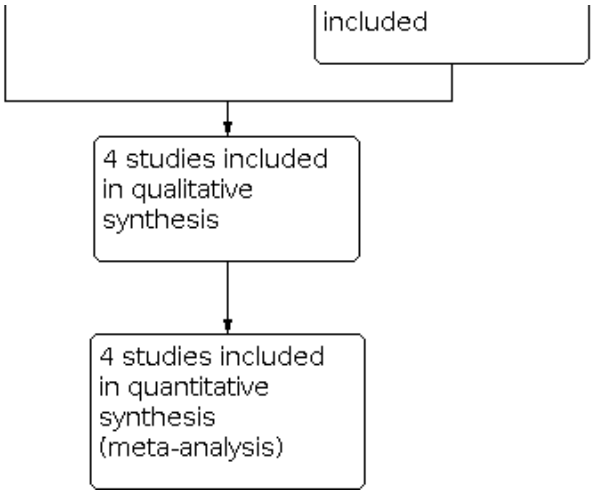


Figure 1. (Continued)



Data extraction and management

Two review authors (SADR and HIS) extracted data independently, using forms designed according to the Cochrane guidelines (Higgins 2011). For each included trial, they collected information regarding the location of the study, methods of the study (as per the 'Risk of bias' assessment checklist), the participants (age range, eligibility criteria), the nature of the interventions, and data relating to the outcomes specified in the section 'Types of outcome measures'.

Assessment of risk of bias in included studies

Two review authors (SADR and HIS) independently assessed the risk of bias for all eligible studies using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). They resolved any discrepancies by discussion. The 'Risk of bias' criteria were as follows.

1. Selection bias (random sequence generation and allocation concealment)

2. Performance bias (blinding of participants and personnel)

3. Detection bias (blinding of outcome assessment)

4. Attrition bias (incomplete outcome data)

5. Reporting bias (selective reporting)

6. Other bias

The review authors assigned each domain a high, low or unclear risk of bias rating. This information is presented in 'Risk of bias' tables for each included study as part of the Characteristics of included studies, displayed in Figure 2 and Figure 3, and described in the text of the review (Risk of bias in included studies).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

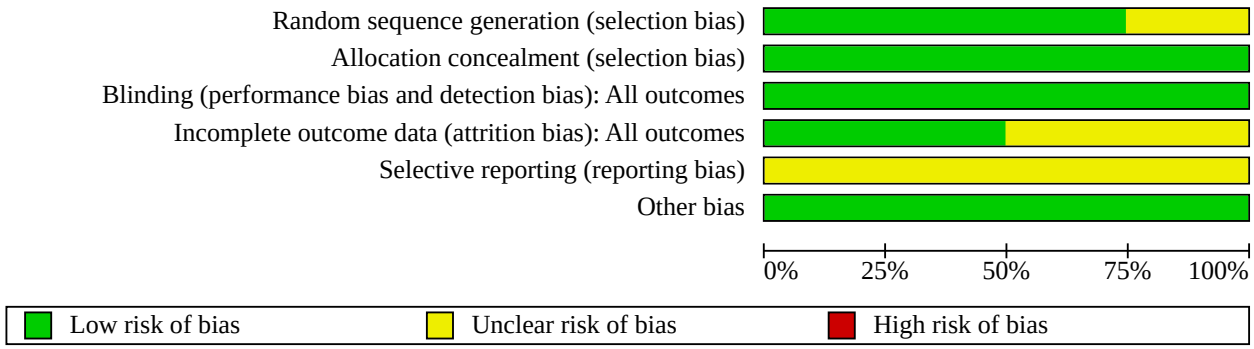
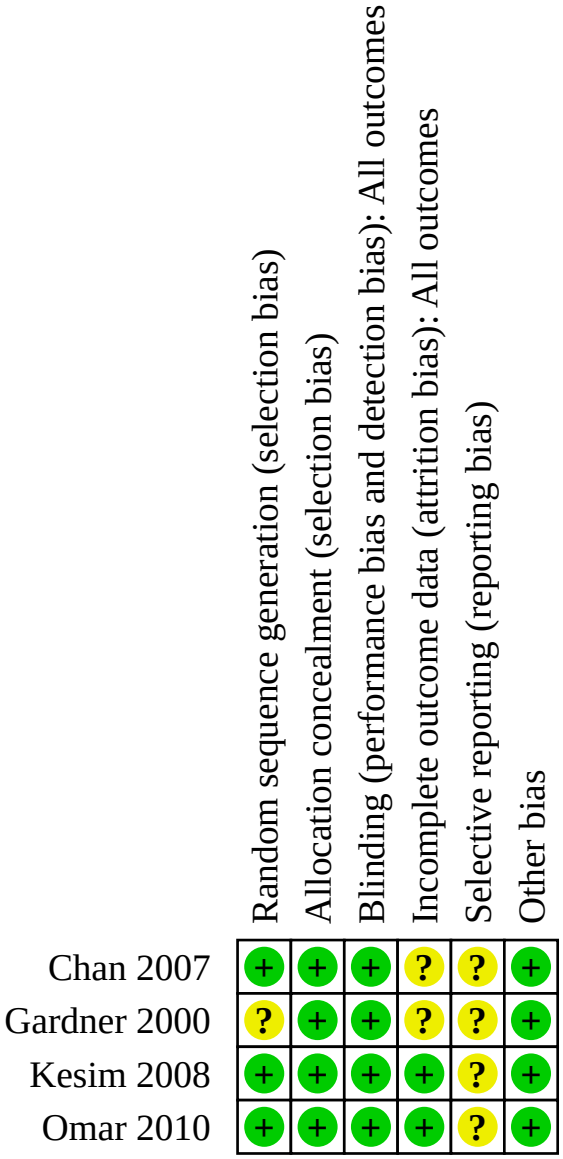


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Measures of treatment effect

For dichotomous data (all the outcome measures in this review), we expressed results for each study as Peto odds ratios (Peto OR) with 95% confidence intervals (CI). We chose the Peto method because it performs well when events are very rare (Higgins 2011). We had no continuous data to consider; however, if we had encountered such data, we would have used mean differences (MDs) or standardised mean differences (SMDs).

Unit of analysis issues

We did not identify any unit of analysis issues due to the nature of the data generated.

Dealing with missing data

We analysed the data on an intention-to-treat basis. If there had been missing data, we would have sought further information directly from the authors of the RCTs, and analysed only the available data if no additional information was forthcoming.

Assessment of heterogeneity

We examined the heterogeneity (variation) between the results of different studies by inspecting the scatter in the data points on a graph and the overlap in their CIs; and, more formally, by considering the I^2 statistic and the Chi^2 test P value. We would have interpreted a low P value (or a large Chi^2 statistic relative to its number of degrees of freedom) as providing evidence of heterogeneity of intervention effects (a variation in effect estimates beyond chance). We interpreted the I^2 statistic, in conjunction with consideration of the magnitude and direction of the effects seen, as follows:

- 0% to 40%, might not be important;
- 30% to 60%, may represent moderate heterogeneity;
- 50% to 90%, may represent substantial heterogeneity;
- 75% to 100%, may represent considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

To minimise the potential impact of reporting biases, the authors conducted a comprehensive search for eligible articles and were alert for potential duplication of data. If we had included 10 or more studies in an analysis, we would have constructed funnel plots to detect reporting biases.

Data synthesis

We pooled the results statistically for each comparison (endometrial polyps, endometrial hyperplasia, endometrial cancer, fibroids, abnormal vaginal bleeding or spotting, breast cancer recurrence and breast cancer-related death). We carried out the meta-analysis using Review Manager 5 (Review Manager 2014). We used the fixed-effect method of synthesising the data for the combined analyses. If we had detected a large degree of heterogeneity, we would have considered using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We did not prespecify any subgroups for analysis. Due to the nature of our findings, we did not require either a post hoc subgroup analysis or an investigation of heterogeneity.

Sensitivity analysis

We planned to conduct the following sensitivity analyses for the primary outcomes:

- restricting eligibility to studies without high risk of bias;
- using a random-effects model; and
- calculating a relative risk rather than Peto odds ratio as the summary effect measure.

Summary of findings and assessment of the certainty of the evidence

We generated a 'Summary of findings' table using GRADEpro GDT. In Summary of findings 1, we have presented our evaluation of the overall certainty of the body of evidence for the review outcomes (endometrial polyps, endometrial hyperplasia, endometrial cancer, fibroids, abnormal vaginal bleeding or spotting, breast cancer recurrence and breast cancer-related death) using GRADE criteria: study limitations (i.e. risk of bias); consistency of effect; imprecision; indirectness and publication bias. We have justified our judgements about the certainty of the evidence (high, moderate or low), documented these and incorporated them into the reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

At the 2015 update:

The electronic search in October 2015 retrieved a total of 315 references: CGFG = 16; CBCG = 8; CENTRAL = 5; DARE = 0; The Cochrane Library = 6; clinicaltrials.gov = 1; The World Health Organisation International Trials Registry = 1; ProQuest Dissertations & Theses = 2; MEDLINE = 54; Embase = 162; CINAHL = 37; Web of Science = 8; PsycINFO = 1; OpenGrey = 0; LILACS = 7; PubMed = 6; and Google = 1. From those, review authors identified six potential studies to be read in full; two of these six studies were already included in the previously published review, with no additional references retrieved from the manual search.

At the 2020 update:

We ran the electronic search between 1 January 2015 to 29 June 2020 and retrieved a total of 78 references. From those titles and abstracts, we did not identify any potential studies. We did not retrieve any additional references from the manual search. See Figure 1 for details of the search, screening and selection process.

Included studies

The searches identified four randomised controlled trials (RCTs) for inclusion in this review (Chan 2007; Gardner 2000; Kesim 2008; Omar 2010). See Characteristics of included studies; Table 1; Table 2; Table 3; Table 4 for detailed information about the included studies.

Study design and setting

The four RCTs took place in Egypt (Omar 2010), Turkey (Kesim 2008), the UK (Gardner 2000), and Hong Kong (Chan 2007). The Gardner 2000 and Chan 2007 trials published long-term follow-up in separate publications (Gardner 2009 and Wong 2013, respectively).

Participants

The trials included 543 pre- and postmenopausal women with breast cancer on adjuvant tamoxifen; 273 women in the treatment groups and 270 women in the control groups.

Interventions

All four trials compared endometrial surveillance plus the LNG-IUS, which releases 20 µg/day of the synthetic progestogen levonorgestrel, to endometrial surveillance alone. The Chan 2007 trial (follow-up: 60 months) compared endometrial surveillance alone versus endometrial surveillance plus the LNG-IUS insertion before the commencement of tamoxifen in pre- and postmenopausal women. The Gardner 2000 trial (follow-up: 48 months) compared endometrial surveillance alone versus endometrial surveillance with insertion of the LNG-IUS in postmenopausal women who had been taking adjuvant tamoxifen treatment for at least one year. The Kesim 2008 trial (follow-up: 36 months) compared endometrial surveillance alone

versus endometrial surveillance with insertion of the LNG-IUS in postmenopausal women who had been taking adjuvant tamoxifen treatment for more than one year. The Omar 2010 trial (follow-up: 24 months) compared endometrial surveillance alone versus endometrial surveillance with insertion of the LNG-IUS before the commencement of tamoxifen in pre- and postmenopausal women who required postoperative adjuvant tamoxifen.

