Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility (Protocol)

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Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the association between ovary-stimulation drugs for the treatment of subfertility and endometrial cancer risk.

BACKGROUND

Description of the condition

Subfertility remains a key issue for modern societies in terms of the psychosocial well-being of the men and women involved, as well as the financial and public health burden (Chambers 2007; Chambers 2013). In the UK, infertility has been defined as failure to conceive after regular unprotected sexual intercourse for two years in the absence of known reproductive pathology (NICE 2004). Recent publications, such as the revised glossary published by the International Committee for Monitoring Assisted Reproductive Technology (ICMART), in collaboration with the World Health Organization (WHO) (Zegers-Hochschild 2009), as well as definitions provided by the Practice Committee of the American

Society for Reproductive Medicine (ASRM 2013), have lowered the time interval to one year.

Subfertility has several causes, with male partners' factors prevailing in about 30% of cases and female partners' factors in 50% of cases (DH 2009). The most commonly identifiable female factors are ovulatory disorders, endometriosis, pelvic adhesions, tubal blockage or other tubal abnormalities and hyperprolactinaemia (Fritz 2010; UpToDate 2013).

Nulliparity is a recognised risk factor for endometrial cancer (Cetin 2008; Venn 1999), and the impact of treatment for subfertility on endometrial cancer risk is also being explored (Siristatidis 2013).

Description of the intervention

Medical treatment for subfertility principally involves the use of fertility medication. Ovary-stimulating drugs are predominantly used for the treatment of women suffering from WHO ovulation disorders Group I (hypothalamic pituitary failure) and Group II (hypothalamic pituitary dysfunction, predominantly polycystic ovary syndrome) (NICE 2004). Fertility drugs are used during the follicular phase of the menstrual cycle to increase the serum concentration of gonadotrophins, which stimulate the ovary and promote follicle maturation and ovulation (Klip 2000). Commonly used agents and their uses are listed here.

- Selective oestrogen receptor modulators (SERMs), such as tamoxifen and clomiphene, make up a class of compounds that act on oestrogen receptors (Steiner 2005).
- Gonadotrophins (luteinising hormone (LH) and follicle-stimulating hormone (FSH)) that stimulate the ovaries may be used in their recombinant form (i.e. rFSH) or as human menopausal gonadotrophins (hMGs), which consist of LH and FSH extracted from the urine of menopausal women (NICE 2004).
- Gonadotrophin-releasing hormone (GnRH) agonists and antagonists are used most often in conjunction with gonadotrophins to achieve pituitary down-regulation and to block spontaneous ovulation, whereas both facilitate cycle control through stimulation of the ovary during in vitro fertilisation (IVF) treatment (NICE 2004).
- Human chorionic gonadotrophin (hCG), used intramuscularly, mimics the role of LH and induces ovulation or maturation of the oocytes (NICE 2004).

How the intervention might work

Fertility drugs raise the serum levels of endogenous gonadal hormones and gonadotrophins and consequently increase the chance of multiple ovulations per menstrual cycle. Although the mechanisms that link fertility drugs to endometrial cancer risk are not completely clear (Jensen 2009), it has been suggested that these agents result in prolonged exposure of the endometrium to 'unopposed' or high levels of oestrogen, hence raising the risk of endometrial cancer by increasing mitotic activity and DNA replication errors. (Akhmedkhanov 2001; Ayhan 2004). However, fertility drugs, by inducing ovulatory cycles and pregnancies, may also induce progesterone production, exerting potentially protective effects in terms of endometrial cancer risk. Specifically, fertility drugs provide the following effects.

- Selective oestrogen receptor modulators (SERMs): Clomiphene citrate is associated with a twofold to threefold increase in the mean oestradiol level, resulting in enhancement of ovulation during treated cycles, as well as an increase in progesterone levels (Dickey 1996; Sovino 2002). Clomiphene might also affect endometrial cancer risk by interacting directly with oestrogen receptors within the uterus (Goldstein 2000; Nakamura 1997). Similarly, tamoxifen (Brown 2009; Dhaliwal

2011) has been associated with increased risk for endometrial cancer (Swerdlow 2005).

