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Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility

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ABSTRACT

Background

The use of assisted reproductive techniques is increasing, but the possible link between fertility drugs and ovarian cancer remains controversial.

Objectives

To evaluate the risk of ovarian cancer in women treated with ovulation stimulating drugs for subfertility.

Search methods

We searched for published and unpublished observational studies from 1990 to February 2013. The following databases were used: the Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register, Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 1, MEDLINE (to February week 4 2013), EMBASE (to 2013 week 09) and databases of conference abstracts. We also scanned reference lists of retrieved articles. The search was not restricted by language of publication.

Selection criteria

We searched for randomised controlled trials (RCTs) and non-randomised studies, and case series including more than 30 participants, reporting on women with exposure to ovarian stimulating drugs for treatment of subfertility and histologically confirmed borderline or invasive ovarian cancer.

Data collection and analysis

At least two review authors independently conducted eligibility and 'Risk of bias' assessment, and extracted data. We grouped studies based on the fertility drug used for two outcomes: borderline ovarian tumours and invasive ovarian cancer. We expressed findings as adjusted odds ratio (OR), risk ratio (RR), hazard ratio (HR) or crude OR if adjusted values were not reported and standardised incidence ratio (SIR) where reported. We conducted no meta-analyses due to expected methodological and clinical heterogeneity.

Main results

We included 11 case-control studies and 14 cohort studies, which included a total of 182,972 women.

Seven cohort studies showed no evidence of an increased risk of invasive ovarian cancer in subfertile women treated with any drug compared with untreated subfertile women. Seven case-control studies showed no evidence of an increased risk, compared with control women of a similar age. Two cohort studies reported an increased incidence of invasive ovarian cancer in subfertile women treated with any fertility drug compared with the general population. One of these reported a SIR of 5.0 (95% confidence interval (CI) 1.0 to 15), based on three cancer cases, and a decreased risk when cancer cases diagnosed within one year of treatment were excluded from the analysis (SIR 1.67, 95% CI 0.02 to 9.27). The other cohort study reported an OR of 2.09 (95% CI 1.39 to 3.12), based on 26 cases.

For borderline ovarian tumours, exposure to any fertility drug was associated with a two to three-fold increased risk in two case-control studies. One case-control study reported an OR of 28 (95% CI 1.5 to 516), which was based on only four cases. In one cohort study, there was more than a two-fold increase in the incidence of borderline tumours compared with the general population (SIR 2.6, 95% CI 1.4 to 4.6) and in another the risk of a borderline ovarian tumour was HR 4.23 (95% CI 1.25 to 14.33) for subfertile women treated with in vitro fertilisation (IVF) compared with a non-IVF treated group with more than one year of follow-up.

There was no evidence of an increased risk in women exposed to clomiphene alone or clomiphene plus gonadotrophin, compared with unexposed women. One case-control study reported an increased risk in users of human menopausal gonadotrophin (HMG) (OR 9.4, 95% CI 1.7 to 52). However, this estimate is based on only six cases with a history of HMG use.

Authors' conclusions

We found no convincing evidence of an increase in the risk of invasive ovarian tumours with fertility drug treatment. There may be an increased risk of borderline ovarian tumours in subfertile women treated with IVF. Studies showing an increase in the risk of ovarian cancer had a high overall risk of bias, due to retrospective study design, lack of accounting for potential confounding and estimates based on a small number of cases. More studies at low risk of bias are needed.

PLAIN LANGUAGE SUMMARY

Is there an increased risk of ovarian cancer in women treated with drugs for subfertility?

Drugs to stimulate ovulation have been widely used for various types of subfertility since the early 1960s and their use has increased in recent years. Subfertile women are commonly exposed to these agents, which may be administered at high doses for long periods of time during treatment for subfertility. There is uncertainty about the safety of these drugs and the potential risk of causing cancers associated with their use.

Overall, based on 25 studies, which included a total of 182,972 women, we found no evidence that the risk of ovarian cancer was increased in women treated with fertility drugs, compared with subfertile women untreated with fertility drugs, or women in the general population.

Five of the 25 studies showed an increase in the risk of ovarian cancer, but these studies were of low methodological quality and therefore the results are too unreliable to conclude that there is a definitive risk of cancer while on treatment for subfertility.

More research studies, which are of high quality, are needed to determine whether there is an increased risk of ovarian cancer in women treated with fertility drugs.

Description of the condition

The prevalence of subfertility in Western societies ranges from 3% to 33% (Boivin 2007; Chandra 1998; Greenhall 1990; Healy

BACKGROUND

1994; Karmaus 1999; Schmidt 1995). It is reported that in the UK one in seven heterosexual couples suffer from subfertility (NICE 2013). In less developed countries the prevalence has been reported as 6.9% to 9.3% (Boivin 2007). It is presumed that the differences in the prevalence of subfertility in different populations in the industrialised countries are mainly due to differences in the definitions and methods of measurement used. Subfertility has been defined as failure to conceive after frequent unprotected sexual intercourse for one year in the absence of known causes of subfertility (NICE 2013).

Description of the intervention

Fertility drugs are used during the follicular phase of the menstrual cycle to increase the serum concentration of gonadotrophins, with the aim of promoting maturation of multiple follicles and consequently multiple ovulations. Commonly used ovulation induction agents include: 1) anti-oestrogens, such as clomiphene citrate; 2) tamoxifen, a selective oestrogen receptor modulator (SERM); 3) human menopausal gonadotrophin (HMG), which contains follicle-stimulating hormone (FSH) and luteinising hormone; 4) human chorionic gonadotrophin (HCG); 5) gonadotrophin-releasing hormone agonists (GnRH-AG); 6) gonadotrophin-releasing hormone antagonist (GnRH-A); 7) purified FSH; 8) growth hormone and 9) insulin-like growth factor (IGF) (Duffy 2010). These hormones are used either alone or in combination depending on the cause of infertility and the protocol used. In addition, other fertility drugs used in most regimes of assisted reproductive technologies, such as in vitro fertilisation (IVF), include progestogens to support the luteal phase of the menstrual cycle (Genc 2011).

