Tamoxifen or letrozole versus standard methods for women with estrogen-receptor positive breast cancer undergoing oocyte or embryo cryopreservation in assisted reproduction (Review)

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[Intervention Review]

Tamoxifen or letrozole versus standard methods for women with estrogen-receptor positive breast cancer undergoing oocyte or embryo cryopreservation in assisted reproduction

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ABSTRACT

Background

Cryopreservation of oocytes or embryos preceded by controlled ovarian stimulation (COS) can increase the chance of future pregnancy in women with breast cancer who risk therapy-induced ovarian failure. In women with estrogen-receptor (ER) positive breast cancer, alternative COS protocols with tamoxifen or letrozole are being used to theoretically inhibit breast cancer growth during COS.

Objectives

To assess the effects of tamoxifen or letrozole, in addition to standard COS protocols, on the breast cancer- free interval in premenopausal women with ER positive breast cancer who undergo COS for embryo or oocyte cryopreservation.

Search methods

We searched the Ovid Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Ovid EMBASE, Ovid PsycINFO, and EBSCOhost CINAHL. We applied no limitations in year of publication or language. In addition, we searched trial registers for ongoing and registered trials, conference abstracts, and sources of grey literature. The search was conducted in January 2013.

Selection criteria

Randomised trials comparing different COS protocols in women with breast cancer were eligible for inclusion.

Data collection and analysis

Two review authors independently scanned the titles, abstracts, or both sections according to Cochrane guidelines. If data to include were provided, data extraction would have been independently performed by two review authors by using forms designed according to Cochrane guidelines.

Main results

No randomised controlled trials were found that met the inclusion criteria.

Authors' conclusions

COS schedules with the additional use of tamoxifen or letrozole are commonly chosen as an alternative regimen in young women with ER positive breast cancer who undergo COS for oocyte or embryo cryopreservation. No randomised controlled trials support the idea that these alternative COS schedules are superior to standard COS.

PLAIN LANGUAGE SUMMARY

Tamoxifen or letrozole versus standard methods for women with breast cancer who freeze egg cells or embryos

Background

Breast cancer treatment can cause infertility. Freezing egg cells (oocytes) or embryos before treatment can increase the chances of future motherhood. Hormonal treatment is required before freezing of oocytes or embryos. In cases of hormone-sensitive breast cancer, this hormonal treatment can theoretically be harmful. Therefore, these women may receive tamoxifen or letrozole in addition to standard hormonal treatment. Cochrane review authors examined the evidence about tamoxifen or letrozole versus standard methods for women with estrogen-receptor positive breast cancer undergoing freezing of oocytes or embryos in assisted reproduction.

Key results

No randomised studies were found in which the different types of treatment available for these women were compared. The evidence is current to October 2013.

BACKGROUND

Description of the condition

Worldwide, around 1.4 million women are diagnosed with breast cancer annually (GLOBOCAN 2008). In 2011, 13,110 new cases were expected to be reported in women of reproductive age in the US (ACS 2011). Adjuvant systemic breast cancer treatment may have a negative impact on fertility. Women with estrogen-receptor (ER) positive breast cancer usually undergo adjuvant hormonal treatment for five years, during which time pregnancy is contraindicated. The ovarian reserve at the age by which conception is considered to be safe for these women might be insufficient for chances of natural conception. The American Society of Clinical Oncology recommends addressing options to preserve fertility for young women early in the breast cancer trajectory (Lee 2006).

Description of the intervention

Cryopreservation of oocytes or embryos is a fertility-preserving technique that requires ovarian stimulation and should be performed before (neo)adjuvant chemotherapy is provided. Standard controlled ovarian stimulation (COS) protocols include high doses of follicle-stimulating hormone (FSH), which cause increased estrogen (estradiol) levels, and concurrent pituitary suppression by down-regulation of a woman's endogenous FSH and luteinising hormone (LH) production with gonadotropin-releasing hormone (GnRH) analogues or antagonists. COS precedes retrieval of oocytes that can be used for direct cryopreservation or in vitro fertilisation (IVF) followed by cryopreservation of embryos. Estrogen levels rise drastically during COS. For women with ER positive breast cancer, elevated estrogen levels may theoretically induce growth of tumour cells. To avoid a potentially harmful impact of COS on breast cancer outcome, women may receive an additional potentially protective endocrine agent- tamoxifen or letrozole- during COS (Oktay 2005; Oktay 2005a; Oktay 2006). Tamoxifen is an orally administered non-steroidal anti-estrogen triphenylethylene derivative with suppressive effects on breast cancer growth (Jordan 2003). The drug is effective as adjuvant treat-