- Treatment with hMG or FSH, as in IVF, may substantially increase the number of ovulations compared with that seen in untreated women (Klip 2000).
- hCG mimics the function of LH by initiating oocyte maturation/ovulation (Klip 2000).
- GnRH modulates the endogenous pituitary release of LH and FSH and subsequent folliculogenesis. GnRH agonists and antagonists are regularly used as an addition to the treatment of female subfertility (Jensen 2009; Klip 2000).

Moreover, exposure to ovulation-inducing agents has been implicated in the development of adenomatous hyperplasia of the endometrium—a precursor of endometrial cancer (Miannay 1994).

Why it is important to do this review

Because exposure to fertility drugs has increased over time, evaluating the long-term effects of ovulation-inducing drugs on risk for endometrial cancer is a matter of great importance. Over past decades, numerous studies investigating the association between fertility drugs and endometrial cancer risk have yielded conflicting or inconclusive results (Li 2013). We have recently examined the association between controlled ovarian hyperstimulation in the context of IVF and endometrial, ovarian or cervical cancer (Siristatidis 2013). We now aim to evaluate all ovary-stimulation drugs, not just those used in the context of IVF treatment. Women of reproductive age today have access to a variety of choices regarding their fertility; therefore, it is paramount that investigators explore the long-term effects of available interventions, so that healthcare professionals can offer women informed choices in family planning.

OBJECTIVES

To evaluate the association between ovary-stimulation drugs for the treatment of subfertility and endometrial cancer risk.

METHODS

Criteria for considering studies for this review

Types of studies

We do not expect to identify any randomised controlled trials (RCTs) in this area. Instead, we will consider prospective and retrospective cohort studies and case-control studies. Case series, case reports and in vitro and animal studies will be excluded.

Types of participants

Women 18 years of age or older, with existing endometrium/uterine body. Women with preexisting cancer diagnoses of any type will be excluded, along with women who have undergone fertility preservation treatment after receiving a cancer diagnosis.

Types of interventions

Any of the following regimens, offered alone or in combination, will be considered as the exposure: clomiphene citrate (CC), gonadotrophins, hCG and GnRH agonists/antagonists.

Outcomes in subfertile women treated with these agents will be compared with those of subfertile women who received no intervention and with those of control groups of women who had no fertility problems.

Types of outcome measures

Primary outcomes

Incidence of endometrial (uterine) cancer, clinically or histologically confirmed at any time following treatment for subfertility.

Secondary outcomes

Incidence of endometrial hyperplasia (complex, simple atypical and complex atypical).

Search methods for identification of studies

Electronic searches

We will search CENTRAL (current issue), MEDLINE via Ovid (1960 to date) and EMBASE via Ovid (1980 to date). We will search the CENTRAL database for reasons of completeness because, although this review will be based on non-randomised studies (NRSs), CENTRAL contains controlled clinical trials (CCTs), interrupted time series and controlled before and after series, in addition to RCTs.

The search terms will include a combination of thesaurus-based and free-text terms. See [Appendix 1](#) for the MEDLINE search strategy, which will be adapted accordingly for searches of the other databases.

We impose no restriction on language and publication status. All databases will be searched from 1960 onwards, as the interventions sought were not available before that date.

Searching other resources

Reference lists of included studies and any relevant systematic reviews identified will also be searched to identify eligible studies for inclusion. The review authors will try to identify the relevant grey literature by looking at the following.