How the intervention might work

Clomiphene citrate and tamoxifen (a selective oestrogen receptor modulator) are used for women whose failure to ovulate is due to a hypothalamic pituitary dysfunction type II (World Health Organization Classification, WHO) (Rowe 1993). Both drugs are prescribed during the early phase of the menstrual cycle (day two to six) in order to reduce the negative feedback caused by oestrogen and to result in an increase in GnRH secretion from the hypothalamus, which in turn leads to a rise in FSH and luteinising hormone production. These natural gonadotrophin hormones then stimulate the ovary to mature a follicle and ovulate. Gonadotrophins (HMG or HCG or FSH) are used in the treatment of subfertility in women with proven hypopituitarism or who have not responded to clomiphene or in superovulation treatment for assisted contraception, such as IVF. They are given with the aim of amplifying and prolonging the endogenous secretion of FSH and to ensure that at least two or three follicles are developed, in order to maximise pregnancy potential.

Growth hormone, insulin-like growth factor (IGF) and GnRH all increase the sensitivities of the ovaries to gonadotrophin stimulation and enhance follicular development (Poretsky 1999) and have been shown to have a role in fertility treatment, since they can improve the outcome of ovarian stimulation therapy. Co-treatment with growth hormone combined with HMG and HCG for ovulation induction has been suggested as a way to improve follicle growth, and probably pregnancy rate, in patients with hypogonadotropic hypogonadism (Homburg 1995). This reduces the gonadotrophin dose requirement, reduces the duration of HMG treatment and improves success rates (Duffy 2010). The IGF system is composed of two ligands (IGF 1 and 2), two receptors and insulin-like growth factor binding proteins (IGFBP). Women treated for subfertility with IGF require a lower gonadotrophin stimulation dose and induction time (Genc 2011).

Studies have suggested that one long-term effect of fertility drugs could be the development of ovarian cancer or borderline ovarian tumours. Borderline ovarian tumours possess many of the same morphological features as their malignant counterparts, but they do not destructively invade the ovarian stroma, and the women in whom they develop have a significantly more favourable prognosis than those with invasive ovarian cancers. Since the aetiology is largely unknown, it is difficult to explain the possible association between invasive ovarian cancers and borderline tumours, reproductive risk factors and the use of fertility drugs. However, it has largely been established that risk factors for the disease relate mostly to reproductive events and there is also a general agreement on the protective effects of pregnancy (Rish 1994) and oral contraceptive use (Whittemore 1992a). Several hypotheses have postulated ovulation as a potential biologic promoter of ovarian cancer. Research has shown that epithelial ovarian cancer might be caused by repeated ovulations, which disrupt the ovarian epithelium and lead to malignant transformation of the epithelial cells, the so called 'incessant ovulation' hypothesis. Genetic alterations may develop, due to the many micro-traumata and the high mitotic activity associated with ovulation, eventually causing autonomic growth of the malignant cells (Fathalla 1971). According to the 'incessant ovulation' theory, promoting ovulation by ovulation induction medications might increase the frequency of invasive ovarian tumours, whilst any factor which suppresses ovulation, such as pregnancy, oral contraception, lactation and an early menopause, might reduce the risk of cancer.

Fertility medication stimulates multiple oocytes so there is simultaneous maturation and ovulation during one cycle. This serves to increase the mechanical trauma and the number of epithelial inclusions in the surface epithelium of the ovary (Meirow 1996). It has been estimated that a single cycle of ovulation induction, preparing for IVF, can be equivalent to two years of normal menstrual cycles, in term of the number of follicles produced and oestrogen concentrations achieved (Artia 2006). However, some epidemiological studies contradict this link (Booth 1989; Brinton 1989; Ron 1987; Rossing 1994; Whittemore 1992a). The risk

of ovarian cancer in these studies was increased in women with ovulatory disturbances (either lack of ovulation or reduction in the number of ovulations over one year), while according to the 'incessant ovulation' theory, these women would have been expected to have a reduced risk of ovarian cancer. Moreover, [Balasch 1993](#) critically reviewed the literature concerning follicular stimulation and ovarian cancer and concluded that even if an association between ovulation induction and ovarian cancer was found, it would not necessarily indicate an effect of ovarian stimulation. A more likely explanation is that an underlying ovulatory disorder or the absence of pregnancy predisposes the woman to cancer of the ovary ([Balasch 1993](#)).

The second hypothesis proposes a model in which persistent stimulation of gonadotrophins increases the risk of malignant changes directly, or by acting in combination with a raised concentration of oestrogen ([Rish 1998](#)). The gonadotrophin theory is based on the animal studies of Biskind carried out in 1944 ([Biskind 1944](#)). In this study, it was found that rats developed ovarian tumours of stromal origin (no epithelial tumours occurred) when they were manipulated to produce high concentrations of gonadotrophins. Nevertheless, these data do not prove the existence of a casual relationship between iatrogenic raised serum gonadotrophin concentrations (i.e. prescribed by a health care provider and not naturally produced by the body) and the development of granulosa cell tumours. Other explanations are possible, such as tumour presence before fertility treatment initiation, or that the onset of the tumour during fertility treatment was coincidental ([Meirow 1996](#)). A study has suggested that persistent stimulation of the ovary by gonadotrophins may have a direct effect or may act through, or in combination with, raised concentrations of oestrogen ([Henderson 1998](#)). The gonadotrophin model is consistent with the known protective effects of each additional pregnancy and duration of oral contraceptive use, since both pregnancy and oral contraceptive use have been shown to lower basal as well as peak gonadotrophin stimulation ([Henderson 1998](#)). Another hypothesis frequently suggested is that an undiagnosed early ovarian cancer causes, in some manner, subfertility. This hypothesis was based upon epidemiological data which showed an increased rate of subfertility in patients with ovarian cancer ([Harris 1992](#); [Whittemore 1992a](#)).