ment in ER positive breast cancer (Clarke 2008). Letrozole is a third-generation aromatase inhibitor (AI), which systemically prevents the synthesis of estrogen from androgens by competitive, reversible binding of the enzyme aromatase CYP19. Use of third-generation AIs has long been restricted to postmenopausal women because preclinical studies have indicated that aromatase inhibition can lead to an increase in gonadotropin levels and multifollicular growth (Shetty 1997). However, with concurrent suppression of ovarian estrogen synthesis, third-generation AIs can now be used safely in premenopausal women for the purpose of providing adjuvant endocrine therapy (Goel 2009). When concurrent FSH is given to stimulate follicle growth, as in the case of COS, the co-administration of an AI attenuates estrogen levels to normal premenopausal preovulatory peak concentrations.

How the intervention might work

After oral administration of tamoxifen, metabolites are formed with high affinity for the ER that, by competitive binding, prevent estrogens from binding and activating the ER (Jordan 2007). The efficacy of tamoxifen in preventing breast cancer growth during COS is unknown. Letrozole decreases the peak estradiol (E2) level during COS (Oktay 2005; Oktay 2005a). Because the main action of AIs in the adjuvant setting is considered to come from decreasing estrogen levels to less than 50 pg/mL by blocking the aromatase enzyme that facilitates the conversion from androgens into estrogens, it is unclear how E2 levels of ~380 pg/mL, measured during COS with letrozole, could prevent breast cancer growth. Whether the addition of tamoxifen or letrozole to standard COS diminishes the risk of subsequent breast cancer recurrence in comparison with standard COS alone in women with ER positive breast cancer remains unknown. In addition, although indications suggest that a higher number of oocytes or embryos are retrieved with the addition of letrozole to standard COS when compared with tamoxifen (Oktay 2005), the participant series are too small to allow any definitive conclusions to be drawn.

Why it is important to do this review

Young women with breast cancer have reported major fertility-related concerns before and during breast cancer treatment and have stressed the need for more information on fertility preservation (Partridge 2007; Partridge 2008). Premenopausal ER positive breast cancer patients who risk therapy-induced impairment of ovarian function rely on fertility-preserving techniques with minimal effects on breast cancer growth and unknown effects on the breast cancer- free interval. Given that most young breast cancer patients who opt for fertility preservation in current clinical practice will undergo ovarian stimulation with an approximately two-week period of iatrogenic high levels of estrogens, reproductive gynaecologists and oncologists face significant management challenges to adequately inform patients about COS.

OBJECTIVES

To assess the effects of tamoxifen or letrozole, in addition to standard controlled ovarian stimulation (COS) protocols, on the breast cancer- free interval in premenopausal women with breast cancer who undergo COS for embryo or oocyte cryopreservation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials comparing different COS protocols in women with breast cancer were eligible for inclusion.

Types of participants

Women between the ages of 18 and 42 years diagnosed with ER positive breast cancer and undergoing COS were eligible for inclusion. For women older than 42 years of age, cryopreservation of oocytes or embryos is no longer considered to be of use because of the natural fertility decline.

Types of interventions

The intervention of interest was COS with the use of FSH alone, which was considered to be the control intervention. Comparison was made with COS protocols that included the additional use of oral tamoxifen or letrozole.

Types of outcome measures

Primary outcomes

- Safety of COS, defined as recurrence-free interval (RFI) of breast cancer (the time between breast cancer diagnosis and breast cancer recurrence; locoregional recurrence, distant metastasis, or death from breast cancer, whichever occurs first) (Hudis 2007).

Secondary outcomes

- COS outcome, defined as the number of oocytes or embryos retrieved and cryopreserved after COS.
- Peak estradiol levels during COS, defined as the level of estradiol on the day of human chorionic gonadotropin (hCG) injection.
- Live birth rate.
- Any adverse events.

