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Hysterectomy versus hysterectomy plus oophorectomy for premenopausal women (Review)

Orozco LJ, Tristan M, Vreugdenhil MMT, Salazar A

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[Intervention Review]

Hysterectomy versus hysterectomy plus oophorectomy for premenopausal women

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ABSTRACT

Background

Prophylactic oophorectomy alongside hysterectomy in premenopausal women is a common procedure. The decision to remove or conserve the ovaries is often based on the perceived risk for ovarian cancer and the need for additional gynaecological surgical interventions, and is weighed against the perceived risk of negative health effects caused by surgically induced menopause. The evidence needed to recommend either prophylactic bilateral oophorectomy or conservation of ovaries at the time of hysterectomy in premenopausal women is limited. This is an update of the original version of this systematic review published in 2008.

Objectives

To compare hysterectomy alone versus hysterectomy plus bilateral oophorectomy in women with benign gynaecological conditions, with respect to rates of mortality or subsequent gynaecological surgical interventions.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register (December 2005 to January 2014) and the following electronic databases: CENTRAL (*The Cochrane Library* 2013, Issue 12), MEDLINE (January 1966 to January 2014), EMBASE (January 1985 to January 2014), and PsycINFO (1806 to January 2014).

Selection criteria

Randomised controlled trials (RCTs) of hysterectomy alone versus hysterectomy with bilateral oophorectomy in premenopausal women with benign gynaecological conditions were eligible. Any surgical approach could be used.

Data collection and analysis

Three review authors independently assessed trials for inclusion. Study authors were contacted if information was unclear.

Main results

Only one RCT comparing the benefits and risks of hysterectomy with or without oophorectomy was identified. The results of this pilot RCT have not been published and we have not been able to obtain the results. Therefore, no data could be included in this review.

Authors' conclusions

The conclusions of this review are limited by a lack of RCTs. Although no evidence is available from RCTs, there is growing evidence from observational studies that surgical menopause may impact negatively on cardiovascular health and all cause mortality.

PLAIN LANGUAGE SUMMARY

Hysterectomy versus hysterectomy plus ovary removal for premenopausal women

Review question: Cochrane authors reviewed the evidence on the risks and benefits of the removal or conservation of ovaries at the time of hysterectomy for benign gynaecological disease in premenopausal women.

Background: removing the ovaries at the time of hysterectomy could potentially reduce the risk of ovarian cancer and the need for future gynaecological procedures. However, premenopausal women who have had their ovaries removed have also been reported to have an increased risk of cardiovascular disease and other complications due to early menopause. It is not clear yet whether premenopausal women should be advised to have their ovaries removed or conserved at the time of hysterectomy.

Study characteristics: studies were sought up to January 2014. No randomised studies were available that compared hysterectomy without removal of the ovaries versus hysterectomy plus removal of the ovaries.

Key results: because of the lack of appropriate studies this review does not provide evidence to support removal or conservation of the ovaries at the time of hysterectomy in premenopausal women. Therefore, until evidence is available prophylactic removal of the ovaries should be regarded with caution.

BACKGROUND

Description of the condition

The ovaries are complex endocrine organs that produce androgens and estrogens. They are involved in many metabolic processes such as bone and lipid metabolism. Androgen and estrogen levels decrease around the time of menopause (ACOG 2008). Significant amounts of testosterone and androstenedione continue to be produced by the ovaries after menopause, and these androgens are converted to estrogen in adipose, muscle and other peripheral tissues (Judd 1974). Because of continuing ovarian function after menopause, the removal of the ovaries in premenopausal women may have clinically significant consequences (ACOG 2008).

The most important reason to recommend prophylactic oophorectomy at the time of hysterectomy for benign disease is to decrease the risk of ovarian cancer (ACOG 2008), which may be of importance because the overall five-year survival rate of ovarian cancer is relatively low, 44% in the USA (SEER 2013). However, ovarian cancer is rather rare with a lifetime risk of 1.4% in the USA between 2006 and 2010 (SEER 2013). Therefore, the reduction in risk of ovarian cancer due to prophylactic oophorectomy at the time of hysterectomy is likely to be low. Parker et al found, in an observational study carried out in the USA, a risk reduction for ovarian cancer due to prophylactic oophorectomy of around 4% and estimated that 220 oophorectomies would need to be performed to prevent one case of ovarian cancer (Parker 2009).