Why it is important to do this review

In spite of the increase in women requesting fertility treatments, and the incidence of ovarian cancer in most Western countries, the question of whether ovarian stimulation increases the incidence of ovarian cancer as an independent factor is still unanswered. Additionally, it is still difficult to separate the possible role of fertility drugs from underlying subfertility as risk factors for ovarian cancer. Although these are seemingly straightforward questions, ovarian cancer is a relatively rare outcome, and mostly occurs late in life, many years after normal childbearing age or fertility therapy. Moreover, there is still uncertainty over the role of various drugs,

since limited information is available on the different potential effects they may have. An evaluation of risk factors for ovarian cancer was published in a combined analysis of 12 US case-control studies of ovarian cancer diagnosed between 1956 and 1986 and conducted by the Collaborative Ovarian Cancer Group (US) ([Whittemore 1992b](#)). Only three of the 12 studies examined the association between the use of fertility drugs and invasive ovarian cancer; the others evaluated different reproductive and menstrual risk factors. The study showed a 2.7-fold increased risk of ovarian cancer in subfertile women who had used fertility drugs as compared to no use and a 27-fold higher risk in subfertile women who had never been pregnant compared to subfertile women who had been treated and conceived. In this study, subfertile women who had not used fertility drugs experienced no increased risk of ovarian cancer compared with women without a history of subfertility ([Whittemore 1992b](#)). This study had limitations, for example few of the women had used fertility medications, making the confidence interval around the risk estimates wide, and some of the fertility drugs when used were outdated (such as conjugated oestrogen and diethylstilbestrol) ([Mahdavi 2006](#)). Moreover, there was poor information given about the reasons for subfertility in the women included which made it impossible to separate the treatment effects from ovulatory abnormalities that themselves may increase the risk of ovarian cancer. Moreover, little or no information on the types of medications used or the duration of treatment was provided and also patients with ovarian cancer may have been more likely than the controls to recall their exposure to fertility drugs (recall bias), which could have overestimated the risk of association. Subsequently, a large cohort study also suggested an increased risk of invasive and borderline ovarian tumours among women using clomiphene citrate for 12 months or more ([Rossing 1994](#)), and between the use of fertility medications and non-epithelial cancers ([Horn-Ross 1992](#)). This finding was also confirmed by other authors ([Harris 1992](#); [Ness 2002](#); [Nugent 1998](#); [Parazzini 1998](#); [Shushan 1996](#)).

In contrast, several other epidemiological studies failed to confirm the above findings and do not show any association between women exposed to treatment with ovulation-inducing drugs and untreated infertile woman ([Brinton 2004](#); [Dor 2002](#); [Doyle 2002](#); [Franceschini 1994](#); [Jensen 2009](#); [Modan 1998](#); [Mosgaard 1997](#); [Mosgaard 1998](#); [Rossing 2004](#); [Venn 1999](#)).

Several reviews have evaluated the long-term effects of ovulation-promoting drugs on cancer risk ([Brinton 2005](#); [Brinton 2012](#); [Gadducci 2013](#); [He 2012](#); [Mahdavi 2006](#)) and, to our knowledge, there are only three systematic reviews and meta-analyses ([Kashyap 2003](#); [Li 2013](#); [Siristatidis 2013](#)) evaluating the literature regarding the relationship between fertility drugs and ovarian cancer. One included seven case-control and three cohort studies ([Kashyap 2004](#)), one included only six cohort studies ([Li 2013](#)) and the last published included only nine cohort studies calculating the risk of ovarian cancer in infertile women treated with fertility drugs. The authors in two of these meta-analyses ([Kashyap 2003](#); [Li 2013](#)) re-

ported a significant elevated risk of ovarian cancer in treated subfertile patients when compared to the general population. However, data from cohort studies that compared treated with untreated subfertile patients suggests that treated patients may tend to have a lower incidence of ovarian cancer (Kashyap 2004). The last published meta-analysis reported that fertility treatment is not associated with an elevated risk of ovarian cancer (Siristatidis 2013). This meta-analysis included only some of the observational studies published on this topic up to 2013. It is therefore important to conduct an updated systematic review including all the available evidence published up to 2013.

OBJECTIVES

To evaluate the risk of ovarian cancer in women treated with ovulation stimulating drugs for subfertility.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), non-randomised studies (cohort studies and case-control studies) and case series including more than 30 participants were eligible for inclusion.

Types of participants

Women aged 18 years and older with at least one ovary.

Types of interventions

The intervention or exposure of interest includes the following fertility medications: clomiphene citrate; selective oestrogen receptor modulator (SERM); luteinising hormone; follicle-stimulating hormone (FSH); purified FSH; human chorionic gonadotrophin (HCG); gonadotrophin-releasing hormone agonist (GnRH-AG); gonadotrophin-releasing hormone antagonist (GnRH-A) and growth hormone. The comparison groups included either subfertile women not treated with any of the above mentioned fertility drugs, or women from the general population who did not receive fertility treatment.

Types of outcome measures

Primary outcomes

The primary outcome or case of interest is a new diagnosis of primary borderline ovarian tumour or malignant ovarian tumour of epithelial, germ cell or stroma origin and confirmed by histology investigations.

Secondary outcomes

None.

Search methods for identification of studies

Electronic searches

We carried out a comprehensive search for published and unpublished observational studies from 1990 to February 2013. We restricted our search to start from 1990 as subfertility and especially fertility treatment increased in the UK and US after 1988. In addition, in initial scoping searches we did not find any articles referring to any significant research in this topic area published before 1990. We used the following databases: the Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register, the Cochrane Central Register of Controlled Trials (CENTRAL 2013, Issue 1) (Appendix 1), MEDLINE (to February week 4 2013) (Appendix 2) and EMBASE (to 2013 week 09) (Appendix 3).