Search methods for identification of studies

The Cochrane Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator (TSC) was consulted regarding development of the search strategy in MEDLINE, CENTRAL, EMBASE and PsycINFO. The TSC for the Cochrane Breast Cancer Group was consulted regarding searching of the Breast Cancer Specialised Register (see Appendix 1).
No language restrictions were applied to any of the searches.

Electronic searches

We searched the following bibliographic database sources from their inception to October 2013:

- Ovid Cochrane Central Register of Controlled Trials (CENTRAL) (not limited by year of publication or language) (see Appendix 2);
- Ovid MEDLINE (not limited by year of publication or language) (see Appendix 3);
- Ovid EMBASE (not limited by year of publication or language) (see Appendix 4);
- Ovid PsycINFO (not limited by year of publication or language) (see Appendix 5); and
- EBSCOhost CINAHL (not limited by year of publication or language) (see Appendix 6).

Both indexed and free text terms were used in the search strategies. In identifying randomised trials, the MEDLINE search was combined with the Cochrane highly sensitive search strategy, which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.1.0, Chapter 6, 6.4.11).
The EMBASE search was combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/ mehodology/filters.html#random).

Searching other resources

Conference proceedings from 2000 to 2012: International Federation of Fertility Societies (IFFS), American Society for Reproductive Medicine (ASRM), British Fertility Society (BFS), European Society for Human Reproduction and Embryology (ESHRE) and International Society for Fertility Preservation (ISFP) were searched. Furthermore, handsearches were performed of the proceedings of the annual meetings of the American Society of Clinical Oncology (2005 to 2010) and the San Antonio Breast Cancer Symposium (2005 to 2010).
Conference abstracts were searched on the Web of Knowledge (http://wokinfo.com/).
Trial registers were searched for ongoing and recently completed trials:

- 'ClinicalTrials.gov', a service of the US National Institutes of Health (http://clinicaltrials.gov/ct2/home); and
- World Health Organization 'International Trials Registry Platform search portal'.

OpenSIGLE database was searched for European grey literature (http://opensigle.inist.fr/).

Data collection and analysis

Selection of studies

As has been mentioned, eligibility criteria for including trials were applied by two review authors (TD and EB), who independently scanned the titles, the abstracts or both sections. All potentially relevant articles that were likely to meet the inclusion criteria were investigated in full text. No studies were found that met the inclusion criteria. When this review is updated and randomised controlled trials are available that meet our inclusion criteria, two review authors will independently investigate full text articles for compliance with the inclusion criteria and will select eligible studies according to Cochrane guidelines. Differences and disagreements will be resolved by consensus or by discussion with a third review author.

Data extraction and management

We planned that two review authors would extract all data by using forms designed in accordance with Cochrane guidelines. Any disagreements would be resolved by discussion with the senior review authors (MG, MvW and SL) and by consensus. Data would be collected from each study that met the inclusion criteria. If studies failed to provide information on time of follow-up, type of COS protocol, dosage of tamoxifen or letrozole, intention-to-treat population size, hormone receptor status, ovarian response and breast cancer outcome, original data would be sought from the principal author.

Assessment of risk of bias in included studies

We planned that all included studies would be randomised trials. The methodological quality of the included randomised trials would be assessed and reported by using the criteria specified

in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors (TD and EB) would independently assess the risk of bias of each included study. Risk of bias assessment would comprise a description and a judgement for each entry in a 'Risk of bias' table, where each entry would address a specific feature of the study. The methodological features to be assessed would include (1) sequence generation, (2) allocation sequence concealment, (3) blinding, (4) incomplete outcome data, (5) selective outcome reporting and (6) other potential sources of bias.

Measures of treatment effect

We planned that ordinal scales such as recurrence-free interval and peak estradiol levels during COS would be treated as continuous outcomes. Means and standard deviations (SDs) would be abstracted, calculated or requested. For continuous outcomes, mean differences (MDs) would be presented. All binary outcomes would be summarised by using the odds ratio (OR) with 95% confidence interval (CI). If data were skewed ($2 \times SD \pm mean$ is greater than the highest or lowest value), we would log-transform the mean and SD within each group and then would make the comparison across groups. SDs would thus be allowed to differ in the two groups with a Taylor series approximation of the standard error (SE) (Higgins 2008).