Women with an inherited mutation of the BRCA1 or BRCA2 genes are much more at risk of developing ovarian cancer; cumulative risks of 59% and 16.5% for BRCA1 and BRCA2 carriers, respectively, by the age of 70 years have been reported (Mavaddat 2013). Therefore, the risk reduction of ovarian cancer due to prophylactic oophorectomy is likely to be much higher in these women than in the general population. Rebbeck et al used the data from an observational study to estimate a risk reduction of around 85% in BRCA carriers after prophylactic oophorectomy (Rebbeck 2002). The American College of Obstetricians and Gynecologists (ACOG) recommends prophylactic oophorectomy in BRCA carriers, advice based on limited evidence (ACOG 2008).

Another reason to consider prophylactic oophorectomy at the time of hysterectomy is to avoid gynaecological surgical interventions in the future. Zalel et al concluded that women with prior hysterectomy with ovarian preservation are prone to subsequent pelvic lesions such as benign ovarian tumours (for example cyst adenoma, peri-ovarian cysts) (Zalel 1997). Casiano et al found in a cohort study of women who had undergone hysterectomy with conservation of the ovaries for benign disease an incidence of subsequent oophorectomy of 9.2% at 30-year follow-up, which was only 1.9 % higher than the incidence of oophorectomy in women with intact reproductive organs (Casiano 2013). The ACOG recommends, based on consensus and expert opinion, that consideration be given to the higher risk of re-operation after hysterectomy without oophorectomy among women with endometriosis, pelvic inflammatory disease and chronic pain in the decision to remove or retain the ovaries (ACOG 2008).

The benefits of prophylactic oophorectomy in premenopausal women have to be weighed against the risk associated with surgically induced menopause. Rocca et al found in a population-based cohort study that prophylactic bilateral oophorectomy before the age of 45 years was associated with an increase in all cause mortality (Rocca 2006). Other prospective cohort studies with follow-up periods of more than 20 years have demonstrated increased risks of cardiovascular disease and cardiovascular mortality (Parker 2009; Rivera 2009). Rocca et al found in an observational study an increased risk of cognitive impairment or dementia after oophorectomy in premenopausal women (Rocca 2007). Also, higher risks of osteoporosis and bone fracture have been described after early menopause (Svejme 2012).

Some of the harms caused by early menopause may be treated with hormonal therapy (HT). A Cochrane systematic review on the chronic use of HT in menopausal women found that bone fractures could be prevented after the use of HT over four or five years (Marjoribanks 2012). However, this same review also demonstrated an increased risk of venous thromboembolism, stroke and gallbladder disease after long term use of estrogen. There was no evidence that HT prevents dementia. There were insufficient data to assess the risk of long term HT use in perimenopausal women or postmenopausal women younger than 50 years of age (Marjoribanks 2012). The findings of this systematic review were confirmed by a recent update of a Cochrane review that found that the use of HT does not prevent cardiovascular disease in postmenopausal women, and that HT increases the risk for stroke and venous thromboembolism. The authors of this review suggest that HT should be used with caution in postmenopausal women who have risk factors for cardiovascular disease (Main 2013).

Description of the intervention

Hysterectomy is the surgical removal of the uterus and there are three main surgical approaches: abdominal, vaginal and laparoscopic (Johnson 2005). The approach used is the scope of another review (Johnson 2005) and, therefore, is not the focus of this review. The ovaries can be removed or conserved regardless of the surgical approach. Hysterectomy is a rather common procedure in developed countries however with varying rates across individual countries, from 55 per 10,000 women of all ages in North America (CDC 2006), 28 per 10,000 in Britain, to 10 per 10,000 in Denmark (Guptaa 2006). This variation across countries has not yet been explained.

Oophorectomy is the surgical removal of the ovaries. The term prophylactic oophorectomy implies that the ovaries are normal at the time of their surgical removal. The procedure is performed with the intention of future benefit, such as prevention of ovarian cancer, alleviation of symptoms related to retained ovaries, or reduction of pelvic pain associated with peri-ovarian adhesions (ACOG 2008). Prophylactic oophorectomy at the time of hysterectomy is common in the USA. In an analysis of a large database representing about 15% of all hospital admissions in the USA, 46.4% of women who had undergone a hysterectomy in the period 2000 to 2010 had had a bilateral oophorectomy at the time of the hysterectomy (Perera 2013). The ACOG recommendation for oophorectomy in premenopausal women without an increased genetic risk of ovarian cancer, based on consensus and expert opinion, is to strongly consider retaining the ovaries, whereas in postmenopausal women oophorectomy should be considered at the time of hysterectomy (ACOG 2008). Predominant practice reflects the principle that prophylactic oophorectomy in women at low risk for ovarian cancer should be avoided under age 40 years, routinely performed over age 55 years, and individualized in the interval between 40 and 55 years (Olive 2005).