Outcomes

All four trials reported endometrial polyps diagnosed at hysteroscopy with endometrial biopsy (Chan 2007; Gardner 2000; Kesim 2008; Omar 2010).

All four trials reported endometrial hyperplasia diagnosed at hysteroscopy with endometrial biopsy (Chan 2007; Gardner 2000; Kesim 2008; Omar 2010).

Two of the four trials reported endometrial cancer (Chan 2007; Gardner 2000).

Three of the four trials reported fibroids (Chan 2007; Gardner 2000; Omar 2010).

Three of the four trials reported abnormal vaginal bleeding or spotting (Chan 2007; Kesim 2008; Omar 2010).

Two of the four trials reported breast cancer recurrence (Chan 2007; Gardner 2000).

Three of the four trials reported breast cancer-related death (Chan 2007; Gardner 2000; Omar 2010).

Excluded studies

There were no excluded studies.

Risk of bias in included studies

See Figure 2 and Figure 3 for detailed information.

Allocation

Three trials had a low risk of selection bias related to sequence generation, as they used computer-generated random number series for allocation (Chan 2007; Kesim 2008; Omar 2010). One trial did not describe the sequence generation method used, so had an unclear risk of selection bias related to sequence generation (Gardner 2000).

All trials used pre-prepared, serially-numbered sealed envelopes, so had a low risk of selection bias related to allocation concealment (Chan 2007; Gardner 2000; Kesim 2008; Omar 2010).

Blinding

All trials had a low risk of detection and performance bias as the pathologists (i.e. outcome assessors) were blinded (Chan 2007; Gardner 2000; Kesim 2008; Omar 2010). Even though the provider and participant were not blinded, given the nature of this clinical intervention (insertion of the LNG-IUS), the blinding of providers and participants is considered unlikely to influence the outcomes.

Incomplete outcome data

Two trials were at low risk of attrition bias as the majority of randomised participants were included in the final analyses (Kesim 2008; Omar 2010). There were no evidence of differences in baseline data between women who completed and did not complete the study in either of these trials.

The trial by Chan 2007 had an unclear risk of attrition bias. At 12 months of follow-up, 16/129 (12%) of the participants were lost to follow-up or dropped out (seven women in the control group and nine in the treatment group). At 60 months of follow-up, 35/129 (27%) participants were lost to follow-up (17 in the control group and 18 in the treatment group).

The Gardner 2000 trial also had an unclear risk of attrition bias. At 12 months of follow-up, 23/122 (19%) of participants were lost to follow-up or dropped out (six in the control group and 17 in the treatment group). There was no evidence of differences in baseline data between women who completed and did not complete the study; hence the 12-month follow-up data are at low risk of attrition bias. However, the follow-up data at 24, 36 and 48 months are at high risk of attrition bias due to their high losses to follow-up. At 24 months of follow-up, 62/122 (51%) of participants were lost to follow-up or dropped out. At 36 months of follow-up, 83/122 (68%) of participants were lost to follow-up or dropped out. At 48 months of follow-up, 107/122 (88%) of participants were lost to follow-up or dropped out.

Selective reporting

Although all four studies reported our review's primary and secondary outcomes, we rated them all to have an unclear risk of reporting bias (Chan 2007; Gardner 2000; Kesim 2008; Omar 2010). We could not obtain protocols for any of the trials, and the studies were not prospectively registered, so there was no information we could use to verify the study details. Due to the small number of included studies (less than 10), it was not appropriate to construct funnel plots to investigate publication bias.

Other potential sources of bias

We did not identify any other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** The LNG-IUS with endometrial surveillance compared to endometrial surveillance alone for endometrial protection in women with breast cancer on adjuvant tamoxifen

See: Summary of findings 1.

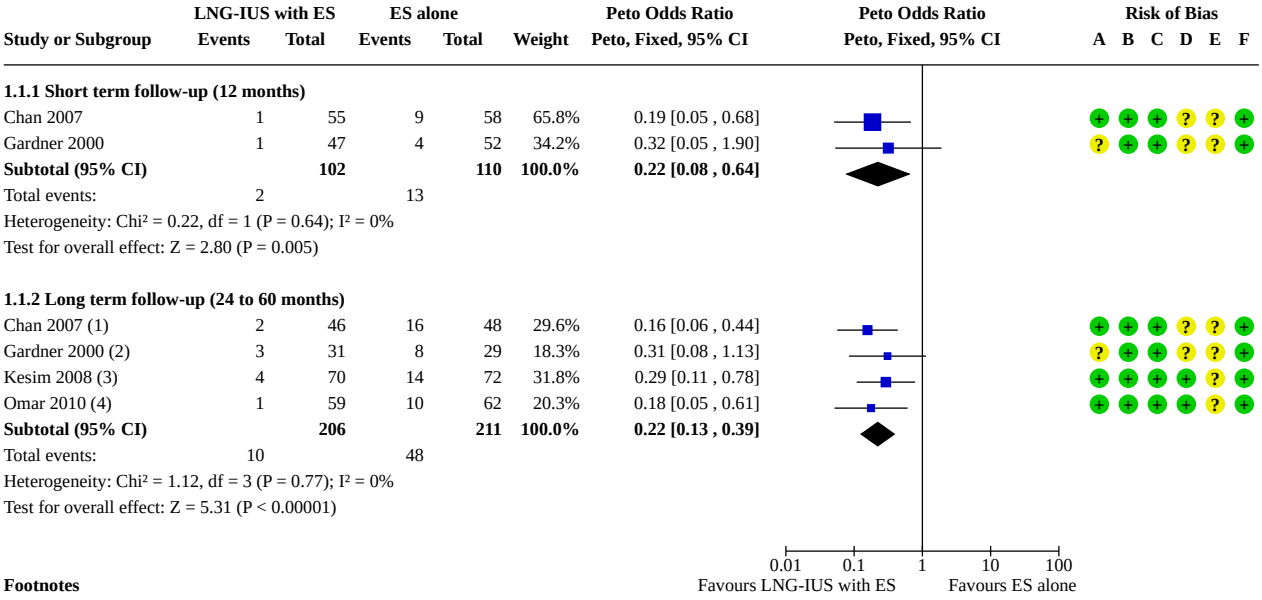
LNG-IUS with endometrial surveillance versus endometrial surveillance alone

Primary outcomes

Endometrial polyps

At short-term follow-up (12 months), we pooled data from two trials (Chan 2007; Gardner 2000). The pooled result suggests that LNG-IUS with endometrial surveillance is probably associated with a slight reduction in the incidence of endometrial polyps compared to endometrial surveillance alone (Peto OR 0.22, 95% CI 0.08 to 0.64; I^2 = 0%; 2 RCTS, n = 212; moderate-certainty evidence; Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 1 LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone, outcome: 1.1 Endometrial polyps.



Footnotes

(1) 60 months follow-up
(2) 24 to 48 months follow-up
(3) 36 months follow-up
(4) 24 months follow-up

Risk of bias legend

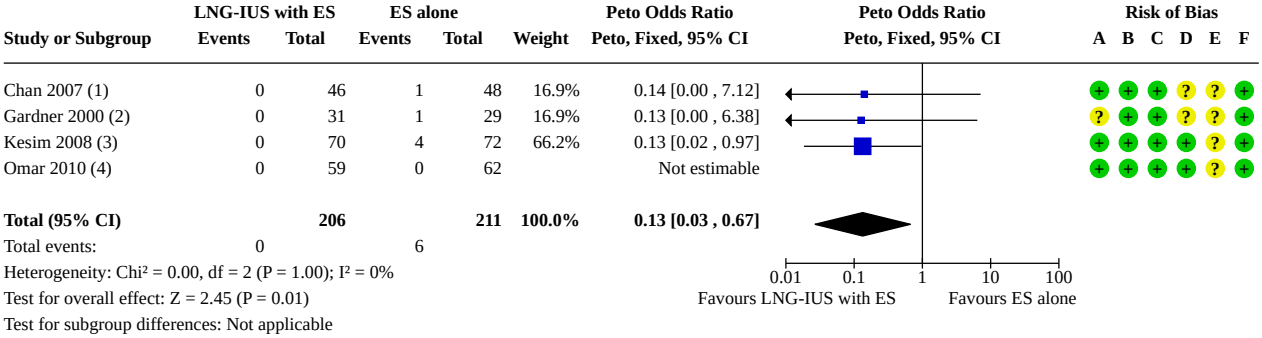
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

At long-term follow-up (24 to 60 months), we pooled data from all four trials (Chan 2007; Gardner 2000; Kesim 2008; Omar 2010). The pooled analysis suggests that LNG-IUS with endometrial surveillance is probably associated with a reduction in the incidence of endometrial polyps compared to endometrial surveillance alone (Peto OR 0.22, 95% CI 0.13 to 0.39; I^2 = 0%; 4 RCTs, n = 417; moderate-certainty evidence; Analysis 1.1; Figure 4). This suggests that if the incidence of endometrial polyps following endometrial surveillance alone is assumed to be 23.5%, the incidence following LNG-IUS with endometrial surveillance would be between 3.8% and 10.7%.

Endometrial hyperplasia

At long-term follow-up (24 to 60 months), the pooled data from all four trials showed only six cases of endometrial hyperplasia in the control group, which suggests that LNG-IUS with endometrial surveillance is probably associated with a slight reduction in the incidence of endometrial hyperplasia compared to endometrial surveillance alone (Peto OR 0.13, 95% CI 0.03 to 0.67; I^2 = 0%; 4 RCTs, n = 417; moderate-certainty evidence; Analysis 1.2; Figure 5). This suggests that if the chance of endometrial hyperplasia following endometrial surveillance alone is assumed to be 2.8%, the chance following LNG-IUS with endometrial surveillance would be between 0.1% and 1.9%.

Figure 5. Forest plot of comparison: 1 LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone, outcome: 1.2 Endometrial hyperplasia.



Footnotes

(1) 60 months follow-up
(2) 24 to 48 months follow-up
(3) 36 months follow-up
(4) 24 months follow-up

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Endometrial cancer

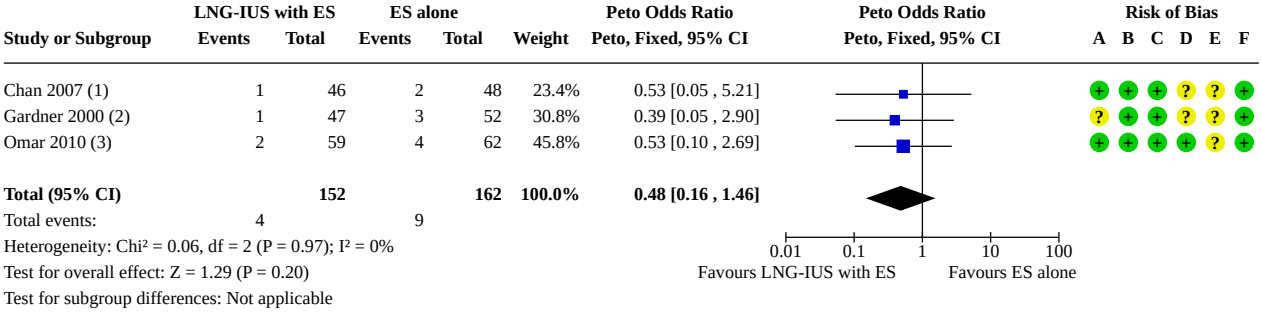
The included studies reported no cases of endometrial cancer. Hence, we could not calculate statistics for the endometrial cancer outcome.