Unit of analysis issues

We planned that all outcomes would be expressed per woman randomly assigned.

Dealing with missing data

We planned that, if we would find insufficient information in the published report of a study, we would attempt to contact the authors for clarification. If missing data became available, these would be included in the analysis. We anticipated that trials conducted over 10 years ago might not have data on live birth rates of study participants. We planned that data extracted from the trials would be analysed on an intention-to-treat basis. Where randomised cases were missing from outcome assessment, we would first contact the authors for additional data. If further data were not available, we would assume that the missing participants had failed to achieve pregnancy.

Assessment of heterogeneity

We planned that the presence of any statistical heterogeneity of treatment effect among trials would be determined using the I^2 statistic. We planned to adopt the following broad interpretation: 0% to 40%, might not be important; 30% to 60%, may represent moderate heterogeneity; 50% to 90%, may represent substantial heterogeneity; and 75% to 100%, considerable heterogeneity present (Higgins 2002; Higgins 2011).

Assessment of reporting biases

We planned that to evaluate external reporting bias, funnel plots for primary outcomes and for the clinical pregnancy rate would be presented, if sufficient studies were identified. If evidence of small-study effects was found, publication bias would be considered as only one of a number of possible explanations. We would also informally compare the results for live birth rates between those studies that reported live birth rates and those that did not.

Data synthesis

If trials were sufficiently similar, Review Manager software would be used to perform meta-analyses using a fixed-effect model. Results for continuous outcomes would be combined using MD and 95% CI. For binary outcomes, the Peto approach would be applied.

Subgroup analysis and investigation of heterogeneity

We planned that if moderate heterogeneity ($I^2 \geq 50\%$) existed within strata, it would be explored informally by using the clinical and design details recorded in the table 'Characteristics of included studies'. Heterogeneity between strata would be anticipated, and possible reasons would be discussed.

Sensitivity analysis

We planned that if data from more than four studies were available, sensitivity analyses would be performed. We would assess the influence of risk of bias on effect size by removing trials deemed to be at high risk. Studies with high risk of bias would include those that were not done by using an intention-to-treat (ITT) approach and those that had inadequate concealment of allocation. Analyses would be repeated by using a random-effects model to explore whether different conclusions were reached. Sensitivity analyses would be reported for the primary outcome only.

Overall quality of the body of evidence: 'Summary of findings' table

We planned that a 'Summary of findings' table would be generated by using GRADEPRO software. This table would evaluate the overall quality of the body of evidence for the main review outcomes using 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) would be justified, documented and incorporated into the report of results for each outcome.