How the intervention might work

The decision whether or not to perform a prophylactic bilateral oophorectomy in premenopausal women with benign gynaecological conditions requiring a hysterectomy is complex. The possible benefits, prevention of ovarian cancer and future gynaecological surgery, have to be weighed against the potential harm caused by surgically induced menopause.

Why it is important to do this review

This review attempts to establish the consequences of performing or not performing an oophorectomy at the time of hysterectomy for non-cancerous conditions in premenopausal women. To date, most of the practices are based on observational studies, consensus and expert opinion (ACOG 2008), but the best approach regarding prophylactic oophorectomy remains uncertain. It is essential that both clinicians and women have access to reliable evidence to support their decision to remove or retain the ovaries at the time of hysterectomy.

OBJECTIVES

To compare hysterectomy alone versus hysterectomy plus bilateral oophorectomy in women with benign gynaecological conditions, with respect to rates of mortality or subsequent gynaecological surgical interventions.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) were eligible for inclusion. We excluded non-randomised studies (for example studies with evidence of inadequate sequence generation such as alternate days, patient numbers) as they are associated with a high risk of bias. Crossover trials could not be included because they are not valid in the context of oophorectomy.

Types of participants

Inclusion criteria

Premenopausal women undergoing hysterectomy for benign gynaecological disease.

Exclusion criteria

Women with gynaecological cancer or postmenopausal women as defined by primary study authors.

Types of interventions

Any surgical approach for hysterectomy without oophorectomy versus any surgical approach for hysterectomy with bilateral oophorectomy. We excluded any type of hysterectomy plus unilateral oophorectomy.

Types of outcome measures

We selected the outcome measures for this review on the basis of their clinical significance.

Primary outcomes

(1) Mortality

- ovarian cancer
- breast cancer
- colon cancer
- myocardial infarction
- stroke
- thromboembolism
- all cause

(2) Future gynaecological surgical interventions

- unilateral or bilateral oophorectomy
- any type of pelvic or gynaecological surgery

Secondary outcomes

(1) Quality of life as defined by trial authors

(2) Patient satisfaction

(3) Adverse events

- ovarian neoplasia
- pathological bone fractures as defined by trial authors
- return of endometriosis
- pelvic or abdominal pain
- pelvic floor condition (prolapse)
- urinary incontinence
- psychological functioning
- sexual functioning
- menopausal symptoms

Search methods for identification of studies

Electronic searches

For the 2014 update of the review we searched for all published and unpublished RCTs, without language restrictions and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator, in the Cochrane MDSG Specialised Register (August 2007 to January 2014), CENTRAL (*The Cochrane Library* 2013, Issue 12), MEDLINE (October 2007 to January 2014), EMBASE (October to January 2014) and PsycINFO (October 2007 to January 2014). The search strategies for each database are described in the appendices (Appendices 1, 2, 3, 4 and 5).

For the previous version of this review we searched the Cochrane MDSG Specialised Register (December 2005 to October 2007), CENTRAL (*The Cochrane Library* 2007, Issue 4), EMBASE (January 1985 to October 2007), MEDLINE (January 1966 to October 2007), LILACS (January 1982 to October 2007), Biological Abstracts (January 1968 to October 2007), NHS Economic Evaluation Database (from inception to October 2007), Health Technology Assessment Database (from inception to October 2007) and the Meta RCTs (from inception to October 2007). (Orozco 2008a)

Searching other resources

For the 2014 version of this review we requested, but have not yet received, information about a pilot RCT on elective bilateral salpingo-oophorectomy versus ovarian conservation in women

aged 40 to 55 years, registered at the ClinicalTrials website in 2009, for which the results have not yet been published (Jacoby 2009).

For the previous version of this review the reference lists of articles retrieved by the search were handsearched and personal contact was made with experts in the field to obtain any additional relevant data. For the original version of the review, authors of main studies were contacted to ascertain if they were aware of any additional published or unpublished studies. We asked two study authors (V Jacoby MD, from the Department of Obstetrics, Gynecology and Reproductive Sciences of the University of California, USA; A Aziz MD, from the Department of Obstetrics and Gynecology, Sahlgrenska Academy at Göteborg University, Sweden) to provide additional data. Dr Jacoby responded.