Secondary outcomes

Fibroids

We pooled data from three trials (Chan 2007; Gardner 2000; Omar 2010). The pooled analysis showed that there is probably little or no difference in the incidence of fibroids between LNG-IUS users compared to the control group with endometrial surveillance (Peto OR 0.48, 95% CI 0.16 to 1.46; I^2 = 0%; 3 RCTs, n = 314; moderate-certainty evidence; Analysis 1.3; Figure 6). This suggests that if the chance of fibroids following endometrial surveillance alone is assumed to be 5.8%, the chance following LNG-IUS with endometrial surveillance would be between 1.0% and 8.2%.

Figure 6. Forest plot of comparison: 1 LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone, outcome: 1.4 Fibroids.



Footnotes

(1) 60 months follow-up
(2) 24 to 48 months follow-up
(3) 24 months follow-up

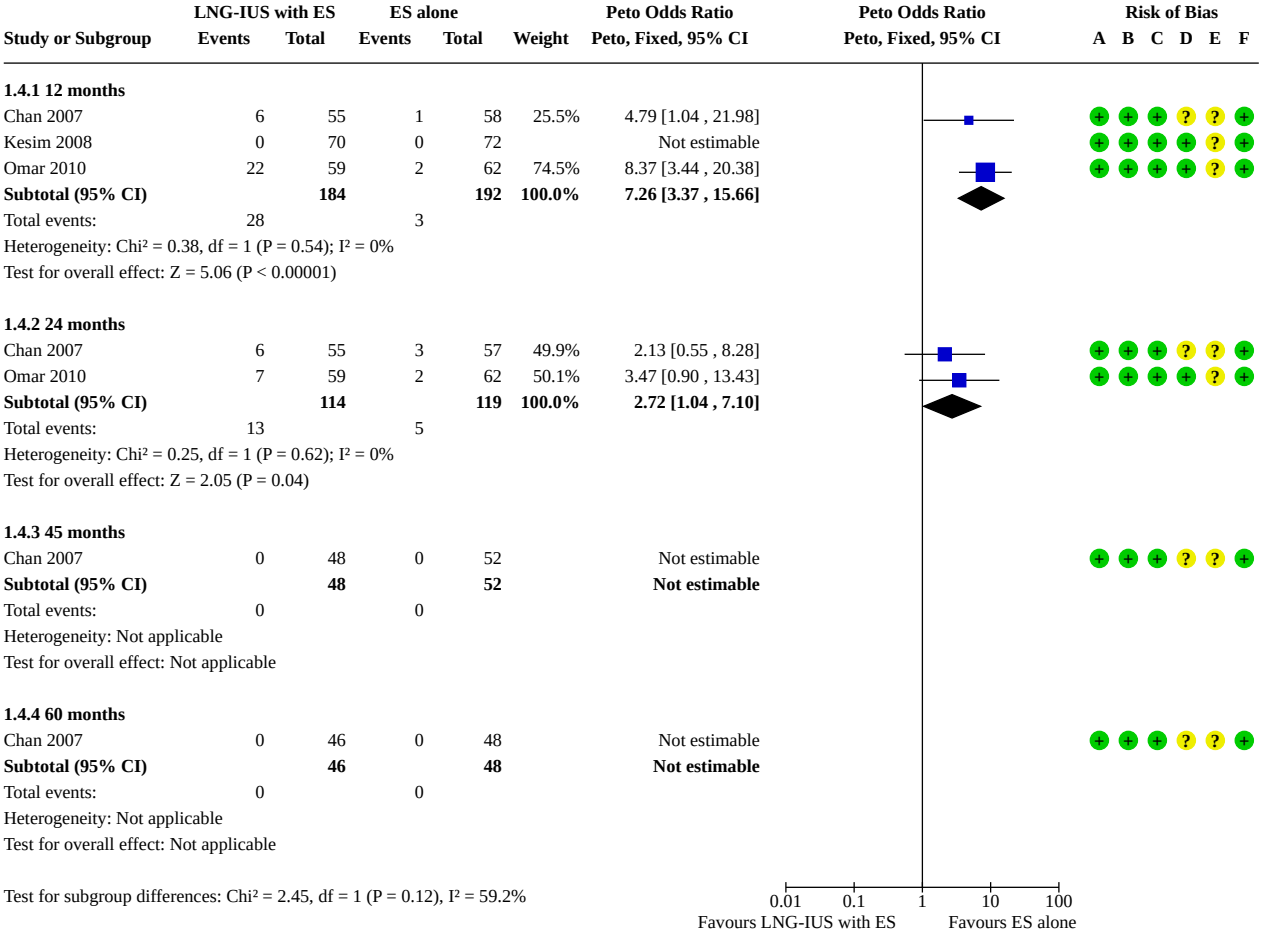
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Abnormal vaginal bleeding or spotting

At 12 months of follow-up, three trials reported on abnormal vaginal bleeding or spotting in the LNG-IUS and control groups (Chan 2007; Kesim 2008; Omar 2010). At 24 months of follow-up, two of these trials reported on abnormal vaginal bleeding or spotting (Chan 2007; Omar 2010). Only the trial by Chan 2007 reported on findings at 45 and 60 months of follow-up. At 12 months of follow-up, LNG-IUS with endometrial surveillance is probably associated with an increase in the incidence of abnormal vaginal bleeding or spotting compared to endometrial surveillance alone (Peto OR 7.26, 95% CI 3.37 to 15.66; I^2 = 0%; 3 RCTs, n = 376; moderate-certainty evidence; Analysis 1.4; Figure 7). This suggests that if the incidence of abnormal vaginal bleeding or spotting following endometrial surveillance alone is assumed to be 1.7%, the incidence following LNG-IUS with endometrial surveillance would be between 5.6% and 21.5%.

Figure 7. Forest plot of comparison: 1 LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone, outcome: 1.5 Abnormal vaginal bleeding or spotting.



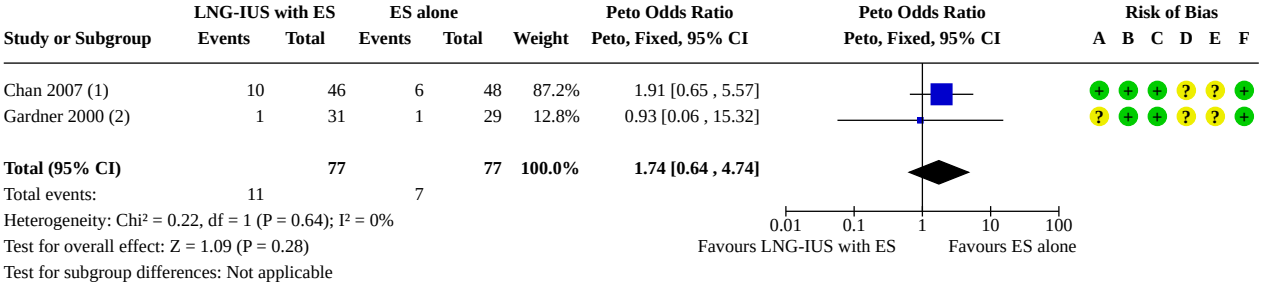
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

At 24 months of follow-up, abnormal vaginal bleeding or spotting was reduced in both groups, but still higher in the LNG-IUS group compared to the control group (Peto OR 2.72, 95% CI 1.04 to 7.10; I^2 = 0%; 2 RCTs, n = 233; moderate-certainty evidence; Analysis 1.4; Figure 7). This suggests that if the chance of abnormal vaginal bleeding or spotting following endometrial surveillance alone is assumed to be 4.2%, the chance following LNG-IUS with endometrial surveillance would be between 4.4% and 23.9%. By 45 and 60 months of follow-up, no cases of abnormal vaginal bleeding or spotting were reported in either group (Analysis 1.4; Figure 7).

Breast cancer recurrence

Pooled data from two trials showed that there is probably little or no difference in breast cancer recurrence between LNG-IUS users compared to the control group with endometrial surveillance (Peto OR 1.74, 95% CI 0.64 to 4.74; I^2 = 0%; 2 RCTs, n = 154; moderate-certainty evidence; Analysis 1.5; Figure 8) (Chan 2007; Gardner 2000). This suggests that if the risk of breast cancer recurrence following endometrial surveillance alone is assumed to be 8.0%, the risk following LNG-IUS with endometrial surveillance would be between 5.3% and 29.1%.

Figure 8. Forest plot of comparison: 1 LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone, outcome: 1.6 Breast cancer recurrence.



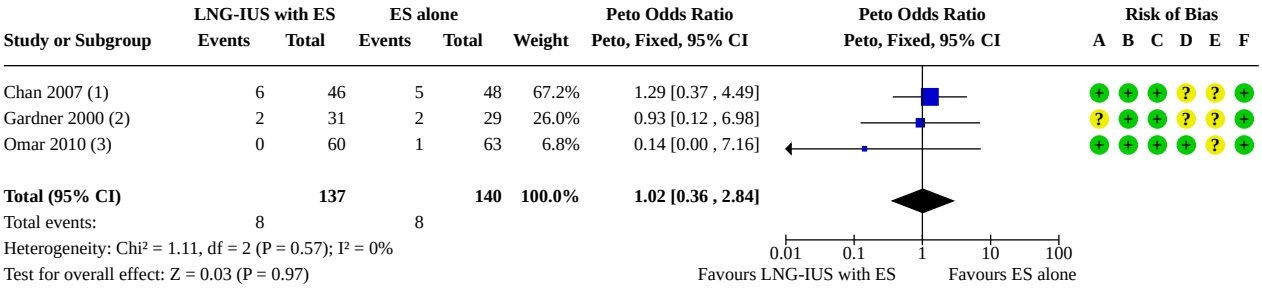
Footnotes
(1) 60 months follow-up
(2) 24 to 48 months follow-up

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Breast cancer-related death

Pooled data from three trials showed that there is probably little or no difference in breast cancer-related deaths in LNG-IUS users compared to the control group with endometrial surveillance (Peto OR 1.02, 95% CI 0.36 to 2.84; I^2 = 0%; 3 RCTs, n = 277; moderate-certainty evidence; Analysis 1.6; Figure 9) (Chan 2007; Gardner 2000; Omar 2010). This suggests that if the risk of breast cancer-related deaths following endometrial surveillance alone is assumed to be 6.9%, the risk following LNG-IUS with endometrial surveillance would be between 2.6% and 17.4%.