- 'Open grey', a system for grey literature produced in Europe, such as research reports, doctoral dissertations and conference papers (<http://www.opengrey.eu/>).
- ProQuest dissertation and thesis databases (<http://www.proquest.com/en-US/catalogs/databases/detail/pqdt.shtml>).
- Published or ongoing trials in the trial registers for ongoing and registered trials: 'ClinicalTrials.gov', a service of the US National Institutes of Health (<http://clinicaltrials.gov/ct2/home>) and <http://www.controlled-trials.com>, as well as the World Health Organization International Trials Registry Platform search portal (<http://www.who.int/trialsearch/Default.aspx>) and Physicians Data Query (<http://www.nci.nih.gov>).
- Conference proceedings and abstracts through ZETOC (<http://zetoc.mimas.ac.uk>) and WorldCat Dissertations.
- Reports of conferences in the following: *Gynecologic Oncology* (Annual Meeting of the American Society of Gynecologic Oncologists), *International Journal of Gynecological Cancer* (Annual Meeting of the International Gynecologic Cancer Society), *British Journal of Cancer*, British Cancer Research Meeting, Annual Meeting of the European Society of Medical Oncology (ESMO) and Annual Meeting of the American Society of Clinical Oncology (ASCO).
- Personal communication with experts in the field who are/have been conducting/have led research in the field and on the specific hypothesis of this review.

Data collection and analysis

Selection of studies

Search results will be transferred to a special processing platform developed by P. Kanavidis, a full description of which can be found in our recent publication ([Siristatidis 2013](#)).

Once duplicates have been removed, all review coauthors will be involved in selecting studies for eligibility. Review coauthors working in pairs will assess an allocation of titles and abstracts, so that each allocation portion will be independently assessed by two review coauthors. We will not be blinded to authors' names and institutions, journal of publication or study results while assessing studies for potential inclusion.

Studies that clearly do not meet the inclusion criteria will be excluded. For 'potentially relevant' studies, the full text will be obtained for further assessment. Letters will be sent to study authors to ask for clarification about 'potentially relevant' studies. All disagreements will be resolved by consensus.

Data extraction and management

The review authors will extract data using a pre-designed Excel file before copying the data into [Review Manager 2011](#) (RevMan 5) for analysis. The data extraction form ([Appendix 2](#)) was piloted previously and was subsequently used in our recently published report ([Siristatidis 2013](#)), which, however, focused solely on IVF. Authors will extract the data independently while working in pairs. Disagreements will be resolved by team consensus.

Data to be extracted include general information (title, author, year, journal, geographical setting and clinical setting), study characteristics (study period, number of participants per exposed/unexposed or case/control group, design, follow-up, ascertainment of exposure and outcome and matching factors), participant characteristics (inclusion/exclusion criteria, age, race, gynaecological and reproductive history, definition and causes of subfertility, gravidity, parity and histological subtype of cancer), interventions (type and agent of fertility treatment, dosage of treatment, number of treatment cycles, age at first use, years since first use, reference population for the comparison and general population or subfertile women) and risk of bias assessment data (cf. below, relevant sections).

In addition, the following results will be extracted, when available.

- Maximally adjusted odds ratio (OR) and associated 95% confidence interval (CI), as defined by the study authors.
- Maximally adjusted relative risk (RR) and associated 95% CI, as defined by the study authors.
- Maximally adjusted hazard ratio (HR) and associated 95% CI, based on the number of events (cases) and with consideration of the time to event.
- Standardised incidence ratio (SIR) and associated 95% CI, estimated as the ratio of observed over expected number of cases for the exposed group of women.
- Incidence rate ratio (IRR) and associated 95% CI, estimated from the number of cases per person-years for exposed and unexposed women.
- Associated raw data for recalculation (data checking) or de novo estimation of missing measures.

Assessment of risk of bias in included studies

No RCTs are anticipated, hence assessment of risk of bias will pertain exclusively to non-randomised studies (NRSs).

An extension to the risk of bias tool for randomised studies is currently under development by a multi-disciplinary working group of experts, with the ultimate aim of creating a risk of bias tool that can be used in systematic reviews of non-randomised studies. This work has advanced enough for the NRS Working Group to consider selecting appropriate systematic reviews to pilot the tool. Our review seems to provide an ideal piloting platform, and the NRS Working Group is considering it as a candidate. This review will be performed with the input of the NRS Working Group; should a timely piloting version of the tool become available, we

will use it to assess the risk of bias in included studies. We will not, however, delay completion of this review until developmental work on the tool is completed.