Data collection and analysis

Data collection and analysis were conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two review authors (LJOS, MT) independently assessed all the abstracts of the studies retrieved from searches to identify those potentially qualifying for inclusion. Full text versions of those studies considered to potentially qualify for inclusion were obtained. Two review authors (MT, MV) determined whether each individual study met the inclusion criteria, or not, using an eligibility form based on our inclusion criteria.

Data extraction and management

We planned that data would be extracted by two of LJOS, AS and MT using a data extraction form based on the primary and secondary outcomes. We intended to extract information on the study design, participants, interventions, outcomes, study risk of bias and the main results of the study.

Assessment of risk of bias in included studies

We planned to use the Cochrane risk of bias tool to assess the risk of bias of the included studies and we intended to resolve any differences of opinion by consensus.

Measures of treatment effect

We planned to use the Peto odds ratio for dichotomous data and mean difference for continuous data, with 95% confidence intervals. We planned to treat ordinal data (for example quality of life scores) as continuous data.

Unit of analysis issues

We planned for the primary analysis to be per woman randomised.

Dealing with missing data

We planned to analyse the data on an intention-to-treat basis as far as possible. We intended to contact trial authors to request data for unreported data on outcomes or clarification of methodological uncertainties. We planned to undertake imputation of individual data for the primary outcomes only if these data could not be obtained. If studies reported sufficient detail to calculate mean differences but no information on associated standard deviations (SD), we planned to assume the outcome to have a SD equal to the highest SD from other studies within the same analysis. For other outcomes, we intended to analyse only the available data. We planned to do sensitivity analysis on any imputation undertaken.

Assessment of heterogeneity

The authors planned to consider whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a meaningful summary. We planned to assess statistical heterogeneity with the Chi^2 test and the I^2 statistic (Higgins 2011).

Assessment of reporting biases

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, the authors aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If there had been 10 or more studies in an analysis, we planned to construct a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies). We planned to assess for within study reporting bias by seeking published protocols and comparing the outcomes between the protocol and the final published study.

Data synthesis

If several comparable RCTs could be identified, we planned to carry out a meta-analysis to summarise their results using a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

In the case of evidence of substantial heterogeneity ($I^2 > 50\%$), we planned to check the effect of using a random-effects model and perform subgroup analyses to examine the effects of age, presence of endometriosis, non-gynaecological comorbidity at the time of the surgery and HT use.

Sensitivity analysis

We planned to conduct sensitivity analysis to determine whether the conclusions would be robust to arbitrary decisions made regarding the eligibility and analysis of studies, as follows:

- restriction of analysis to studies with low risk of bias;
- use of risk ratios rather than odds ratios.

Summary of findings

We planned to present a summary of findings table using Guideline Development Tool software. This table would evaluate the overall quality of the body of evidence for the primary review outcomes (mortality and and future gynaecological surgical interventions) using the GRADE criteria (study limitations (that is risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality (high, moderate or low) were to be justified, documented, and incorporated into reporting of results for each outcome.