RESULTS

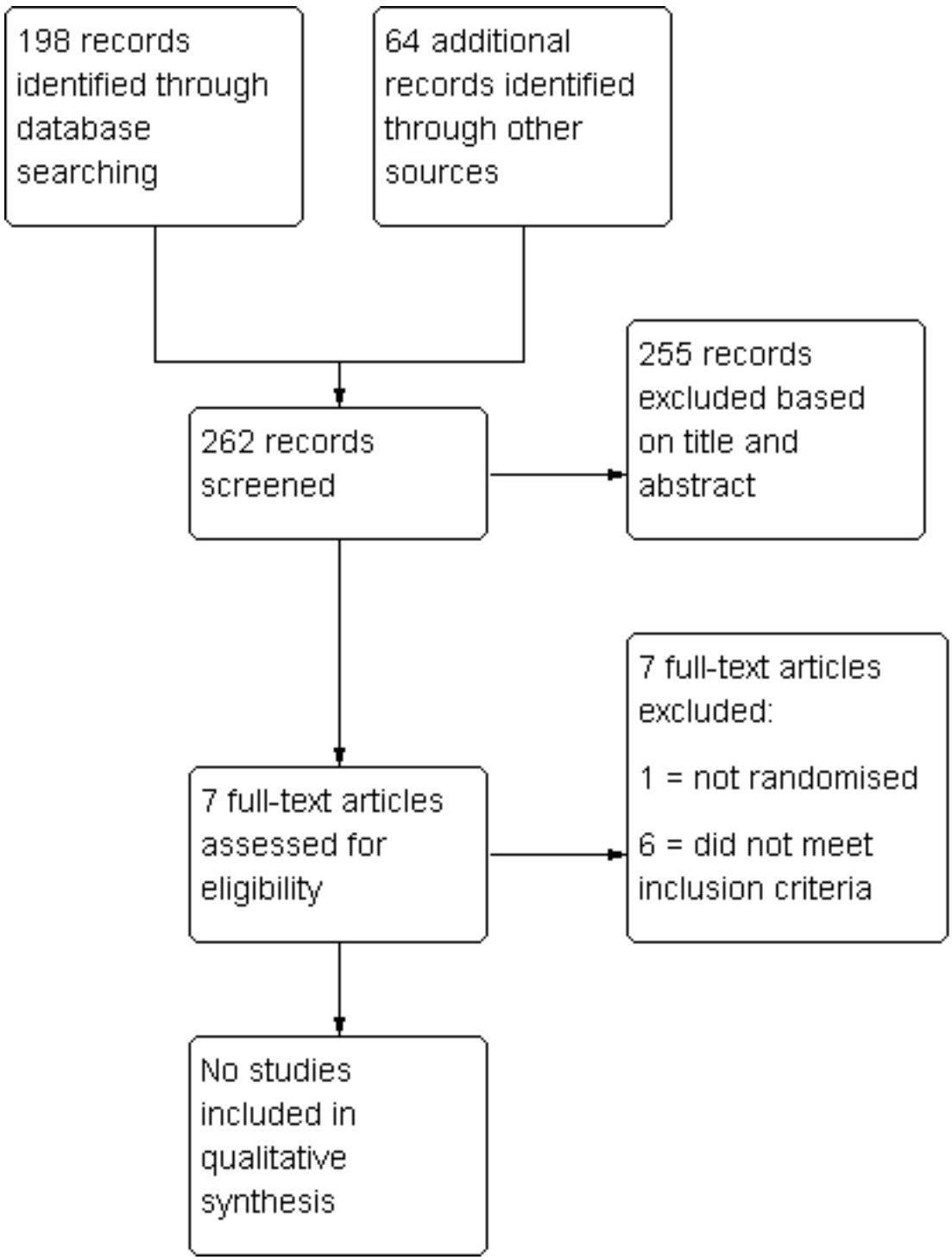
Description of studies

No randomised controlled trials comparing different COS protocols in women with breast cancer were found.

Results of the search

Two review authors independently screened 262 titles and abstracts that were identified by the conducted electronic searches and by screened conference proceedings, abstracts, sources of grey literature and trial registers. No randomised controlled trials were identified (Figure 1).

Figure 1. Study flow diagram.



Included studies

No studies met our inclusion criteria.

Excluded studies

In total, seven studies were excluded after the full text of the article had been read, because the studies did not meet our inclusion criteria. In particular, one study was excluded from the review because it was not randomised (Oktay 2005). This study compared different COS protocols in which protocols with recFSH-tamoxifen, tamoxifen alone and recFSH-letrozole were compared in 60 women with breast cancer undergoing COS for cryopreservation of embryos (Oktay 2005). A total of 29 women who underwent 33 stimulation cycles with tamoxifen alone (60 mg/d) or recFSH-tamoxifen (60 mg/d) or recFSH-letrozole (5 mg/d) were compared with a control group of 31 women with breast cancer who did not opt for fertility preservation. Compared with women who received tamoxifen alone, women who received the combination recFSH-tamoxifen or recFSH-letrozole, had a greater number of follicles. Peak E2 levels in the recFSH-letrozole group were significantly lower than in the group receiving tamoxifen alone or recFSH-tamoxifen. After 554 ± 31 days (range 153 to 1441 days) of follow-up, cancer recurrence rate was similar between women undergoing COS and women who served as a control group (three of 29 vs three of 31 women, respectively; hazard ratio, 1.5; 95% CI 0.29 to 7.4).

Risk of bias in included studies

Not applicable.

Effects of interventions

Not applicable.

DISCUSSION

Summary of main results

No randomised controlled trials were found that compared COS protocols with additional tamoxifen or letrozole versus standard COS protocols in women with breast cancer. Cryopreservation of oocytes or embryos is a common form of fertility preservation in women with breast cancer who risk therapy-induced ovarian failure. No evidence indicates that standard COS promotes breast cancer growth in the setting of fertility preservation before adjuvant treatment. Nevertheless, alternative COS protocols with tamoxifen or letrozole are being used on the basis of the idea that standard COS promotes breast cancer growth. Given the lack of evidence to support this idea, the use of COS protocols that include tamoxifen or letrozole should be restricted to the setting of randomised controlled trials.