If the tool is not available for pilot use in time, the risk of bias will be assessed in accordance with relevant sections of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), as well as in keeping with the rationale adopted in the most recent Cochrane review examining the association between ovarian cancer and ovary-stimulation drugs for subfertility ([Rizzuto 2013](#)). As suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 13.5.2.3), items included in the Newcastle-Ottawa scale ([Wells 2011](#)) will be customised for inclusion in the detailed item-to-item list below.

The assessment of risk of bias will encompass the examination of selection bias (comparability of groups and confounding/adjustment), performance bias, detection bias, attrition bias and reporting bias. The qualifications 'low risk', 'high risk' and 'unclear risk' will be adopted for each risk of bias domain, in accordance with the guidelines published by the Newcastle-Ottawa scale ([Wells 2011](#)). The 'critical risk category' in the risk of bias tool will also be taken into account.

Selection bias

The following features of the study design will be assessed for selection bias.

Comparability of groups

- Consecutive recruitment cases (case-control studies).
- Population-based controls derived from the same population as cases (case-control studies).
- Non-exposed women drawn from the same population as the exposed cohort (cohort studies).

Confounding/Adjustment

For all studies, the following factors will be evaluated as potential confounders, given that they represent known risk factors for endometrial cancer ([Adami 2008](#)).

- Age.
- Use of oral contraceptives.
- Use of hormone replacement treatment (HRT).
- Age at menarche.
- Age at menopause.
- Parity.
- Smoking.
- Alcohol intake.
- Body mass index (BMI).
- Diabetes mellitus.

As mandated by the *Cochrane Handbook for Systematic Reviews of Interventions*, an additional table will be created that will list the

pre-stated confounders as columns and the studies as rows. This additional table will indicate whether each study:

- restricted participant selection so that all groups had the same value for the confounder;
- demonstrated balance between groups for the confounder;
- matched on the confounder; or
- adjusted for the confounder in statistical analyses to quantify the effect size.

Performance bias

The following features of the study design will be evaluated.

- Exposure to ovary-stimulation drugs was ascertained by a secure source, namely, medical records or structured interviews (all studies).
- In cases in which a structured interview was performed, interviewers assessing exposure to fertility treatment were blinded to the presence of endometrial cancer (all studies).
- The same method was used to ascertain exposure to fertility drugs for both cases and controls (case-control studies).

Detection bias

The following feature will be assessed.

- Assessors of cancer status were blinded to exposure status (all studies).

Attrition bias

With respect to attrition bias, the following features will be examined.

- Length of follow-up was at least 10 years for the exposed group (Siristatidis 2013), as endometrial cancer reaches its peak incidence after the age of 55 years, whereas IVF exposure occurs mostly during the late reproductive years (cohort studies).
- At least 80% of women in all groups were included in the final analysis (all studies).

Measures of treatment effect

Both primary and secondary outcome measures will be expressed as odds ratios (ORs), relative risks (RRs), hazard ratios (HRs), standardised incidence ratios (SIRs) or incidence rate ratios (IRRs). Ideally, separate analyses by type of effect estimate will be performed. However, should only a small number of studies be available, we will attempt to transform ORs, RRs and HRs into a single metric to reduce heterogeneity and to provide more robust estimates. SIRs and IRRs will be analysed separately. The 95% confidence interval (CI) for log(SIR) will be reconstructed via the term $\pm 1.96/(\text{square root } (O))$, where 'O' represents the observed number of events (Alder 2006).

Unit of analysis issues

None expected. The unit of analysis will always be the participant.

Dealing with missing data

The corresponding authors of 'potentially relevant' and eligible studies will be contacted by email when the need arises to obtain potentially useable missing data, to ask for additional information or to request methodological clarification.