Searching other resources

Unpublished and grey literature

We searched for studies published or ongoing using the MetaRegister (<http://www.controlled-trials.com>), Physicians Data Query (<http://www.nci.nih.gov>), <http://www.clinicaltrials.gov> and <http://www.cancer.gov/clinicaltrials>.

We searched conference proceedings and abstracts through ZETOC (<http://zetoc.mimas.ac.uk>) and WorldCat Dissertations. Moreover, we checked the citation lists of included studies, key text books and previous systematic reviews through handsearching, and contacted experts in the field to identify further reports of trials. If other relevant articles were identified, we searched them for candidate articles. We handsearched reports of conferences in the following sources: *Gynecologic Oncology* (Annual Meeting of the American Society of Gynecologic Oncologist), *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 the Annual Meeting of the American Society of Clinical Oncology (ASCO).

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to a reference management database (Reference Manager), removed duplicates and two review authors (IR, RB) independently examined the remaining references. Those studies which clearly did not meet the inclusion criteria were excluded and we obtained copies of the full text of potentially relevant references. At least two review authors (IR and RB or LS) assessed independently the eligibility of the retrieved papers. Disagreements were resolved by discussion between the two review authors and if necessary by the third review author. We documented reasons for exclusion.

Data extraction and management

For included studies we extracted data on study design, characteristics of patients (such as eligibility criteria, age, parity, use of oral contraceptive pill, medical diagnosis of subfertility, age of menarche and family history of ovarian cancer), interventions (type of treatment, dosage and number of treatment cycles), risk of bias, duration and person-years of follow-up, histological type of ovarian cancer, summary effect estimates, factors adjusted for, unadjusted and adjusted summary statistics and where the study was conducted.

We extracted the number of participants with ovarian cancer in each treatment or exposure group and the number of participants assessed at endpoint and unadjusted and adjusted summary statistics. We noted the time points at which outcomes were collected and reported. Two review authors (IR, RB) abstracted data independently onto a data abstraction form specially designed for the review and a third review author (LS) checked the extraction, in addition to resolving any differences between review authors.

Assessment of risk of bias in included studies

As we did not find any RCTs the assessment of risk of bias focused exclusively on non-randomised studies.

We assessed the risk of bias in non-randomised studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* sections 13.5 and 8.5 (Higgins 2011).

We assessed the likelihood of bias due to selection bias, control of confounding, performance bias, detection bias and attrition bias. We rated studies eliciting a positive response to the following questions as low risk of bias.

Selection bias and control of confounding

- Demonstration that women did not have ovarian cancer at the start of the study and had at least one ovary (cohort studies).
- All eligible cases over a defined period of time or a random sample or consecutive series of those cases (case-control studies).
- Community controls derived from the same population as the cases (case-control studies).

Control of confounding

We pre-specified the following factors as potential confounders and noted whether they were balanced at baseline (or at outcome assessment for studies where participants were allocated to groups on the basis of outcome) between the two groups, or balanced through matching at the time when participants were allocated to groups or adjusted through an adjusted analysis. These factors were chosen as they are known risk factors for ovarian cancer (cohort studies/case-control studies).

Risk factors: age, parity, use of oral contraceptive pill, family history of ovarian cancer, age of menarche, age of menopause, smoking, body mass index (BMI), breast-feeding, use of hormone replacement therapy (HRT), social class, hysterectomy status and causes of subfertility.

Performance bias

- Exposure to fertility drugs was ascertained by medical record review (cohort studies/case-control studies).
- The same method to ascertain exposure to fertility drugs was used for cases and controls (case-control studies).
- Assessors of exposure to fertility drugs were blinded to the presence or absence of ovarian cancer (cohort studies/case-control studies).

Detection bias

- Ovarian cancer was confirmed by histology (cohort studies).
- Ovarian cancer confirmed by histology in the cases and no clinical evidence of cancer in the controls (case-control studies).
- Assessors of cancer status were blinded to exposure status (cohort studies/case-control studies).

Attrition bias

- Women exposed to ovarian stimulating drugs and unexposed women in the control group were followed up for the same length of time (cohort studies/case-control studies).
- At least 80% of women in all groups were included in the final analysis, or the description of those not included was not suggestive of bias (cohort studies/case-control studies).

Measures of treatment effect

We extracted all the summary statistics as reported from each study. These included the crude and adjusted odds ratio (OR), risk ratio (RR), hazard ratio (HR) with their respective 95% confidence interval (CI). For studies not reporting relative treatment effects we report the standardised incidence ratio (SIR) with 95% CI. For studies that reported both relative treatment effects and incidence ratios, we preferentially focus on the relative effect estimates in the text but report incidence ratios for completeness.

Unit of analysis issues

None were expected.

Dealing with missing data

We did not impute missing outcome data for the primary outcome. We did not contact study authors to obtain missing outcome data.

Assessment of heterogeneity

As non-randomised studies are expected to be more heterogeneous than randomised trials, due to methodological diversity and greater susceptibility to bias, we showed the variation in study findings by presenting a forest plot with the pooled estimate suppressed.

Assessment of reporting biases

We did not formally assess publication bias as we did not anticipate conducting a meta-analysis. We conducted a qualitative assessment of the likely impact of publication bias only.

Data synthesis

Our protocol specified that meta-analysis would be conducted where appropriate. However, meta-analysis was not performed due to methodological and clinical heterogeneity between studies, suggesting that any overall statistical summary may be misleading.

Instead we grouped studies by type of drug given and present results as a narrative summary in the text and in tables and a forest plot without an overall summary statistic. Synthesis of the data focused on describing the consistency of effect of ovulation stimulating drugs in causing ovarian cancer, assessing the risk of bias and investigating factors that may explain differences between the results of studies.

Subgroup analysis and investigation of heterogeneity

As we did not perform a meta-analysis due to expected heterogeneity, we were unable to conduct quantitative subgroup analyses. Instead, we provide a qualitative description of the differences in the results between different types of fertility drugs, by whether control groups included infertile women untreated with ovarian stimulating drugs or women from the general population, by parity and for different histological types of ovarian cancer.