Figure 9. Forest plot of comparison: 1 LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone, outcome: 1.7 Breast cancer-related death.



Footnotes
(1) 60 months follow-up
(2) 24 to 48 months follow-up
(3) 12 months follow-up

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Sensitivity analyses

We did not conduct the planned sensitivity analysis by risk of bias, because risk of bias was similar across the included studies.

We conducted the planned sensitivity analyses by statistical model and effect estimate. When switching the pooled estimate from Peto odds ratio to Mantel-Haenszel risk ratio, and from fixed-effect to random-effects models for all outcomes, only the pooled estimate for the endometrial hyperplasia outcome changed. This showed little or no difference in endometrial hyperplasia between the groups (RR fixed-effect 0.19, 95% CI 0.03 to 1.15; 4 RCTs, n = 417).

DISCUSSION

Summary of main results

See Summary of findings 1.

This review included four randomised controlled trials that compared endometrial protection by the 20 µg/day levonorgestrel-releasing intrauterine system (LNG-IUS) plus endometrial surveillance versus endometrial surveillance alone in women with breast cancer on adjuvant tamoxifen. The pooled data from the included studies showed that the LNG-IUS probably reduces the incidence of endometrial polyps over a 12-month period and a long-term follow-up period (24 to 60 months) among women with breast cancer taking tamoxifen. The LNG-IUS probably also slightly reduces the incidence of endometrial hyperplasia over a long-term follow-up period (24 to 60 months). The pooled data showed the LNG-IUS probably increases abnormal vaginal bleeding or spotting compared to the control group at 12 months and 24 months of follow-up. However, there was a gradual reduction of abnormal vaginal bleeding or spotting from 12 to 24 months, and no bleeding or spotting in either group was reported at 45 or 60 months of follow-up. Additionally, there was probably little or no difference in the risk of fibroids (n = 13), breast cancer recurrence (n = 18), and breast cancer-related deaths (n = 16) between the LNG-IUS treatment group and the control group. Since none of the studies reported cases of endometrial cancer, there were insufficient data to show an effect on the incidence of endometrial cancer.

Overall completeness and applicability of evidence

All four included studies used the 'gold standard' of hysteroscopy and endometrial biopsy to diagnose endometrial pathology (ACOG 2015; Chan 2007; Gardner 2000; Kesim 2008; Omar 2010). Endometrial pathology prior to randomisation was excluded by hysteroscopy and endometrial biopsy; any endometrial pathology detected at baseline was treated. Endometrial pathology was the primary end point for all four studies. However, the timing of the primary end point assessment varied by study, ranging from 12 to 60 months.

While the four included studies differed in their participant selection, inclusion criteria, secondary outcomes assessed, and overall study design (see Characteristics of included studies), they provided adequate information to answer the review question. The findings of this review provide evidence that the LNG-IUS prevents endometrial polyps and endometrial hyperplasia in women with breast cancer using tamoxifen. However, the data are insufficient to determine if the LNG-IUS protects or does not protect tamoxifen users from endometrial cancer.

Quality of the evidence

Using the GRADE system, we assessed the certainty of the evidence to be moderate for all study outcomes (i.e. endometrial polyps, endometrial hyperplasia, endometrial cancer, fibroids, abnormal vaginal bleeding or spotting, breast cancer recurrence and breast cancer-related death). For all four studies, we downgraded the evidence by one level for imprecision due to limited sample sizes and low event rates for the study outcomes. Of note, none of the studies were sufficiently powered to address whether the LNG-IUS protects women on tamoxifen against endometrial cancer.

Further, a potential limitation of this review is the inclusion of both pre- and postmenopausal women in two of the included studies (Chan 2007; Omar 2010). This may have underestimated the effect of the LNG-IUS in preventing endometrial pathology in postmenopausal women.

Potential biases in the review process

The authors did not identify any potential biases in the review process. Based on the comprehensive literature search and included search terms, we are confident that all relevant studies were identified and included in this review.

Agreements and disagreements with other studies or reviews

We did not identify any other reviews.

AUTHORS' CONCLUSIONS

Implications for practice

The levonorgestrel-releasing intrauterine system (LNG-IUS) probably reduces the risk of benign polyps in tamoxifen users. This is clinically significant since polyps may be symptomatic; when identified they require removal, which is likely to include a general anaesthetic and hysteroscopy. The LNG-IUS probably slightly reduces the incidence of endometrial hyperplasia in women on tamoxifen following breast cancer. There is no evidence that the LNG-IUS reduces or does not reduce the risk of endometrial cancer in women on tamoxifen following breast cancer, as there were no cases in any of the included studies. The LNG-IUS probably increases abnormal vaginal bleeding or spotting for up to 24 months in tamoxifen users, which may increase the need for invasive diagnostic procedures to exclude hyperplasia and malignancy. The safety of the LNG-IUS in women with breast cancer in terms of prognosis, breast cancer recurrence, or breast cancer-related deaths is uncertain.

Implications for research

Studies powered to detect changes in the incidence of endometrial cancer in women with breast cancer using tamoxifen are needed. Since endometrial cancer risks with tamoxifen are limited to postmenopausal women, future studies should focus on this population. Larger studies are also necessary to assess whether the LNG-IUS may impact prognosis after breast cancer or secondary breast cancer events. Since aromatase inhibitors have been shown to be more effective than tamoxifen in preventing recurrence of oestrogen receptor-positive breast cancer, prescribing patterns of tamoxifen as adjuvant endocrine therapy have changed in the past decade (EBCTCG 2015; NCCN 2020). As a result, endometrial

stimulation with tamoxifen and the need for LNG-IUS to lower this risk may be less clinically significant.

ACKNOWLEDGEMENTS

We thank the Cochrane Gynaecology and Fertility Group for providing us with the search strategy, support, and advice for this review. In particular, we wish to acknowledge Helen Nagels, Marian Showell and Ava Tan-Koay for their contributions to this review.

The authors of the 2020 update thank Dr Jason Chin, Dr Justin C. Konje, and Jane Marjoribanks for their contributions to previous versions of this review, and also thank Dr Michelle Wise and Dr Vanessa Jordan for providing peer review feedback.

REFERENCES

References to studies included in this review

Chan 2007 *{published data only}*

* Chan SS, Tam WH, Yeo W, Yu MM, Ng DP, Wong AW, et al. A randomised controlled trial of prophylactic levonorgestrel intrauterine system in tamoxifen treated women. *BJOG* 2007;**114**(12):1510–5.

Wong AW, Chan SS, Yeo W, Yu MY, Tam WH. Prophylactic use of levonorgestrel-releasing intrauterine system in women with breast cancer treated with tamoxifen: a randomized controlled trial. *Obstetrics and Gynecology* 2013;**121**(5):943-50.

Gardner 2000 *{published data only}*

* Gardner FJ, Konje JC, Abrams KR, Brown LJ, Khanna S, Al-Azzawi F, et al. Endometrial protection from tamoxifen-stimulated changes by a levonorgestrel-releasing intrauterine system: a randomised controlled trial. *Lancet* 2000;**356**(9243):1711-7.

Gardner FJ, Konje JC, Bell SC, Abrams KR, Brown LJ, Taylor DJ, Habiba M. Prevention of tamoxifen induced endometrial polyps using levonorgestrel releasing intrauterine system: long-term follow-up of a randomised control trial. *Gynecologic Oncology* 2009;**114**(3):452-6.

Kesim 2008 *{published data only}*

Kesim MD, Aydin Y, Atis A, Mandiraci G. Long-term effects of the levonorgestrel-releasing intrauterine system on serum lipids and the endometrium in breast cancer patients taking tamoxifen. *Climacteric* 2008;**11**(3):252-7.

Omar 2010 *{published data only}*

Omar H, Elkhayat W, Aboulkasem M. The use of levonorgestrel-releasing intrauterine system in prevention of endometrial pathology in women with breast cancer treated with tamoxifen. *International Journal of Medicine* 2010;**3**(1):327-330.

Additional references

ACOG 2014

ACOG Committee Opinion No 601. Tamoxifen and uterine cancer. *Obstetrics and Gynecology* 2014;**123**(6):1394-7.

ACOG 2015

ACOG Committee Opinion No 631. Endometrial intraepithelial neoplasia. *Obstetrics and Gynecology* 2015;**125**(5):1272-8.

ACS 2020

American Cancer Society. How common is breast cancer? www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html accessed 16 October 2020.

Davies 2013

Davies C, Pan H, Godwin J, Gray R, Arriagada R, et al for the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;**381**(9869):805-16.

EBCTCG 2011

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, Gray R, Clarke M, Cutter D, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;**378**(9793):771-84.

EBCTCG 2015

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* 2015;**386**(10001):1341-52.

Fisher 1998

Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *Journal of the National Cancer Institute* 1998;**90**(18):1371-88.

Gardner 2009

Gardner FJ, Konje JC, Bell SC, Abrams KR, Brown LJ, Taylor DJ, Habiba M. Prevention of tamoxifen induced endometrial polyps using levonorgestrel releasing intrauterine system: long-term follow-up of a randomised control trial. *Gynecologic Oncology* 2009;**114**(3):452-6.

Gizzo 2014

Gizzo S, Di Gangi S, Bertocco A, Noventa M, Fagherazzi S, Ancona E, et al. Levonorgestrel intrauterine system in adjuvant tamoxifen treatment: balance of breast risks and endometrial benefits — systematic review of literature. *Reproductive Science* 2014;**21**(4):423-31.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), accessed 9 May 2020. Available at gradepro.org.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Lyytinen 2009

Lyytinen HK, Dyba T, Ylikorkala O, Pukkala EI. A cases control study on hormone therapy as a risk factor for breast cancer in Finland. *International Journal of Cancer* July 2009;**126**(2):483-9.

Mittermeier 2020

Mittermeier T, Farrant C, Wise MR. Levonorgestrel-releasing intrauterine system for endometrial hyperplasia. *Cochrane Database of Systematic Reviews* 2020, Issue 9. Art. No: CD012658. [DOI: 10.1002/14651858.CD012658.pub2]

NCCN 2020

National Comprehensive Cancer Network. Breast Cancer (Version 6.2020). Available at www.nccn.org/professionals/physician_gls/pdf/breast.pdf Accessed 16 October 2020.

Philip 2019

Philip S, Taylor AH, Konje JC, Habiba M. The levonorgestrel-releasing intrauterine device induces endometrial decidualisation in women on tamoxifen. *Journal of Obstetrics and Gynaecology* 2019;**39**(8):1117-22.

Polin 2008

Polin SA, Ascher SM. The effect of tamoxifen on the genital tract. *Cancer Imaging* 2008;**8**(1):135-45.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Scommegna 1970

Scommegna A, Pandya GN, Christ M, Lee AW, Cohen MR. Intrauterine administration of progesterone by a slow releasing device. *Fertility and Sterility* 1970;**21**(3):201-10.