AUTHORS' CONCLUSIONS

Implications for practice

No available evidence supports the idea that women with breast cancer should undergo COS with the addition of tamoxifen or letrozole. Therefore, standard COS remains the first-choice regimen for women with breast cancer who wish to undergo COS for cryopreservation of oocytes or embryos.

Implications for research

Regarding the current lack of randomised controlled trials comparing standard COS protocols with alternative COS protocols, which include tamoxifen or letrozole, we stress the need for a randomised controlled trial. Tamoxifen or letrozole should be given in addition to COS only in the setting of a randomised controlled trial undertaken to compare the effects on the breast cancer- free interval of standard versus alternative COS protocols.

ACKNOWLEDGEMENTS

We want to thank Marian Showell and the editorial staff of the Cochrane Menstrual Disorders and Subfertility Group for their assistance and support, Rob Scholten of the Dutch Cochrane Center for his help during the process of title registration and Fergus Tai of the Cochrane Breast Cancer Group for his search.

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Kovacs 2008 *{published data only}*

Kovacs P, Matyas S, Ungar L. Preservation of fertility in reproductive-age women with the diagnosis of cancer. *European Journal of Gynaecological Oncology* 2008;**29**(5): 425–34. [PUBMED: 19051806]

Marhhom 2007 *{published data only}*

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Mitwally 2007 *{published data only}*

Mitwally MF. Fertility preservation and minimizing reproductive damage in cancer survivors. *Expert Review of Anticancer Therapy* 2007;**7**(7):989–1001. [PUBMED: 17627459]

Oktay 2005 *{published data only}*

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Partridge 2007 *{published data only}*

Partridge AH, Ruddy KJ. Fertility and adjuvant treatment in young women with breast cancer. *Breast (Edinburgh, Scotland)* 2007;**16 Suppl 2**:S175–81. [PUBMED: 17804236]

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Azim 2008	Not randomised controlled trial that meets our inclusion criteria
Kovacs 2008	Not randomised controlled trial that meets our inclusion criteria
Marhhom 2007	Not randomised controlled trial that meets our inclusion criteria
Mitwally 2007	Not randomised controlled trial that meets our inclusion criteria
Oktay 2005	Not randomised controlled trial that meets our inclusion criteria
Partridge 2007	Not randomised controlled trial that meets our inclusion criteria
Sonmezer 2006	Not randomised controlled trial that meets our inclusion criteria

Not applicable.

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 16 October 2013.

Date	Event	Description
22 January 2014	Review declared as stable	No studies were found. This review will be updated if and when new studies published are eligible for inclusion

CONTRIBUTIONS OF AUTHORS

Taghride Dahhan wrote the first draft of the protocol, performed the search and wrote the review.

Eva Balkenende wrote the revised draft of the protocol, performed the search and commented on the draft of the review.

Madelon van Wely contributed to the protocol with methodological and statistical expertise and commented on the drafts of the review.

Sabine Linn commented on all drafts of the protocol and review from an oncologist's point of view.

Mariëtte Goddijn, as a reproductive gynaecologist, initiated the review and supervised the development of the protocol and review.

DECLARATIONS OF INTEREST

None to declare.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

'Randomised trial' was replaced by 'randomised controlled trial'.

We deleted the following sentences.

- 'For each reference reporting a potentially eligible trial, a copy of the full text article will be obtained'.
- 'We will also use personal communication with manufacturers, experts and specialists in the field.'
- 'Citation lists from review articles and other relevant publications will be searched.'

The definition of RFI for breast cancer was adjusted.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cryopreservation; *Embryo, Mammalian; *Oocytes; Breast Neoplasms [*drug therapy; metabolism]; Nitriles [*therapeutic use]; Receptors, Estrogen [metabolism]; Reproductive Techniques, Assisted; Selective Estrogen Receptor Modulators [*therapeutic use]; Tamoxifen [*therapeutic use]; Triazoles [*therapeutic use]

MeSH check words

Female; Humans; Pregnancy