Sensitivity analysis

Sensitivity analysis was not specified as we did not plan meta-analysis.

RESULTS

Description of studies

Results of the search

The search of all the databases resulted in a large number of studies (5176), of which we deemed 216 potentially eligible after having read the titles and abstracts and for which we obtained hard copies of the full article for further scrutiny. From these 116 were excluded (Figure 1). There were no articles meeting the eligibility criteria that required translation. All the articles had an abstract in the English language. We did not identify any RCTs to include.

Figure 1. Identification and selection of studies.

Included studies

Cohort studies

Fourteen cohort studies (Brinton 2004; Calderon-Margalit 2009; Dor 2002; Dos Santos Silva 2009; Doyle 2002; Kallen 2011; Lerner-Geva 2003; Lerner-Geva 2012; Modan 1998; Potashnik 1999; Sanner 2009; Van Leeuwen 2011; Venn 1999; Yli-Kuha 2012) were included. Seven studies (Brinton 2004; Calderon-Margalit 2009; Dos Santos Silva 2009; Doyle 2002; Modan 1998;

Sanner 2009; Van Leeuwen 2011) compared the risk of ovarian cancer in subfertile women treated with ovarian stimulating drugs with the risk in untreated subfertile women attending the same fertility clinics. Four of these cohort studies also reported the standardised incidence ratio (SIR) for comparison with the general population (Brinton 2004; Sanner 2009; Van Leeuwen 2011; Venn 1999). Five (Dor 2002; Lerner-Geva 2003; Lerner-Geva 2012; Modan 1998; Venn 1999; Yli-Kuha 2012) only compared the risk of ovarian cancer in women treated with ovarian stimulating drugs with the risk in the general population. One compared

the risk in women who gave birth after IVF treatment with women who gave birth during the same observation period (Kallen 2011). One cohort study was conducted in the US (Brinton 2004), six in Israel (Calderon-Margalit 2009; Dor 2002; Lerner-Geva 2003; Lerner-Geva 2012; Modan 1998; Potashnik 1999), two in the UK (Doyle 2002; Dos Santos Silva 2009), one in Australia (Venn 1999); two in Sweden (Kallen 2011; Sanner 2009), one in the Netherlands (Van Leeuwen 2011) and one in Finland (Yli-Kuha 2012). Twelve were multicentre studies while the other two were conducted in single centres. All cohort studies were conducted retrospectively and almost all (12 out of 13) sampled women from fertility clinics, while one selected their sample from women enrolled in the Jerusalem Perinatal Study (Calderon-Margalit 2009). All cohort studies were conducted between 1960 and 2009. All women in the cohort studies were either premenopausal or with a premature menopause, with at least one ovary and free from ovarian cancer at the start of the study. Almost all the studies used HCG, clomiphene citrate, HMG and GnRH alone or as co-therapy with each other as ovarian stimulating drugs, but the number of cycles and doses used were not reported in 10 studies (Calderon-Margalit 2009; Dor 2002; Dos Santos Silva 2009; Doyle 2002; Kallen 2011; Lerner-Geva 2003; Lerner-Geva 2012; Modan 1998; Potashnik 1999; Venn 1999; Yli-Kuha 2012). Duration of follow-up was more than 10 years in eight studies (Brinton 2004; Calderon-Margalit 2009; Dos Santos Silva 2009; Lerner-Geva 2012; Modan 1998; Potashnik 1999; Venn 1999; Van Leeuwen 2011). In two cohort studies (Dor 2002; Lerner-Geva 2003) the length of follow-up was not reported clearly, and in three cohort studies (Doyle 2002; Kallen 2011; Yli-Kuha 2012) the subfertile women treated were followed up for less than 10 years. One study reported 30 years of follow-up (Lerner-Geva 2012).

Case-control studies

Eleven case-control studies (Franceschini 1994; Jensen 2009; Kurta 2012; Mosgaard 1997; Mosgaard 1998; Parazzini 1997; Parazzini 1998; Parazzini 2001; Rossing 1994; Rossing 2004; Shushan 1996), two of which were nested case-control studies (Jensen 2009; Rossing 1994) were included. All studies were conducted between 1994 and 2008. One was conducted in Israel (Shushan 1996), three in the US (Kurta 2012; Rossing 2004; Rossing 1994), three in Denmark (Jensen 2009; Mosgaard 1997; Mosgaard 1998) and four in Italy (Franceschini 1994; Parazzini 1997; Parazzini 1998; Parazzini 2001). Characteristics of the study samples can be seen in [Characteristics of included studies](#). Two of eight case-control studies (Parazzini 1998; Rossing 1994) involved women from a single hospital, while the others were multicentre studies. In one study the cases and controls were selected from the Hormones and Ovarian Cancer Prediction (HOPE) study, a national population case-control study (Kurta 2012). In six case-control studies (Jensen 2009; Mosgaard 1997; Mosgaard

1998; Rossing 1994; Rossing 2004; Shushan 1996), the cases were selected from the National Cancer Registry and controls from the same hospital or from the same geographical area as the cases. In the other four case-control studies (Franceschini 1994; Parazzini 1997; Parazzini 1998; Parazzini 2001) the cases were selected from hospitals. The cases had ages ranging from 22 to 79 years old and included invasive ovarian cancer and borderline ovarian tumours. The controls were of a similar age, ranging from 16 to 79 years old.

Only in five case-control studies was the type of ovarian-stimulating drug clearly reported (Jensen 2009; Kurta 2012; Mosgaard 1997; Mosgaard 1998; Rossing 1994) and was clomiphene citrate, HCG, HMG and gonadotrophins alone or as co-therapy, while in six the specific drugs used were unreported (Franceschini 1994; Parazzini 1997; Parazzini 1998; Parazzini 2001; Rossing 2004; Shushan 1996). Moreover, the number of cycles and dose used were clearly reported for some of the drugs used in two studies only (Jensen 2009; Rossing 2004). The duration between exposure and follow-up was the same for cases and controls in four case-control studies (Mosgaard 1998; Parazzini 1998; Parazzini 1997; Parazzini 2001). It was unclear in two studies (Kurta 2012; Shushan 1996) and it was not the same in three studies (Franceschini 1994; Mosgaard 1997; Rossing 2004).