Trinh 2008

Trinh XB, Tjalma WA, Makar AP, Buytaert G, Weyler J, van Dam Pa. Use of the levonorgestrel-releasing intrauterine system in breast cancer patients. *Fertility and Sterility* 2008;**90**(1):17-22.

Wong 2013

Wong AW, Chan SS, Yeo W, Yu MY, Tam WH. Prophylactic use of levonorgestrel-releasing intrauterine system in women with breast cancer treated with tamoxifen: a randomized controlled trial. *Obstetrics and Gynecology* 2013;**121**(5):943-50.

Xiao 1990

Xiao BL, Zhou LY, Zhang XL, Jia MC, Luukkainen T, Allonen H. Pharmacokinetic and pharmacodynamic studies of levonorgestrel-releasing intrauterine device. *Contraception* 1990;**41(4)**:353-62.

References to other published versions of this review

Chin 2009a

Chin J, Hickey M, Konje J. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No: CD007245. [DOI: 10.1002/14651858.CD007245]

Chin 2009b

Chin J, Konje JC, Hickey M. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No: CD007245. [DOI: 10.1002/14651858.CD007245.pub2]

Dominick 2015

Dominick S, Hickey M, Chin J, Su HI. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No: CD007245. [DOI: 10.1002/14651858.CD007245.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chan 2007

Study characteristics	
Methods	Randomised controlled trial
Participants	Pre- and postmenopausal women who required adjuvant tamoxifen for breast cancer after completion of postoperative radiotherapy and chemotherapy. 129 women randomised. Exclusion criteria included contraindication for intrauterine device, such as pelvic inflammatory disease, congenital uterine anomaly or uterine cavity length > 10 cm.
Interventions	Two interventions compared: 1. endometrial surveillance alone (transvaginal ultrasound, hysteroscopy and endometrial sampling at base and 6, 12, 24, 45 and 60 months); and 2. endometrial surveillance with insertion of the levonorgestrel intrauterine system before the commencement of tamoxifen.

Chan 2007 *(Continued)*

Outcomes	1. Development of endometrial polyps at 12 months (113 participants completed 12-month follow-up, 58 in control group and 55 in treatment group) and at 60 months (94 participants completed 60-month follow-up, 48 in control and 46 in treatment group) 2. Endometrial hyperplasia at 60 months 3. Endometrial cancer at 60 months 4. Submucosal fibroids at 12 months 5. Abnormal vaginal bleeding or spotting at 6, 12, 24, 45 and 60 months. 6. Breast cancer recurrence at 60 months 7. Breast cancer-related death at 60 months
Notes	Study funding: The Chinese University of Hong Kong Department of Obstetrics and Gynaecology

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Women were randomized to either LNG-IUS treatment or control according to a computer-generated random number series in serially numbered sealed envelopes."
Allocation concealment (selection bias)	Low risk	"Serially numbered sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	"A histopathologist was blinded to the randomisation and the stage of tamoxifen treatment." Even though the provider and participant were not blinded given the clinical intervention (insertion of the LNG-IUS), the blinding of providers and participants is considered very unlikely to influence the outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	At 12 months of follow-up, 16/129 (12%) participants (7 in the control group and 9 in the treatment group) were lost to follow up or dropped out. 113 women (58 in the control and 55 in the treatment group) were analysed. At 60 months of follow up, 35/129 (27%) participants (17 in the control group and 18 in the treatment group) were lost to follow up. 94 women (48 in the control and 46 in the treatment group) were analysed. There is no description of the population who dropped out or comparison of drop-outs to participants who remained in the study; as such this is judged as unclear risk of bias.
Selective reporting (reporting bias)	Unclear risk	Although this study reported our review's outcomes, we could not obtain a study protocol and the study was not prospectively registered so there was no information we could use to verify the study details.
Other bias	Low risk	No additional biases to report.

Gardner 2000

Study characteristics

Methods	Randomised controlled trial
Participants	Postmenopausal women who had been on adjuvant tamoxifen for at least 12 months. Postmenopause was defined by serum estradiol < 50 pmol/L.

Gardner 2000 *(Continued)*

	122 women randomised; 9 were excluded after randomisation (6 were premenopausal, 3 with unsatisfactory hysteroscopy). Additional exclusion criteria included suspected pelvic inflammatory disease, active liver disease, history of malignant disease other than breast cancer, grade 3 submucous fibroid, endometrial polyps, and refusal to receive the levonorgestrel intrauterine system.
Interventions	Two interventions compared: 1. endometrial surveillance alone (transvaginal ultrasound at base, 6 months, 12 months, 24 months, 36 months, and 48 months; hysteroscopy at base, 12 months, 24 months, 36 months, and 48 months; endometrial sampling at base, 12 months, 24 months, 36 months, and 48 months); and 2. endometrial surveillance with insertion of the levonorgestrel intrauterine system.
Outcomes	1. Development of endometrial polyps at 12 months (52 in control group and 47 in treatment group) and at final study visit ranging from 24 months (29 in control group and 31 in treatment group) to 48 months (9 in control group and 6 in treatment group) 2. Endometrial hyperplasia at final study visit (24 to 48 months) 3. Endometrial cancer at final study visit (24 to 48 months) 4. Submucosal fibroids at 12 months 5. Breast cancer recurrence at final study visit (24 to 48 months) 6. Breast cancer-related death at final study visit (24 to 48 months)
Notes	Study funding: a grant from Trent NHS Research and Development, with support from The University of Leicester and The University Hospitals of Leicester NHS Trust

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided on random sequence generation.
Allocation concealment (selection bias)	Low risk	"Randomisation was done by pre-prepared serially numbered sealed envelopes. Each woman was allocated the next envelope in the series and received either an LNG-IUS (LNG-IUS Group) or endometrial surveillance only (Surveillance Group)."
Blinding (performance bias and detection bias) All outcomes	Low risk	"To keep interobserver error to a minimum, one consultant histopathologist, who was unaware of the randomisation, used standard criteria to assess all endometrial specimens." Even though the provider and participant were not blinded, given the clinical intervention (insertion of the LNG-IUS), the blinding of providers and participants is considered very unlikely to influence the outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	At 12 months of follow-up, 23/122 (19%) of participants (6 in control group and 17 in treatment group) were lost to follow-up or dropped out. 99 women (52 in control and 47 in treatment) were included in the analyses. There were no evidence of differences in baseline data between women who completed and did not complete the study. These data are at low risk of attrition bias. The 24, 36 and 48 months follow up data are considered at high risk of attrition bias. At 24 months of follow-up, 62/122 (51%) of participants were not included in the analyses as they were lost to follow-up or dropped out. At 36 months of follow-up, 83/122 (68%) of participants were lost to follow-up or dropped out. At 48 months of follow-up, only 15 women were included in the analyses, due to 107/122 (88%) of participants lost to follow-up or dropped out.

Gardner 2000 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Although this study reported our review's outcomes, we could not obtain a study protocol and the study was not prospectively registered so there was no information we could use to verify the study details.
Other bias	Low risk	No additional bias to report.

Kesim 2008

Study characteristics	
Methods	Randomised controlled trial
Participants	Postmenopausal women who had been on adjuvant tamoxifen for more than 12 months. 148 women randomised; 6 were excluded after randomisation (2 who refused LNG-IUS, and 4 in whom the LNG-IUS could not be fitted). Exclusion criteria included contraindication for intrauterine device (such as pelvic inflammatory disease), progestogen treatment since diagnosis of breast cancer, history of malignant disease other than breast cancer, allergy to polyethylene, and refusal to receive the levonorgestrel intrauterine system.
Interventions	Two interventions compared: 1. endometrial surveillance alone (transvaginal ultrasound, hysteroscopy, and endometrial sampling at base and 36 months); and 2. endometrial surveillance with insertion of the levonorgestrel intrauterine system.
Outcomes	1. Development of endometrial polyps at 36 months 2. Endometrial hyperplasia at 36 months 3. Abnormal vaginal bleeding or spotting at 5 and 12 months
Notes	Study funding: not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed by computer-aided numbering of sealed envelopes."
Allocation concealment (selection bias)	Low risk	"Sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Biopsy specimens were fixed and hemotoxylin-eosin stained sections were produced in a standard manner and evaluated by the same histopathologist, who was unaware of the randomization." Even though the provider and participant were not blinded given the clinical intervention (insertion of the LNG-IUS), the blinding of providers and participants is considered very unlikely to influence the outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	After randomisation, 6/148 (4%) of women were excluded (2 who refused LNG-IUS, and 4 in whom the LNG-IUS could not be fitted).

Kesim 2008 *(Continued)*

		At 36 months of follow-up, 0 participants were lost to follow-up or dropped out. 142 women were included in the analyses. These data are at low risk of attrition bias.
Selective reporting (reporting bias)	Unclear risk	Although this study reported our review's outcomes, we could not obtain a study protocol and the study was not prospectively registered so there was no information we could use to verify the study details.
Other bias	Low risk	No additional bias to report.

Omar 2010

Study characteristics	
Methods	Randomised controlled trial
Participants	Pre- and postmenopausal women with early stage breast cancer who required adjuvant tamoxifen after completion of postoperative radiation and chemotherapy. 150 women randomised; 18 were excluded after randomisation (8 from the control and 10 from the treatment group declined participation). At baseline, 9 women (4 from control and 5 from treatment) were excluded due to an unsuccessful hysteroscopy. Exclusion criteria included age > 60 years, contraindications for intrauterine device (such as pelvic inflammatory disease, uterine cavity > 8 cm), active liver disease, history of progestogen treatment since diagnosis of breast cancer, history of malignant disease other than breast cancer, allergy to polyethylene, and refusal to receive the levonorgestrel intrauterine system.
Interventions	Two interventions compared: 1. endometrial surveillance alone (transvaginal ultrasound at base, 12 and 24 months; hysteroscopy and endometrial sampling at base and 24 months); and 2. endometrial surveillance with insertion of the levonorgestrel intrauterine system
Outcomes	1. Development of endometrial polyps at 24 months 2. Endometrial hyperplasia at 24 months 3. Submucosal fibroids at 24 months 4. Abnormal vaginal bleeding or spotting at 12 months and 24 months 5. Breast cancer-related death at 12 months
Notes	Study funding: not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Women who consented to participate in the study were randomized to the LNG-IUS treatment or control group according to a computer generated random number series in serially numbered sealed envelopes."
Allocation concealment (selection bias)	Low risk	"serially numbered sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	"All specimens were fixed with hematoxylin and eosin and examined with a pathologist who was blinded to the randomizations."

Omar 2010 *(Continued)*

		Even though the provider and participant were not blinded given the clinical intervention (insertion of the LNG-IUS), the blinding of providers and participants is considered very unlikely to influence the outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	After randomisation, 18/150 (12%) of women were excluded (8 from the control and 10 from the treatment group declined participation). At baseline, 9/150 (6%) of women (4 from control and 5 from treatment) were excluded due to an unsuccessful hysteroscopy. At 12 months of follow-up, 2/123 (2%) of participants (1 in control group (breast cancer-related death) and 1 in treatment group (hysterectomy)) were lost to follow up. At 24 months of follow-up (62 in the control group and 59 in the treatment group), 0 participants were lost to follow up. At both follow-up time points, 121 women were included in the analyses. There were no evidence of differences in baseline data between women who completed and did not complete the study. These data are at low risk of attrition bias.
Selective reporting (reporting bias)	Unclear risk	Although this study reported our review's outcomes, we could not obtain a study protocol and the study was not prospectively registered so there was no information we could use to verify the study details.
Other bias	Low risk	No additional bias to report.