Assessment of heterogeneity

It is generally expected that non-randomised studies will be more heterogeneous than randomised studies (*Cochrane Handbook for Systematic Reviews of Interventions*, Section 13.6.1 (Higgins 2011)), hence heterogeneity tolerance levels will be adjusted accordingly. Inconsistency among studies will be quantified by estimating I^2 (Higgins 2011). When considerable heterogeneity is noted ($I^2 > 80\%$), the pooled estimate will be suppressed in the forest plot, and results will be reported as narrative text or in descriptive tables. For levels of I^2 between 50% and 80%, heterogeneity will be considered as moderate, and pooled analysis will be attempted by using a random-effects model to allow for heterogeneity. Heterogeneity will also be explored by means of a priori agreed subgroup analyses.

Assessment of reporting biases

If more than 10 studies are available, publication bias will be assessed using Egger's formal statistical test (Egger 1997) at the 90% level, and a funnel plot will be constructed. An Egger's modified test (Harbord's test) will be used to assess possible small-study effect biases (Harbord 2006).

Data synthesis

To our knowledge, no RCTs will be available for inclusion in the analysis, and all included studies are expected to be case-control or cohort studies. If RCTs are found and included, meta-analyses will be carried out separately for RCTs in accordance with the intention-to-treat principle and for any non-randomised studies (cohort and case-control studies).

Random-effects models will be used to calculate separate pooled effect estimates for each of the risk ratio (RR) measures (OR, HR, SIR, IRR) (DerSimonian 1986). As the absolute risk for cancer is rather small, the four relative measures are expected to yield similar estimates (Adami 2008; Larsson 2007). Yet, as described earlier, if feasible, separate analyses by type of effect estimate will be performed. Should only a small number of studies be available, we will attempt to transform ORs, RRs and HRs into a single metric to reduce heterogeneity and to provide more robust estimates. SIRs and IRRs will be analysed separately. Data permitting, the

proposed data synthesis strategy will be supported by sensitivity analysis by type of measure. Separate analyses will be carried out for the different reference populations available (general population of women and subfertile women who did not receive fertility treatment).

A comparison of fixed-effect and random-effects summary effects would be used to explore small-study effect biases.

Subgroup analysis and investigation of heterogeneity

Should data be available, the various therapeutic agents will be evaluated by drug subtype (SERMs, gonadotrophins, GnRH agonists and antagonists, hCG) and as individual drugs. If sufficient studies are available, subgroup analyses will be performed for each ovary-stimulation agent by:

- type of effect measures;
- gravidity and/or parity;
- age groups;
- causes of subfertility;
- histological type of cancer;
- dosage and/or number of cycles; and
- studies including or excluding events during the first year of follow-up (Siristatidis 2013).

Although separate subgroup analyses will be attempted, it is well known that some of these factors may interact with each other; therefore, inferences will not be based solely on subgroup analyses, but meta-regression analysis will be additionally performed to adjust for mutual confounding.

Sensitivity analysis

As mentioned earlier (under Data synthesis) sensitivity analysis for each type of effect measure will be employed if sufficient numbers of studies are available. Sensitivity analyses based on the risk of bias assessment will also be carried out for the selection, performance and attrition bias domains.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

APPENDICES

Appendix I. MEDLINE search strategy

MEDLINE Ovid

1 exp Ovulation Induction/

2 (ovar* adj5 (stimulat* or hyperstimulat* or hyper-stimulat* or enhanced follicular recruitment)).mp.

3 exp Fertility Agents/

4 ((fertil* or infertil* or subfertil*) adj5 (drug* or agent*)).mp.

5 exp Reproductive Techniques, Assisted/

6 ((assist* adj5 reproduct*) or ART or (in vitro adj5 fertili*) or IVF or ICSI or intracytoplasmic sperm injection).mp.