RESULTS

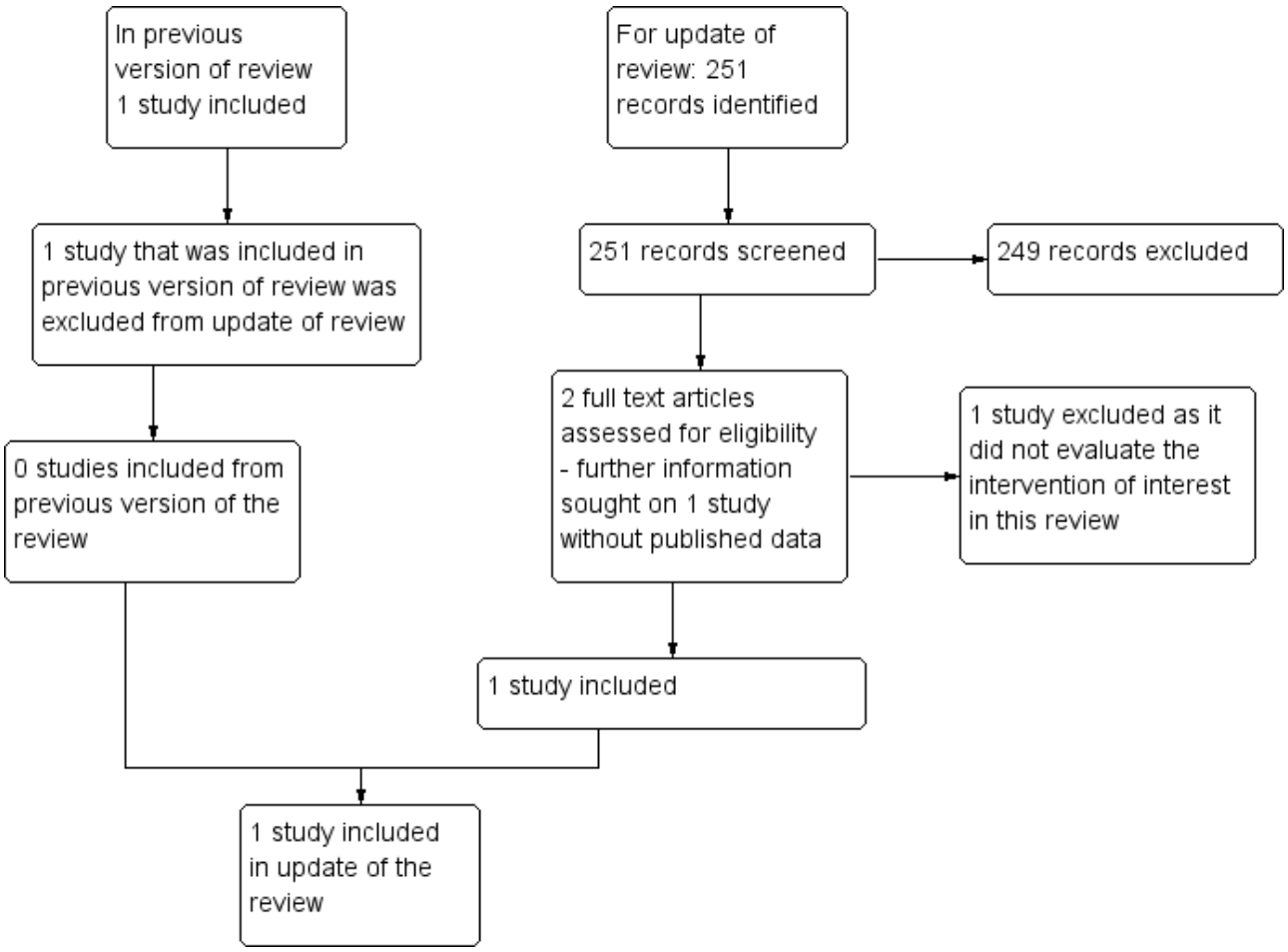
Description of studies

Results of the search

We identified 119 abstracts in the original review and 251 records in this update, which were screened for inclusion. Three abstracts,

reporting on two studies, had been identified as potentially relevant for the previous version of this review (Aziz 2005; Aziz 2005b; Teplin 2007). For the current update of the review two more records were identified (Ellstrom 2010; Jacoby 2009). See Figure 1.

Figure 1. PRISMA.



Included studies

Only one (pilot) RCT was identified that compared hysterectomy without oophorectomy with hysterectomy plus oophorectomy. The trial was identified on a trial registration website and has been completed but the results have not been published. The author did not make the data available for this review (Jacoby 2009).

Excluded studies

Four studies (Aziz 2005; Ellstrom 2010; Orozco 2008; Teplin 2007) were identified as potentially relevant but were excluded for the following reasons.

- Study design: the studies by Aziz et al (Aziz 2005) and Teplin et al (Teplin 2007) were excluded based on the design of the studies, as both studies did not have a RCT design.
- Interventions: the study by Ellstrom et al (Ellstrom 2010) was excluded because the intervention that was investigated in this study was not hysterectomy without or with oophorectomy; the study by Teplin et al (Teplin 2007) did not investigate the interventions hysterectomy with or without oophorectomy but compared the interventions total hysterectomy and supravaginal hysterectomy. This was another reason to exclude this study.
- Data unavailable: the study Orozco 2008 was planned but has not been conducted.

Risk of bias in included studies

Because insufficient details were available about the included study (Jacoby 2009), we were unable to assess the risk of bias.

Effects of interventions

Because no data were available for the included study (Jacoby 2009) no effects of the interventions could be reported.