LNG-IUS: levonorgestrel intrauterine system

DATA AND ANALYSES

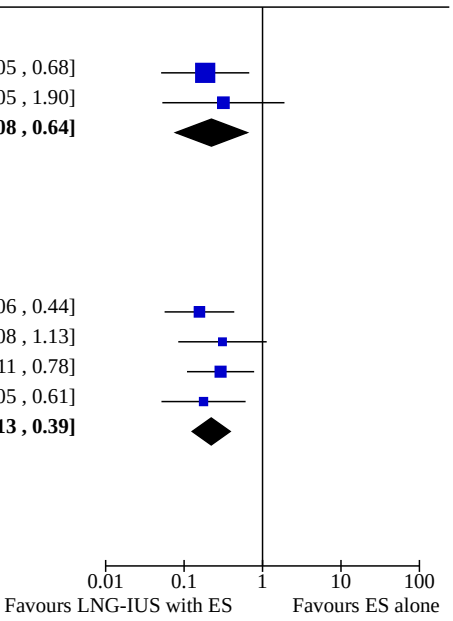
Comparison 1. LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Endometrial polyps	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1.1 Short term follow-up (12 months)	2	212	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.08, 0.64]
1.1.2 Long term follow-up (24 to 60 months)	4	417	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.13, 0.39]
1.2 Endometrial hyperplasia	4	417	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.03, 0.67]
1.3 Fibroids	3	314	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.16, 1.46]
1.4 Abnormal vaginal bleeding or spotting	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.4.1 12 months	3	376	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [3.37, 15.66]
1.4.2 24 months	2	233	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.72 [1.04, 7.10]
1.4.3 45 months	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.4.4 60 months	1	94	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Breast cancer recurrence	2	154	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.74 [0.64, 4.74]
1.6 Breast cancer-related death	3	277	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.36, 2.84]

Analysis 1.1. Comparison 1: LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone, Outcome 1: Endometrial polyps

Study or Subgroup	LNG-IUS with ES Events	LNG-IUS with ES Total	ES alone Events	ES alone Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 Short term follow-up (12 months)						
Chan 2007	1	55	9	58	65.8%	0.19 [0.05 , 0.68]
Gardner 2000	1	47	4	52	34.2%	0.32 [0.05 , 1.90]
Subtotal (95% CI)		**102**		**110**	**100.0%**	**0.22 [0.08 , 0.64]**
Total events:	2		13			
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 2.80 (P = 0.005)						
1.1.2 Long term follow-up (24 to 60 months)						
Chan 2007 (1)	2	46	16	48	29.6%	0.16 [0.06 , 0.44]
Gardner 2000 (2)	3	31	8	29	18.3%	0.31 [0.08 , 1.13]
Kesim 2008 (3)	4	70	14	72	31.8%	0.29 [0.11 , 0.78]
Omar 2010 (4)	1	59	10	62	20.3%	0.18 [0.05 , 0.61]
Subtotal (95% CI)		**206**		**211**	**100.0%**	**0.22 [0.13 , 0.39]**
Total events:	10		48			
Heterogeneity: Chi² = 1.12, df = 3 (P = 0.77); I² = 0%						
Test for overall effect: Z = 5.31 (P < 0.00001)						



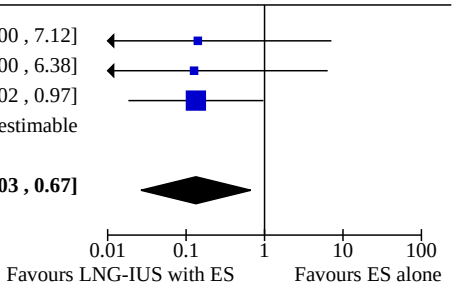
Footnotes

(1) 60 months follow-up
(2) 24 to 48 months follow-up
(3) 36 months follow-up
(4) 24 months follow-up

Analysis 1.2. Comparison 1: LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone, Outcome 2: Endometrial hyperplasia

Study or Subgroup	LNG-IUS with ES Events	LNG-IUS with ES Total	ES alone Events	ES alone Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chan 2007 (1)	0	46	1	48	16.9%	0.14 [0.00 , 7.12]
Gardner 2000 (2)	0	31	1	29	16.9%	0.13 [0.00 , 6.38]
Kesim 2008 (3)	0	70	4	72	66.2%	0.13 [0.02 , 0.97]
Omar 2010 (4)	0	59	0	62		Not estimable
Total (95% CI)		**206**		**211**	**100.0%**	**0.13 [0.03 , 0.67]**
Total events:	0		6			

Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Not applicable

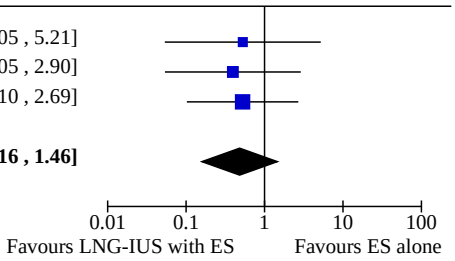


Footnotes
(1) 60 months follow-up
(2) 24 to 48 months follow-up
(3) 36 months follow-up
(4) 24 months follow-up

Analysis 1.3. Comparison 1: LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone, Outcome 3: Fibroids

Study or Subgroup	LNG-IUS with ES Events	LNG-IUS with ES Total	ES alone Events	ES alone Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chan 2007 (1)	1	46	2	48	23.4%	0.53 [0.05 , 5.21]
Gardner 2000 (2)	1	47	3	52	30.8%	0.39 [0.05 , 2.90]
Omar 2010 (3)	2	59	4	62	45.8%	0.53 [0.10 , 2.69]
Total (95% CI)		**152**		**162**	**100.0%**	**0.48 [0.16 , 1.46]**
Total events:	4		9			

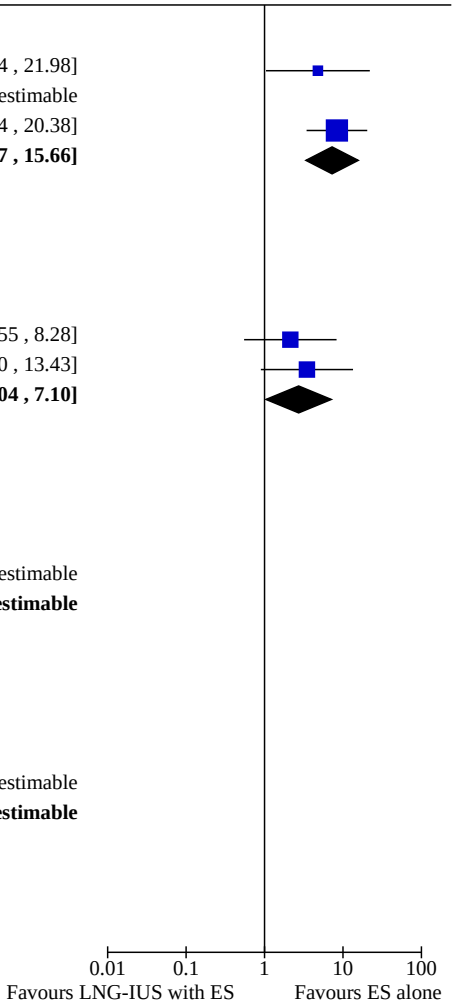
Heterogeneity: Chi² = 0.06, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable



Footnotes
(1) 60 months follow-up
(2) 24 to 48 months follow-up
(3) 24 months follow-up

Analysis 1.4. Comparison 1: LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone, Outcome 4: Abnormal vaginal bleeding or spotting

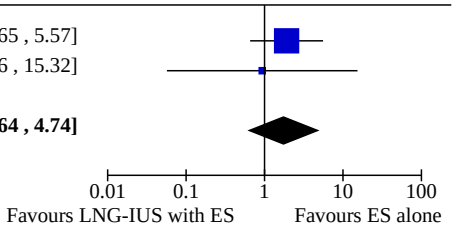
Study or Subgroup	LNG-IUS with ES Events	LNG-IUS with ES Total	ES alone Events	ES alone Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.4.1 12 months						
Chan 2007	6	55	1	58	25.5%	4.79 [1.04 , 21.98]
Kesim 2008	0	70	0	72		Not estimable
Omar 2010	22	59	2	62	74.5%	8.37 [3.44 , 20.38]
Subtotal (95% CI)		**184**		**192**	**100.0%**	**7.26 [3.37 , 15.66]**
Total events:	28		3			
Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 5.06 (P < 0.00001)						
1.4.2 24 months						
Chan 2007	6	55	3	57	49.9%	2.13 [0.55 , 8.28]
Omar 2010	7	59	2	62	50.1%	3.47 [0.90 , 13.43]
Subtotal (95% CI)		**114**		**119**	**100.0%**	**2.72 [1.04 , 7.10]**
Total events:	13		5			
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 2.05 (P = 0.04)						
1.4.3 45 months						
Chan 2007	0	48	0	52		Not estimable
Subtotal (95% CI)		**48**		**52**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.4.4 60 months						
Chan 2007	0	46	0	48		Not estimable
Subtotal (95% CI)		**46**		**48**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Chi² = 2.45, df = 1 (P = 0.12), I² = 59.2%						



Analysis 1.5. Comparison 1: LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone, Outcome 5: Breast cancer recurrence

Study or Subgroup	LNG-IUS with ES Events	LNG-IUS with ES Total	ES alone Events	ES alone Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chan 2007 (1)	10	46	6	48	87.2%	1.91 [0.65 , 5.57]
Gardner 2000 (2)	1	31	1	29	12.8%	0.93 [0.06 , 15.32]
Total (95% CI)		**77**		**77**	**100.0%**	**1.74 [0.64 , 4.74]**
Total events:	11		7			

Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable

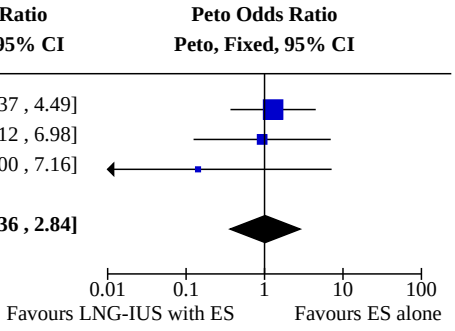


Footnotes
(1) 60 months follow-up
(2) 24 to 48 months follow-up

Analysis 1.6. Comparison 1: LNG-IUS with endometrial surveillance (ES) versus endometrial surveillance alone, Outcome 6: Breast cancer-related death