Excluded studies

We excluded 116 studies after having read the entire text, mostly because they reported on multiple risk factors for invasive ovarian cancer in subfertile women and/or subfertility and other known risk factors for epithelial ovarian cancer. Four studies (Artini 1997; Balasch 1993; Franco 2000; Lopes 1993) were excluded because they were reviews of case reports. Three studies were excluded (Dos Santos 2002; Goldberg 1992; Willemsen 1993) as they were case series reporting 30 cases or fewer, and one study was excluded as the diagnosis of ovarian cancer in the cases was not confirmed by histological reports, but was diagnosed according to ultrasonographic findings (Pozlep 2001). Eight articles (Franceschini 1994; Harris 1992; Horn-Ross 1992; Negri 1991; Ness 2000; Ness 2002; Whittemore 1992a; Whittemore 1994) were excluded as they were not primary studies, but were pooled (secondary) analyses of case-control and cohort studies reporting the risk of ovarian cancer in subfertile women using ovarian-stimulating drugs. One study was excluded because the data were published only as an abstract and were not fully informative of the risk of ovarian cancer calculated by the author (Croughan-Minihane 2001).

Risk of bias in included studies

Overall study quality was highly variable between studies and as all the studies were non-randomised we judged none of them to be of low risk of bias (Figure 2).

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

Allocation

In all 13 cohort studies selection bias was minimised. The sample consisted of all women attending fertility or gynaecological clinics (or both) during the defined study period and they were recruited consecutively. At the study inception women had no history of ovarian cancer and all had at least one ovary.

In six case-control studies (Jensen 2009; Mosgaard 1997; Mosgaard 1998; Rossing 1994; Rossing 2004; Shushan 1996), the cases were selected from the National Cancer Registry and controls from the same hospital or from the same geographical area as the cases. On the contrary, in the other four case-control studies (Franceschini 1994; Parazzini 1997; Parazzini 1998; Parazzini 2001) the cases were selected from hospitals. Age-matched controls were selected from the general population in the same geographic area from which cases arose in three studies (Mosgaard 1997; Mosgaard 1998; Rossing 2004). In four studies hospital-based controls were selected from hospital clinics for non-gynaecological conditions serving the same areas as those from which cases were selected (Franceschini 1994; Parazzini 1997; Parazzini 1998; Parazzini 2001). In four studies controls were women attending hospital clinics for non-neoplastic gynaecologic conditions (Franceschini 1994; Parazzini 1997; Parazzini 1998; Parazzini 2001) and in one women were part of the control group used in the Women's Contraceptive and Reproductive Experiences (CARE) study of breast cancer which was another study conducted contemporaneously (Rossing 2004). Two nested case-control studies randomly selected controls from the entire cohort of women in the study (Jensen 2009; Rossing 1994). One case-control study obtained cases and controls from a national case-control study in-

volving several hospitals (Kurta 2012).

Only two studies matched or adjusted for all or most of the pre-specified risk factors that we identified as potential confounders, such as age, parity, use of oral contraceptive pill, family history of ovarian cancer, age of menarche, age of menopause, smoking, high BMI, breast-feeding and use of HRT (Jensen 2009; Mosgaard 1997).

Of the 13 cohort studies, five (Dor 2002; Lerner-Geva 2003; Modan 1998; Potashnik 1999; Venn 1999) only reported the SIR which was adjusted for age. Two studies adjusted for calendar time (Brinton 2004); one for area of residence (Brinton 2004); two studies for type of infertility (Brinton 2004; Sanner 2009); three studies for parity (Brinton 2004; Rossing 1994; Sanner 2009); six studies for age (Brinton 2004; Calderon-Margalit 2009; Kallen 2011; Rossing 2004; Sanner 2009; Van Leeuwen 2011); two for use of the oral contraceptive pill (Brinton 2004; Sanner 2009); one only for smoking and year of delivery after IVF (Kallen 2011); one for the presence of endometriosis or tubal factor as reason for subfertility (Van Leeuwen 2011) and one for marital status and socioeconomic position (Yli-Kuha 2012).

Of the 11 case-control studies only one did not control for confounding in the analyses and only reported a crude estimate (Parazzini 2001). All the other studies adjusted for age (Franceschini 1994; Jensen 2009; Kurta 2012; Mosgaard 1997; Mosgaard 1998; Parazzini 1997; Parazzini 1998; Rossing 1994; Rossing 2004; Shushan 1996). Two adjusted for ethnicity (Kurta 2012; Rossing 2004) and one for region of birth (Shushan 1996). Four studies adjusted for family history of ovarian cancer (Jensen 2009; Kurta 2012; Mosgaard 1997; Shushan 1996);

one for smoking (Mosgaard 1998); seven for parity (Franceschini 1994; Jensen 2009; Parazzini 1997; Parazzini 1998; Rossing 1994; Rossing 2004; Shushan 1996); one for history of previous cancer (Mosgaard 1997); four for area of residence (Franceschini 1994; Mosgaard 1997; Mosgaard 1998; Rossing 2004); six for education (Franceschini 1994; Jensen 2009; Kurta 2012; Parazzini 1997; Parazzini 1998; Shushan 1996); two for hormonal replacement therapy (Mosgaard 1997; Mosgaard 1998); one for intrauterine device (Mosgaard 1997); two for oral contraceptive pill use (Jensen 2009; Kurta 2012); two for body mass index (Mosgaard 1997; Shushan 1996); one for menopausal status (Mosgaard 1997; Jensen 2009); one for age at menopause, history of subfertility, spontaneous miscarriage and termination of pregnancy (Jensen 2009); two for the number of births (Kurta 2012; Rossing 2004) and one for race, tubal ligation, age at menarche, duration of breast-feeding, perineal talc use and family history of ovarian or breast cancer (or both) (Kurta 2012). See Table 1 and Table 2.