7 exp Selective Estrogen Receptor Modulators/

8 (selective adj (estrogen or oestrogen) adj receptor adj modulator*).mp.

9 (SERM* or tamoxifen or clomiphene or clomifen*).mp.

10 exp Gonadotropins/

11 exp Gonadotropin-Releasing Hormone/

12 (gonadotropin* or luteinizing hormone* or follicle stimulating hormone* or LH or FSH or hMG or hCG or GnRH*).mp.

13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14 exp Endometrial Neoplasms/

15 Endometrial Hyperplasia/

16 ((endometr* or ((uter* or womb) and (body or cavity or corpus or lining))) adj5 (cancer* or carcinoma* or malignan* or neoplas* or tumor* or tumour* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or hyperplasia*)).mp.

17 14 or 15 or 16

18 13 and 17

19 exp animals/ not humans.sh.

20 18 not 19

key:

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier

Appendix 2. Data extraction form

General information
Title
Author
Year
Journal
Geographical setting (country, region)
Clinical setting
Study characteristics
Study period
Study design
Cohort size (for cohort studies only)
Cohort characteristics (for cohort studies only)
Number of incident cases in the cohort (for cohort studies only)
Number of cases (for case-control studies only)
Number of controls (for case-control studies only)
Reference group (general population or subfertile women)
Characteristics of participants
Inclusion and exclusion criteria
Mean age of total cohort (for cohort studies only)
Mean age of exposed women (for cohort studies only)
Mean age of cases (for case-control studies only)
Mean age of controls (for case-control studies only)
Race
Gynaecological and reproductive history

(Continued)

Gravidity
Parity
Definition of infertility
Type of infertility
Histology
Interventions
Type and agent of fertility treatment
Dosage of fertility treatment
Number of fertility treatment cycles
Age at time of first fertility treatment
Years since time since first fertility treatment
Results
Effect estimate type
Exclusion of first year of follow-up
Subanalyses provided
Effect estimate (maximally adjusted)
Lower confidence limit
Upper confidence limit
Data for recalculation or de novo estimation of measures
Observed number of exposed cases (for cohort studies only)
Observed number of unexposed cases (for cohort studies only)
Expected number of exposed cases (for cohort studies only)
Expected number of unexposed cases (for cohort studies only)
Total number of person-years among exposed cases (for cohort studies only)

(Continued)

Total number of person-years among unexposed cases (for cohort studies only)
Number of exposed cases (for case-control studies only)
Number of exposed controls (for case-control studies only)
Assessment of risk of bias
Consecutive series of cases (for case-control studies)
Population-based or hospital-based controls (for case-control studies)
Controls derived from the same population as cases (for case-control studies)
Non-exposed women drawn from the same population as the exposed cohort (for cohort studies)
Matching factors
Adjusting factors
Ascertainment of exposure
Ascertainment of cancer
Mean follow-up in total cohort (for cohort studies only)
Mean follow-up in exposed women (for cohort studies only)
At least 80% of women in all groups included in the final analysis

CONTRIBUTIONS OF AUTHORS

- Skalkidou A: conceived of the idea of the review, contributed to study design, provided clinical gynaecological expertise and prepared the draft.
- Sergentanis TN: conceived of the idea of the review, contributed to study design and prepared the draft.
- Evangelou E: contributed to study design and provided statistical and methodological expertise.
- Psaltopoulou T: contributed to study design and contributed endocrinological clinical expertise in drafting the protocol.
- Sotiraki M: contributed to study design and to preparation of the draft.
- Trivella M: contributed to study design and provided statistical and methodological expertise.
- Siristatidis CS: contributed to study design and provided clinical gynaecological expertise in drafting the protocol.
- Petridou E: conceived of the idea, selected coauthors, contributed to study design, provided training, convened meetings, provided final approval and acted as a guarantor of the study protocol.

All authors reviewed the protocol before the time of submission.

DECLARATIONS OF INTEREST

None declared.

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- None, Not specified.

External sources

- None, Not specified.