Study or Subgroup	LNG-IUS with ES Events	LNG-IUS with ES Total	ES alone Events	ES alone Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chan 2007 (1)	6	46	5	48	67.2%	1.29 [0.37 , 4.49]
Gardner 2000 (2)	2	31	2	29	26.0%	0.93 [0.12 , 6.98]
Omar 2010 (3)	0	60	1	63	6.8%	0.14 [0.00 , 7.16]
Total (95% CI)		**137**		**140**	**100.0%**	**1.02 [0.36 , 2.84]**
Total events:	8		8			

Heterogeneity: Chi² = 1.11, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable



Footnotes
(1) 60 months follow-up
(2) 24 to 48 months follow-up
(3) 12 months follow-up

ADDITIONAL TABLES

Table 1. Chan 2007 & Wong 2013

	Treatment Group	Control	P value
6 months follow-up			
Randomised	64	65	—
Completed	55	58	—
Abnormal vaginal bleeding or spotting	20	1	<0.001

Table 1. Chan 2007 & Wong 2013 *(Continued)*

12 months follow-up			
Completed	55	58	—
Abnormal vaginal bleeding or spotting	6	1	0.06
Endometrial polyps	1	9	0.02
Endometrial hyperplasia	0	0	NA
Fibroids	1	2	1.0
24 months follow-up			
Completed	55	57	—
Abnormal vaginal bleeding or spotting	6	3	0.45
45 months follow-up			
Completed	48	52	—
Abnormal vaginal bleeding or spotting	0	0	NA
60 months follow-up			
Completed	46	48	—
Abnormal vaginal bleeding or spotting	0	0	NA
Endometrial polyps	2	16	< 0.001
Endometrial hyperplasia	0	1	1.0
Endometrial cancer	0	0	NA
Fibroids	1	2	1.0
Breast cancer recurrence	10	6	0.25
Breast cancer-related deaths	6	5	0.71

NA: not applicable

Table 2. Gardner 2000 & 2009

	Treatment Group	Control	P value
12 months follow-up			
Randomised	64	58	—
Completed	47	52	—
Endometrial polyps	1	4	0.4

Table 2. Gardner 2000 & 2009 *(Continued)*

Endometrial hyperplasia	0	1	0.001
Fibroids	1	3	0.2
Final follow-up (24, 36, or 48 months)			
Completed at 24 months	31	29	—
Completed at 36 months	19	20	—
Completed at 48 months	6	9	—
Endometrial polyps	3	8	0.2
Endometrial hyperplasia	0	1	NR
Endometrial cancer	0	0	NA
Breast cancer recurrence	1	1	NR
Breast cancer-related deaths	2	2	NR

NA: not applicable
NR: not reported

Table 3. Kesim 2008

	Treatment Group	Control	P value
5 months follow-up			
Randomised	70	72	—
Completed	70	72	—
Abnormal vaginal bleeding or spotting	7	0	NR
12 months follow-up			
Randomised	70	72	—
Completed	70	72	—
Abnormal vaginal bleeding or spotting	0	0	NA
36 months follow-up			
Randomised	70	72	—
Completed	70	72	—
Endometrial polyps	4	14	< 0.05
Endometrial hyperplasia	0	4	< 0.05

NA: not applicable
NR: not reported

Table 4. Omar 2010

	Treatment Group	Control	P value
12 months follow-up			
Randomised	75	75	—
Completed	60	63	—
Abnormal vaginal bleeding or spotting	22	2	<0.001
Breast cancer-related deaths	0	1	NR
24 months follow-up			
Completed	59	62	—
Abnormal vaginal bleeding or spotting	7	2	0.08
Endometrial polyps	1	10	0.02
Endometrial hyperplasia	0	0	NA
Fibroids	2	4	1.1

NA: not applicable
NR: not reported

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Group's (CGFG) specialised register search strategy

PROCITE platform

Searched 29 June 2020

Keywords CONTAINS "IUD" or "levonorgestrel intrauterine system" or "levonorgestrel-releasing intrauterine device" or "levonorgestrel-releasing intrauterine system" or "Levonorgestrel-Therapeutic-Use" or "LNG-IUS" or "LNG20"or "Intrauterine Releasing Devices" or "Intrauterine Devices Medicated" or "intrauterine devices" or "intrauterine device" or "intrauterine contraceptive devices" or "Mirena" or Title CONTAINS "IUD" or "levonorgestrel intrauterine system" or "levonorgestrel-releasing intrauterine device" or "levonorgestrel-releasing intrauterine system" or "Levonorgestrel-Therapeutic-Use" or "LNG-IUS" or "LNG20"or "Intrauterine Releasing Devices" or "Intrauterine Devices Medicated" or "intrauterine devices" or "intrauterine device" or "intrauterine contraceptive devices" or "Mirena"

AND

Keywords CONTAINS "breast cancer" or "breast cancer incidence" or "breast changes" or "breast disease" or "breast outcomes"or "cancer risk"or "endometrial cancer"or "endometrial hyperplasia"or"endometrial pathology"or"endometrial polyps" or "endometrial proliferation" or "polyps" or Title CONTAINS "breast cancer" or "breast cancer incidence" or "breast changes"or "breast disease"or "breast outcomes" or "cancer risk" or "endometrial cancer" or "endometrial hyperplasia" or "endometrial pathology" or "endometrial polyps" or "endometrial proliferation" or "polyps"

21 records

Appendix 2. Cochrane Breast Cancer Group's (CBCG) specialised register search strategy

Searched 4 March 2020

Details regarding the search strategies used by the Cochrane Breast Cancer Group for the identification of studies and procedures used to code references for the Specialised Register are outlined in the Group's module: www.onlinelibrary.wiley.com/o/cochrane/clabout/articles/BREASTCA/frame.html

The following key words were used to identify relevant studies for consideration: "IUD", "intrauterine devices", "intrauterine system", "levonorgestrel intrauterine system", "levonorgestrel-releasing intrauterine device", "levonorgestrel-releasing intrauterine system", "levonorgestrel-therapeutic use", "LNG-IUS", "LNG20" and "Mirena".

Appendix 3. CENTRAL via the Cochrane Register of Studies Online (CRSO) search strategy

Web platform

Searched 29 June 2020

#1 MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES 12743

#2 (Breast adj2 cancer*):TI,AB,KY 33473

#3 (Breast adj2 neoplasm*):TI,AB,KY 13818

#4 (Breast adj2 carcinoma*):TI,AB,KY 1720

#5 #1 OR #2 OR #3 OR #4 35387

#6 MESH DESCRIPTOR Intrauterine Devices, Medicated EXPLODE ALL TREES 400

#7 (Intrauterine Device*):TI,AB,KY 1292

#8 (LNG IUS or LNG IUD):TI,AB,KY 316

#9 (Levonorgestrel-releasing intrauterine system*):TI,AB,KY 243

#10 (Levonorgestrel-releasing intrauterine device*):TI,AB,KY 63

#11 mirena:TI,AB,KY 148

#12 IUD*:TI,AB,KY 1196

#13 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 1960

#14 MESH DESCRIPTOR Intrauterine Devices, Medicated EXPLODE ALL TREES WITH QUALIFIERS AE 175

#15 MESH DESCRIPTOR Neoplasm Recurrence, Local EXPLODE ALL TREES 4041

#16 MESH DESCRIPTOR Endometrial Hyperplasia EXPLODE ALL TREES 146

#17 MESH DESCRIPTOR Endometrial Neoplasms EXPLODE ALL TREES 595

#18 MESH DESCRIPTOR Adenocarcinoma EXPLODE ALL TREES 7265

#19 MESH DESCRIPTOR Neoplasm Metastasis EXPLODE ALL TREES 5057

#20 MESH DESCRIPTOR Antineoplastic Agents, Hormonal EXPLODE ALL TREES WITH QUALIFIERS AE 2568

#21 MESH DESCRIPTOR Tamoxifen EXPLODE ALL TREES WITH QUALIFIERS AE 459

#22 (breast cancer adj2 recurrence*):TI,AB,KY 490

#23 (recurrent breast cancer):TI,AB,KY 258

#24 (Local Neoplasm Recurrence*):TI,AB,KY 0

#25 (secondary breast cancer*):TI,AB,KY 12

#26 (secondary neoplasm*):TI,AB,KY 166

#27 (secondary cancer*):TI,AB,KY 67

#28 (Neoplasm Metastasis):TI,AB,KY 3317

#29 (cancer metastasis):TI,AB,KY 92

#30 (advanced breast cancer):TI,AB,KY 3005

#31 (breast cancer survival):TI,AB,KY 112

#32 (Endometrial Hyperplasia):TI,AB,KY 406

#33 (Endometri* patholog*):TI,AB,KY 263

#34 (Endometri* polyp*):TI,AB,KY 212

#35 (Endometr* adenocarcinoma*):TI,AB,KY 103

#36 (endometri* adj2 cancer*):TI,AB,KY 1627

#37 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 22918

#38 #5 AND #13 AND #37 11

Appendix 4. MEDLINE search strategy

OVID platform

Searched from 1946 to 29 June 2020

1 exp Breast Neoplasms/ (291348)
2 Breast Neoplasms, Male/ (3028)
3 1 not 2 (288320)
4 (Breast cancer$ or Breast Neoplasm$).tw. (273937)
5 3 or 4 (369193)
6 exp Intrauterine Devices, Medicated/ (3345)
7 Intrauterine Device$.tw. (5471)
8 (LNG IUS or LNG IUD).tw. (870)
9 Levonorgestrel-releasing intrauterine system$.tw. (668)
10 Levonorgestrel-releasing intrauterine device$.tw. (205)
11 (IUD$ or Mirena).tw. (9070)
12 or/6-11 (12985)
13 Intrauterine Devices, Medicated/ae [Adverse Effects] (484)
14 exp Neoplasm Recurrence, Local/ (117316)
15 exp Endometrial Hyperplasia/ (3515)
16 exp Endometrial Neoplasms/ (21628)
17 exp Adenocarcinoma/ (378194)
18 exp Neoplasm Metastasis/ (202842)
19 exp Antineoplastic Agents, Hormonal/ae [Adverse Effects] (18050)
20 exp Tamoxifen/ae [Adverse Effects] (3058)
21 breast cancer recurrence$.tw. (1614)
22 recurrent breast cancer.tw. (1471)
23 Local Neoplasm Recurrence$.tw. (4)
24 secondary breast cancer$.tw. (102)
25 secondary neoplasm$.tw. (534)
26 secondary cancer$.tw. (1225)
27 Neoplasm Metastasis.tw. (93)
28 cancer metastasis.tw. (11227)
29 advanced breast cancer.tw. (8489)
30 breast cancer survival.tw. (1428)
31 Endometrial Hyperplasia.tw. (3099)
32 Endometri$ patholog$.tw. (834)
33 Endometri$ polyp$.tw. (1559)
34 Endometrial adenocarcinoma$.tw. (3157)

35 endometrial cancer.tw. (16521)
36 or/13-35 (673432)
37 5 and 12 and 36 (64)