DISCUSSION

Summary of main results

No RCTs were found that compare the benefits and harms of conservation of the ovaries with prophylactic oophorectomy at the time of hysterectomy for benign gynaecological disease in premenopausal women, except for a pilot RCT for which the results were not available for this review. Therefore, this systematic review does not provide evidence from RCTs to support clinicians and

women in the decision whether to remove or conserve the ovaries at the time of hysterectomy.

Overall completeness and applicability of evidence

The objective of this review was to locate and synthesise the evidence regarding a controversial clinical question in women's health, which remains unanswered.

Quality of the evidence

Because of the lack of available data, this review does not provide evidence from RCTs on the benefits and harms of oophorectomy or conservation of the ovaries at the time of hysterectomy.

Potential biases in the review process

Only one pilot RCT was found comparing hysterectomy without oophorectomy and hysterectomy plus oophorectomy, for which the results were not available for this review. It is unlikely that we missed information from other unpublished RCTs due to publication bias because of the extensive search strategy and the difficulty of conducting a RCT on this subject.

Agreements and disagreements with other studies or reviews

This review does not provide evidence to recommend or discourage prophylactic bilateral oophorectomy in premenopausal women because no RCTs that examined hysterectomy without or with oophorectomy could be included.

In the previous version of the review one observational study was included that investigated psychological and sexual well-being and the climacteric symptoms of women after hysterectomy with and without oophorectomy (Aziz 2005). This study demonstrated that prophylactic oophorectomy at the time of hysterectomy did not negatively affect sexual and psychological well-being in women using HT, but the quality of the evidence was considered low because of methodological limitations of the study. Because the current review only included studies with a RCT design, this study was excluded from the review.

The lack of RCTs on hysterectomy with or without oophorectomy may be explained by the unfeasibility of conducting a RCT on this topic, due to the difficulty of recruiting women willing to participate in a RCT in which they cannot choose whether or not their ovaries will be removed. Jacoby et al (Jacoby 2009) conducted a pilot study to assess the feasibility of a RCT on hysterectomy with or without oophorectomy; unfortunately the results of this study have not been published yet. Orozco et al have registered a protocol for a RCT on prophylactic oophorectomy at the time of hysterectomy in menopausal women (Orozco 2008). This study has not been conducted yet and is still awaiting approval from the ethical committee in El Salvador.

Recently the results of a prospective cohort study of 30,117 participants of the Nurses' Health Study have been published (Parker 2013). This study demonstrated, after a follow-up period of 28 years, a lower risk of mortality from ovarian cancer in women who had had a bilateral oophorectomy, and a lower risk of breast cancer in women younger than 47.5 years who had had an oophorectomy. However, all cause mortality was higher in the women with oophorectomy and also in those who were younger than 50 years and never used HT. Furthermore, in this study hysterectomy with oophorectomy was at no age associated with increased survival (Parker 2013). Because this was an observational study without randomised allocation to either oophorectomy or ovarian conservation the results may have been subject to selection bias, but as women in both groups were similar in baseline characteristics this may have been of limited importance. The findings may have been influenced by confounding due to differences in use of medication (statins for example) or diet. Because the participants of the Nurses' Health Study are mainly white women, the results may not be generalizable to other populations of women.

AUTHORS' CONCLUSIONS

Implications for practice

In clinical practice the controversial decision of whether to perform prophylactic bilateral oophorectomy at the time of hysterectomy in premenopausal women remains at the discretion of the clinician rather than based on evidence obtained from randomised controlled studies. Evidence on the benefits and harms of a bilateral oophorectomy with hysterectomy derives solely from observational studies. These have not demonstrated higher all cause mortality rates in women who had a hysterectomy with ovarian conservation. The evidence provided by observational studies does not support high numbers of prophylactic oophorectomy in premenopausal women without BRCA mutations. Until more data become available, prophylactic oophorectomy should be approached with great caution. The clinician must consider the individual implications for each woman with regard to her baseline risk for developing breast and ovarian cancer, coronary heart disease, and osteoporotic hip fracture.

Implications for research

There remains a need for randomised controlled trials designed to resolve this question. We do not think it likely that more randomised controlled trials will be carried out on this subject, although we keenly await publication of the results of Jacoby 2009 and we do hope that the Orozco study (Orozco 2008) will be carried out in the near future. However, in default of results from randomised controlled trials, we think that a systematic review of high quality observational studies may be useful to assist clinicians and patients in the choice of conservation or removal of the ovaries at the time of hysterectomy.