Blinding

Recall bias may be a factor in all the studies as fertility drug treatment received was obtained by self report or retrospective review of case notes and therefore may be incompletely or inaccurately recalled or recorded.

In 11 cohort studies ascertainment of the exposure to fertility drugs was conducted by reviewing medical records (Brinton 2004; Dor 2002; Dos Santos Silva 2009; Doyle 2002; Kallen 2011; Lerner-Geva 2003; Modan 1998; Potashnik 1999; Sanner 2009; Venn 1999; Yli-Kuha 2012) and in one cohort study by using a self completed questionnaire given to all women in the study (Calderon-Margalit 2009). In one cohort study information was obtained using a self completed questionnaire and also by reviewing medical records (Van Leeuwen 2011). Blinding of assessors to the presence or absence of ovarian cancer status was not reported in the 13 cohort studies.

In two case-control studies exposure to fertility drugs was conducted by reviewing medical records (Jensen 2009; Rossing 1994). In eight of the case-control studies exposure to fertility drugs was ascertained by a standard questionnaire given to all women in case and control groups and some information was also derived from the medical notes (Franceschini 1994; Kurta 2012; Mosgaard 1997; Mosgaard 1998; Parazzini 1997; Parazzini 2001; Rossing 2004; Shushan 1996); in one the method used was unclear (Parazzini 1998). In five case-control studies it was unclear if assessors were blinded to the case/control status (Kurta 2012; Mosgaard 1997; Parazzini 1998; Parazzini 2001; Rossing 2004), while in the other four studies assessors were not blind to the presence or absence of ovarian cancer (Franceschini 1994; Jensen

2009; Mosgaard 1998; Parazzini 1997; Rossing 1994; Shushan 1996). In all the studies the same method was used to ascertain the exposure to fertility drugs for the cases and for the controls.

Detection bias in relation to ascertainment of outcome was rare across all the studies as all used histology reports to confirm the diagnosis of ovarian cancer, and all of the control groups had no histological evidence of previous ovarian cancer. However, blinding of investigators to exposure status was not reported.

Incomplete outcome data

Six studies were at risk of attrition bias due to fewer than 80% of the sample being followed up (Dor 2002; Franceschini 1994; Parazzini 1998; Rossing 2004; Shushan 1996; Van Leeuwen 2011); in one study it was unclear (Rossing 1994).

Selective reporting

In three cohort studies the fertility drugs investigated were clearly reported and therefore we judged the risk of reporting bias to be low (Mosgaard 1997; Mosgaard 1998; Van Leeuwen 2011). In six of the cohort studies the risk of reporting bias was high: it was unclear if all fertility drugs given were investigated as it was difficult to judge if there was a mismatch between drugs investigated and those reported in the final analysis (Calderon-Margalit 2009; Dos Santos Silva 2009; Kallen 2011; Lerner-Geva 2003; Lerner-Geva 2012; Modan 1998; Yli-Kuha 2012).

Other potential sources of bias

No other potential sources of bias were identified.

Effects of interventions

Invasive ovarian cancer

Any fertility drug

Six cohort studies (Dos Santos Silva 2009; Doyle 2002; Kallen 2011; Lerner-Geva 2012; Potashnik 1999; Yli-Kuha 2012) and seven case-control studies (Franceschini 1994; Kurta 2012; Mosgaard 1997; Parazzini 1997; Parazzini 2001; Rossing 2004; Shushan 1996) evaluated the incidence of invasive ovarian cancer with any fertility drug use (Figure 3). The study by Rossing 1994 included borderline tumours and did not present results by tumour type.

Figure 3. Forest plot of comparison: I Infertility drugs versus no infertility drug, outcome: 1.2 Invasive ovarian cancer.

- (1) multiparous subgroup of women
- (2) nulliparous subgroup of women
- (3) multiparous subgroup of women
- (4) nulliparous subgroup of women
- (5) multiparous subgroup of women
- (6) nulliparous subgroup of women
- (7) nulliparous subgroup women
- (8) multiparous subgroup women
- (9) nulliparous subgroup women
- (10) multiparous subgroup women
- (11) multiparous subgroup women
- (12) nulliparous subgroup women
- (13) nulliparous subgroup women
- (14) multiparous subgroup women

There was no evidence of an increased risk with any fertility drug used compared with non-use in the general population in one cohort study which reported a hazard ratio (HR) of 0.61 (95% confidence interval (CI) 0.08 to 4.42) and another which reported an odds ratio (OR) of 2.75 (95% CI 0.69 to 9.63) (Calderon-Margalit 2009; Yli-Kuha 2012) (Table 1).

Five studies only reported the standardised incidence ratio (SIR) for exposure to any fertility drug use and invasive ovarian cancer (Dor 2002; Lerner-Geva 2003; Lerner-Geva 2012; Sanner 2009; Venn 1999; Van Leeuwen 2011). Three analysed the risk of invasive ovarian cancer according to the number of IVF cycles used (Dor 2002; Van Leeuwen 2011; Venn 1999). None showed evidence of a difference in SIR with the number of cycles. One study (Lerner-Geva 2003) reported an increased risk of ovarian cancer in subfertile women treated with ovarian stimulating drugs when compared to the general population (SIR 5.0, 95% CI 1.02 to 14.6), which decreased when cancer cases diagnosed within one year of treatment were excluded from the analysis (SIR 1.67, 95% CI 0.02 to 9.27) (Lerner-Geva 2003). One study showed no evidence of an increase in SIR (Sanner 2009) (Table 1).

Seven case-control studies showed no evidence of increased risk in women who used any fertility drug compared with controls who were women of a similar age and variably matched for reproductive risk factors (Table 2; Figure 3)

Only two cohort studies clearly reported the different histologic types of cancers among the cases included (Kallen 2011; Van Leeuwen 2011).