Appendix 5. EMBASE search strategy

OVID platform

Searched from 1980 to 29 June 2020

1 exp breast tumor/ (517080)
2 (Breast cancer$ or Breast Neoplasm$).tw. (391862)
3 breast tumor$.tw. (27398)
4 or/1-3 (565673)
5 exp intrauterine contraceptive device/ (16040)
6 Intrauterine Device$.tw. (6363)
7 (LNG IUS or LNG IUD).tw. (1420)
8 Levonorgestrel-releasing intrauterine system$.tw. (908)
9 Levonorgestrel-releasing intrauterine device$.tw. (277)
10 (IUD$ or Mirena).tw. (9347)
11 or/5-10 (19511)
12 intrauterine contraceptive device/ae [Adverse Drug Reaction] (630)
13 exp tumor recurrence/ (55980)
14 exp endometrium hyperplasia/ (7326)
15 exp endometrium tumor/ (61399)
16 exp breast adenocarcinoma/ or exp adenocarcinoma/ (216342)
17 exp metastasis/ (610807)
18 "antineoplastic hormone agonists and antagonists"/ae [Adverse Drug Reaction] (601)
19 exp tamoxifen/ae [Adverse Drug Reaction] (7165)
20 breast cancer recurrence$.tw. (2744)
21 recurrent breast cancer$.tw. (2059)
22 Local Neoplasm Recurrence$.tw. (6)
23 secondary breast cancer$.tw. (211)
24 secondary neoplasm$.tw. (753)
25 secondary cancer$.tw. (1929)
26 Neoplasm Metastasis.tw. (89)
27 cancer metastasis.tw. (15530)
28 advanced breast cancer.tw. (12415)
29 breast cancer survival.tw. (1994)
30 Endometrial Hyperplasia.tw. (4378)
31 Endometri$ patholog$.tw. (1328)
32 Endometri$ polyp$.tw. (2590)
33 Endometrial adenocarcinoma$.tw. (4117)
34 endometrial cancer.tw. (25327)
35 or/12-34 (892520)
36 4 and 11 and 35 (201)
37 Clinical Trial/ (966546)
38 Randomized Controlled Trial/ (604378)
39 exp randomization/ (87180)
40 Single Blind Procedure/ (39259)
41 Double Blind Procedure/ (170471)
42 Crossover Procedure/ (63399)
43 Placebo/ (337665)
44 Randomi?ed controlled trial$.tw. (230377)
45 Rct.tw. (37455)
46 random allocation.tw. (2017)
47 randomly allocated.tw. (35256)
48 allocated randomly.tw. (2545)
49 (allocated adj2 random).tw. (816)
50 Single blind$.tw. (24736)
51 Double blind$.tw. (202894)
52 ((treble or triple) adj blind$).tw. (1151)
53 placebo$.tw. (303091)

54 prospective study/ (607350)
55 or/37-54 (2193765)
56 case study/ (69905)
57 case report.tw. (403638)
58 abstract report/ or letter/ (1100959)
59 or/56-58 (1563903)
60 55 not 59 (2140187)
61 36 and 60 (68)

Appendix 6. PyscINFO search strategy

OVID platform

Searched from 1806 to 29 June 2020

1 exp Intrauterine Devices/ (141)
2 Levonorgestrel.tw. (117)
3 intrauterine device$.tw. (301)
4 iud.tw. (238)
5 mirena.tw. (11)
6 intrauterine system$.tw. (47)
7 exp Breast Neoplasms/ (9851)
8 breast neoplasm$.tw. (160)
9 breast tumor$.tw. (101)
10 (breast adj5 ca).tw. (1)
11 (breast adj5 cancer$).tw. (13688)
12 or/1-6 (518)
13 or/7-11 (13957)
14 12 and 13 (2)

Appendix 7. CINAHL search strategy

EBSCO platform

Searched from 1961 to 29 June 2020

#	Query	Results
S13	S6 AND S13	78
S12	S7 OR S8 OR S9 OR S10 OR S11 OR S12	4,877
S11	TX(IUD* or Mirena*)	1,968
S10	TX (Levonorgestrel-releasing intrauterine)	402
S9	TX (LNG IUD)	106
S8	TX (LNG IUS)	276
S7	TX Intrauterine Device*	4,245
S6	(MM "Intrauterine Devices")	2,072
S5	S1 OR S2 OR S3 OR S4 OR S5	110,002
S4	TX (Breast cancer* or Breast Neoplasm*)	109,268
S3	TX breast tumour*	1,141

(Continued)

S2	TX breast tumor*	5,634
S1	(MM "Breast Neoplasms+")	72,057

Appendix 8. The Cochrane Library

Web platform

Searched 29 June 2020

#1 "Clinical Trial" or "Phase I Clinical Trial" or "Phase II Clinical Trial" or "Phase III Clinical Trial" or "Phase IV Clinical Trial" or "Controlled Clinical Trial" or "Multicenter Study" or "Randomized Controlled Trial" or "Pragmatic Clinical Trial" in Cochrane Reviews (Reviews and Protocols) and Trials

#2 mh "Breast Neoplasms" not mh "Breast Neoplasms, Male" or "Breast cancer" or "Breast Neoplasms"

#3 mh "Intrauterine Devices" or mh "Levonorgestrel" or "Intrauterine Devices" or "IUD" or "Medicated Intrauterine Devices" or "LNG IUS" or "Levonorgestrel-releasing intrauterine system" or "Mirena" or "Levonorgestrel"

#4 mh "Intrauterine Devices/adverse effects" or mh "Levonorgestrel/adverse effects" or mh "Neoplasm Recurrence, Local" or mh "Breast Neoplasms/secondary" or mh "Neoplasms/secondary" or mh "Endometrial Hyperplasia" or mh "Neoplasm Metastasis" or "breast cancer recurrence" or "recurrent breast cancer" or "Local Neoplasm Recurrence" or "secondary breast cancer" or "secondary neoplasms" or "secondary cancers" or "Neoplasm Metastasis" or "cancer metastasis" or "breast cancer metastasis" or "advanced breast cancer" or "breast cancer survival" or "Endometrial Hyperplasia" or "Endometrial pathology" or "Endometrial polyps" or "Endometrial adenocarcinoma" or "endometrial cancer"

#5 #1 and #2 and #3 and #4

Appendix 9. PubMed search

Searched from 1946 to 29 June 2020

(("Clinical Trial"[Publication Type]) OR ("Phase I Clinical Trial" OR "Phase II Clinical Trial" OR "Phase III Clinical Trial" OR "Phase IV Clinical Trial" OR "Controlled Clinical Trial" OR "Multicenter Study" OR "Randomized Controlled Trial" OR "Pragmatic Clinical Trial"))

AND

(("Breast Neoplasms"[Mesh] NOT "Breast Neoplasms, Male"[Mesh]) OR ("Breast cancer" OR "Breast Neoplasms"))

AND

(("Intrauterine Devices, Medicated"[Mesh]) OR ("Intrauterine Devices" OR "IUD" OR "Medicated Intrauterine Devices" OR "LNG IUS" OR "Levonorgestrel-releasing intrauterine system" OR "Mirena"))

AND

(("Intrauterine Devices, Medicated/adverse effects"[Mesh]) OR ("Neoplasm Recurrence, Local"[Mesh] OR "Breast Neoplasms/secondary"[Mesh] OR "Neoplasms/secondary"[Mesh] OR "Endometrial Hyperplasia"[Mesh] OR "Endometrial Neoplasms"[Mesh] OR "Adenocarcinoma" [Mesh] OR "Neoplasm Metastasis"[Mesh] OR "Antineoplastic Agents, Hormonal/adverse effects"[Mesh] OR "Tamoxifen/adverse effects"[Mesh]) OR ("breast cancer recurrence" OR "recurrent breast cancer" OR "Local Neoplasm Recurrence" OR "secondary breast cancer" OR "secondary neoplasms" OR "secondary cancers" OR "Neoplasm Metastasis" OR "cancer metastasis" OR "breast cancer metastasis" OR "advanced breast cancer" OR "breast cancer survival" OR "Endometrial Hyperplasia" OR "Endometrial pathology" OR "Endometrial polyps" OR "Endometrial adenocarcinoma" OR "endometrial cancer"))

WHAT'S NEW

Date	Event	Description
15 February 2021	Review declared as stable	No new studies are expected; any future evidence is unlikely to change the conclusions of this review

HISTORY

Protocol first published: Issue 3, 2008
Review first published: Issue 4, 2009

Date	Event	Description
2 July 2020	New citation required but conclusions have not changed	No new studies were identified for inclusion at this update.
8 May 2020	New search has been performed	Review updated to reflect current formatting of Cochrane Reviews and updated search.
9 November 2015	New citation required but conclusions have not changed	No changes to conclusions of this review.
9 November 2015	New search has been performed	Two new studies (Kesim 2008; Omar 2010) and a follow up of two previously included studies (Chan 2007; Gardner 2000) were identified for inclusion in this update.
20 September 2010	Amended	Contact details updated. New RCT included into review.
6 November 2008	Amended	Converted to new review format.
26 April 2007	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

SADR: revised and updated the text for this 2020 update.

KY: revised and updated the text for this 2020 update.

MH: revised and updated the 2015 update, and approved the draft 2020 update.

HIS: revised and updated both the 2015 and 2020 versions of the review.

DECLARATIONS OF INTEREST

SR: this author has no conflicts of interest to declare

KY: this author has no conflicts of interest to declare

MH: this author has no conflicts of interest to declare

HS: this author has no conflicts of interest to declare

SOURCES OF SUPPORT

Internal sources

- King Edward Memorial Hospital for Women, Western Australia, Australia

  Employer of Dr Jason Chin, an author on the 2015 review
- School of Women's and Infants' Health, Western Australia, Australia

  Reference to Dr Jason Chin, an author on the 2015 review

External sources

- Cochrane Gynaecology and Fertility Group, New Zealand

  Support of search strategy, advice and statistical analysis
- California Breast Cancer Research Program (CBCRP), USA

  Award Numbers: 20OB-0144 and 25AB-1800 made to H Irene Su

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The authors have updated methods according to MECIR standards.

NOTES

Former review author Professor Justin C Konje is a co-author for one of the randomised controlled trials included in this review (Gardner 2000)

INDEX TERMS

Medical Subject Headings (MeSH)

Adenocarcinoma [chemically induced] [prevention & control]; Antineoplastic Agents, Hormonal [adverse effects]; Breast Neoplasms [chemistry] [mortality] [*prevention & control]; Chemotherapy, Adjuvant; Confidence Intervals; Contraceptive Agents, Female [administration & dosage]; Endometrial Hyperplasia [chemically induced] [epidemiology] [*prevention & control]; Endometrial Neoplasms [chemically induced] [epidemiology] [*prevention & control]; *Intrauterine Devices, Medicated; Levonorgestrel [*administration & dosage] [adverse effects]; Neoplasm Recurrence, Local [mortality] [*prevention & control]; Polyps [chemically induced] [epidemiology] [prevention & control]; Randomized Controlled Trials as Topic; Tamoxifen [adverse effects]; Uterine Hemorrhage [chemically induced] [epidemiology]; Uterus [drug effects]

MeSH check words

Female; Humans