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Zalel 1997

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CHARACTERISTICS OF STUDIES

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

Jacoby 2009

Methods	Allocation: Randomized Intervention model: Parallel assignment Masking: Double blind (subject, investigator, outcomes assessor)
Participants	Women 40 years to 55 years Inclusion criteria: 1. Plans to undergo hysterectomy for any non-cancerous gynaecologic condition, including symptomatic fibroids, abnormal bleeding, pelvic pain, or pelvic organ prolapse. Hysterectomy may be done abdominally, vaginally or laparoscopically 2. Premenopausal defined as having at least one menses in the 3 months prior to surgery 3. Age ≥ 40 years 4. Speaks English or Spanish Exclusion criteria: 1. Personal or family history of breast and/or ovarian cancer (at least one first degree relative with a diagnosis of breast or ovarian cancer) or a known BRCA mutation 2. Known or suspected adnexal mass by physical examination or radiologic imaging study 3. Gynaecologist recommends BSO for treatment of pelvic pain and/or endometriosis 4. Known history of coronary heart disease defined as any of the following: prior myocardial infarction, history of angioplasty, history of angina, admission to the hospital for evaluation of chest pain, or use of nitroglycerin to treat angina 5. History of stroke

Jacoby 2009 *(Continued)*	6. History of osteoporosis
Interventions	Experimental: Bilateral salpingo-oophorectomy Removal of both ovaries and fallopian tubes at the time of hysterectomy for benign conditions Active comparator: Ovarian conservation No ovaries or fallopian tubes removed at the time of hysterectomy for benign conditions
Outcomes	• Recruitment rate [Time Frame: start of study] [Designated as safety issue: No] • Flow-mediated diameter of the brachial artery [Time Frame: Baseline and 6 months follow-up] [Designated as safety issue: No] • Serum bone turnover markers [Time Frame: Baseline and 6 months follow-up] [Designated as safety issue: No] • Sexual functioning and quality of life questionnaires [Time Frame: Baseline and 6 months follow-up] [Designated as safety issue: No]
Notes	Pilot study to assess the feasibility of conducting a randomised, blinded, controlled trial of bilateral salpingo-oophorectomy (BSO, removal of the ovaries and fallopian tubes) versus ovarian conservation among premenopausal women age 40 years and greater who planned to undergo hysterectomy for a benign gynecologic condition. Subjects will be randomised to BSO or ovarian conservation concomitant with hysterectomy and remain blinded to group assignment. May 2009 to April 2011 All information is from the clinicaltrials.gov website

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

Study	Reason for exclusion
Aziz 2005	This study did not have a RCT design
Ellstrom 2010	This RCT compared sexual health and psychological well-being in women after subtotal and total hysterectomy. It did not compare the interventions hysterectomy without oophorectomy and hysterectomy with oophorectomy
Orozco 2008	Trial planned but not carried out
Teplin 2007	The design of this study was not a RCT. The study was a secondary analysis of data from a RCT comparing total hysterectomy with supravaginal hysterectomy. Participants had not been randomised according to the intervention hysterectomy without or with oophorectomy

APPENDICES

Appendix 1. EMBASE search strategy

1 exp perimenopause/ or exp premenopause/ (13853)
2 pre$menopaus$.tw. (13361)
3 peri$menopaus$.tw. (3165)
4 or/1-3 (22447)
5 exp Hysterectomy/ (33208)

6 hysterectom$.tw. (24970)
7 exp OVARIECTOMY/ (21097)
8 Ovariectom$.tw. (19862)
9 oophorectom$.tw. (6324)
10 or/5-6 (39505)
11 or/7-9 (31657)
12 10 and 11 (4561)
13 4 and 12 (321)
14 Clinical Trial/ (810344)
15 Randomized Controlled Trial/ (282199)
16 exp randomization/ (52560)
17 Single Blind Procedure/ (13388)
18 Double Blind Procedure/ (99421)
19 Crossover Procedure/ (29371)
20 Placebo/ (168808)
21 Randomi?ed controlled trial$.tw. (56645)
22 Rct.tw. (5994)
23 random allocation.tw. (992)
24 randomly allocated.tw. (14696)
25 allocated randomly.tw. (1673)
26 (allocated adj2 random).tw. (677)
27 Single blind$.tw. (10423)
28 Double blind$.tw. (113531)
29 ((treble or triple) adj blind$).tw. (225)
30 placebo$.tw. (151100)
31 prospective study/ (156334)
32 or/14-31 (1089273)
33 case study/ (10349)
34 case report.tw. (191711)
35 abstract report/ or letter/ (755895)
36 or/33-35 (954413)
37 32 not 36 (1057585)
38 13 and 37 (63)

Appendix 2. MEDLINE search strategy

1 exp perimenopause/ or exp premenopause/ (5459)
2 pre$menopaus$.tw. (11836)
3 peri$menopaus$.tw. (2578)
4 or/1-3 (15407)
5 exp Hysterectomy/ (21523)
6 hysterectom$.tw. (21331)
7 exp Ovariectomy/ (17944)
8 Ovariectom$.tw. (19802)
9 oophorectom$.tw. (5728)
10 or/5-6 (30831)
11 or/7-9 (30607)
12 10 and 11 (4144)
13 4 and 12 (248)
14 randomized controlled trial.pt. (302726)
15 controlled clinical trial.pt. (82927)
16 randomized.ab. (208354)
17 placebo.tw. (126990)
18 clinical trials as topic.sh. (151928)
19 randomly.ab. (151883)
20 trial.ti. (89881)
21 (crossover or cross-over or cross over).tw. (47058)
22 or/14-21 (715052)
23 exp animals/ not humans.sh. (3583071)
24 22 not 23 (659598)
25 13 and 24 (34)

Appendix 3. CENTRAL search strategy

1 exp perimenopause/ or exp premenopause/ (591)
2 pre$menopaus$.tw. (1607)
3 peri$menopaus$.tw. (297)
4 or/1-3 (1941)
5 exp Hysterectomy/ (1279)
6 hysterectom$.tw. (1969)
7 exp Ovariectomy/ (210)
8 Ovariectom$.tw. (75)
9 oophorectom$.tw. (312)
10 or/5-6 (2182)
11 or/7-9 (458)
12 10 and 11 (175)
13 4 and 12 (21)

Appendix 4. PsycINFO search strategy

1 premenopaus$.tw. (556)
2 perimenopaus$.tw. (386)
3 or/1-2 (866)
4 exp Hysterectomy/ (336)
5 hysterectom$.tw. (572)
6 exp Ovariectomy/ (1112)
7 ovariectom$.tw. (2626)
8 oophorectom$.tw. (134)
9 or/4-5 (592)
10 or/6-7 (2716)
11 3 and 9 and 10 (5)

Appendix 5. Cochrane Menstrual Disorders and Subfertility Group Trials Register search strategy

"hysterectomised" or "hysterectomized" or "Hysterectomy" or Title CONTAINS "hysterectomised" or "hysterectomized" or "Hysterectomy"

AND

Keywords CONTAINS "oophorectomized women"or"Oophorectomy"or"ovariectomy"or"ovariectomized" or Title CONTAINS "oophorectomized women"or"Oophorectomy"or"ovariectomy"or"ovariectomized"

"hysterectom*" AND "oophorectom*"

WHAT'S NEW

Date	Event	Description
6 August 2014	Review declared as stable	New trials are not anticipated. This review will not be updated unless new evidence is published.

HISTORY

Protocol first published: Issue 1, 2006
Review first published: Issue 3, 2008

Date	Event	Description
8 May 2014	New search has been performed	We excluded one previously included observational study (Aziz 2005) and revised the methods, results and discussion sections.

Date	Event	Description
8 May 2014	New citation required but conclusions have not changed	We have updated this review. Only one eligible RCT was identified but no data are yet available from this study.
9 November 2012	New search has been performed	Review full update
11 September 2012	New search has been performed	New search. Updated methods .
13 February 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Leonardo Orozco, Mario Tristan, Maria Vreugdenhil and Arturo Salazar planned, co-drafted, and finalised the review update.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Central American Branch of the Iberoamerican Cochrane Network, Costa Rica.
- International Health Central American Institute (IHCAI Foundation), Costa Rica.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We modified the original search strategy that was published in the protocol for this review, see the appendices. We changed the inclusion criteria for type of studies; this updated version only includes RCTs and not controlled or observational trials.

INDEX TERMS

Medical Subject Headings (MeSH)

*Premenopause; Combined Modality Therapy [methods]; Genital Diseases, Female [*surgery]; Hysterectomy [*methods]; Ovariectomy [*methods]

MeSH check words

Female; Humans