Clomiphene

Four cohort studies (Brinton 2004; Lerner-Geva 2012; Rossing 1994; Sanner 2009) and five case-control studies (Jensen 2009; Kurta 2012; Mosgaard 1997; Rossing 2004; Shushan 1996) evaluated the incidence of invasive ovarian cancer with clomiphene. Three cohort studies showed no convincing evidence for an increased risk of invasive cancer with clomiphene use compared with no use in women with subfertility (Table 1). Five case-control studies showed no evidence of an increased risk in women who used clomiphene compared with women of a similar age and variably matched for reproductive risk factors (Table 2; Figure 3).

One cohort study reported a hazard ratio of 0.98 (95% CI 0.14 to 7.11), indicating no evidence of an increased risk with clomiphene compared with non-use in the general population (Calderon-Margalit 2009).

Two studies only reported SIR for exposure to clomiphene and invasive ovarian cancer (Modan 1998; Venn 1999) and showed no evidence of an increase in women who used clomiphene when compared to subfertile untreated women in one study (Modan 1998), and when compared to the general population in two studies (Lerner-Geva 2012; Venn 1999), one with 30 years follow-up

(Lerner-Geva 2012) (Table 1; Analysis 1.1).

Clomiphene plus gonadotrophin

Three cohort studies (Brinton 2004; Lerner-Geva 2012; Modan 1998; Sanner 2009) and four case-control studies (Kurta 2012; Mosgaard 1997; Rossing 2004; Shushan 1996) evaluated the incidence of invasive ovarian cancer with clomiphene plus gonadotrophin. Two cohort studies showed no convincing evidence for an increased risk of invasive cancer with clomiphene plus gonadotrophin use compared with no use in women with subfertility.

Two studies only reported SIR for exposure to clomiphene and human menopausal gonadotrophin (HMG) and invasive ovarian cancer (Modan 1998; Venn 1999) and showed no evidence of an increase in women who used clomiphene plus HMG when compared to infertile women not treated (Modan 1998) or when compared to the general population (Lerner-Geva 2012; Venn 1999) (Table 1).

Four case-control studies also showed no evidence of an increased risk in women who used clomiphene plus gonadotrophin compared with women of a similar age and variably matched for reproductive risk factors (Table 2; Analysis 1.2).

Gonadotrophin

Four cohort studies (Brinton 2004; Lerner-Geva 2012; Sanner 2009; Van Leeuwen 2011) and five case-control studies (Jensen 2009; Kurta 2012; Mosgaard 1997; Rossing 1994; Shushan 1996) evaluated the incidence of invasive ovarian cancer with gonadotrophin use. The cohort studies showed no convincing evidence for an increased risk of invasive cancer with gonadotrophin use compared with no use in women with subfertility. The study by Sanner 2009 showed an increased risk (OR 5.21, 95% CI 1.67 to 16), adjusted for age and indication. The confidence interval reflects a high degree of uncertainty about this estimate which is based on only six cases of ovarian cancer in women exposed to gonadotrophin.

One study reported SIR for invasive ovarian cancer with exposure to HMG and showed no evidence of an increase in women who used HMG when compared to the general population (Lerner-Geva 2012) (Table 1).

Three case-control studies showed no evidence of an increased risk in women who used gonadotrophin compared with women of a similar age and variably matched for reproductive risk factors (Table 1).

Two case-control studies reported results separately by parity (Mosgaard 1997; Rossing 2004). Whilst risk estimates for invasive ovarian cancer were slightly lower for parous women compared

with nulliparous women, there was no evidence of a real difference between these two groups for any of the drugs investigated (Table 2; Analysis 1.2)

Borderline cancer

Any fertility drug

One cohort study only reported a SIR for exposure to any fertility drug use and borderline ovarian tumours (Sanner 2009). There was some evidence of a difference in SIR 2.62 (95% CI 1.35 to 4.58) in treated subfertile women compared with the general population based on 12 cases (Sanner 2009). One study reported a significantly increased risk for borderline ovarian tumours in IVF-treated versus subfertile untreated women with more than one year

of follow-up (HR 4.23, 95% CI 1.25 to 14.33) (Van Leeuwen 2011). One cohort study did not show any significant increase in the risk of borderline ovarian cancer and reported an OR of 2.25 (95% CI 0.59 to 8.68) in the exposed group compared to the general population, excluding the first year after IVF (Yli-Kuha 2012) (Table 1).

Three case-control studies (Mosgaard 1998; Parazzini 1998; Shushan 1996) reported the incidence of borderline ovarian cancer, and showed an increased risk in women who used any fertility drug compared with women of a similar age and variably matched for reproductive risk factors (Table 2). The magnitude of these estimates was similar for two studies (Mosgaard 1998; Shushan 1996). The estimate for Parazzini 1998 should be interpreted with caution as there were only four cases exposed to fertility drugs compared with none of the controls, generating a wide confidence interval (Figure 4).

Figure 4. Forest plot of comparison: I Infertility drugs versus no infertility drug, outcome: 1.2 Borderline ovarian cancer.

- (1) nulliparous and multiparous women
- (2) multiparous subgroup of women
- (3) nulliparous subgroup women
- (4) multiparous subgroup women
- (5) nulliparous subgroup women
- (6) multiparous subgroup women
- (7) nulliparous subgroup women

Clomiphene

One cohort study showed no convincing evidence for an increased risk of borderline tumours with clomiphene compared with women in the cohort unexposed to hormonal fertility treatment, adjusted for the factors shown in Table 1 (Sanner 2009). Two case-control studies (Mosgaard 1998; Shushan 1996) showed no convincing evidence for an increased risk of borderline tumours with clomiphene compared with no use in women of a similar age and variably matched for reproductive risk factors (Table 2; Figure 4).

Clomiphene plus gonadotrophin

One cohort study showed no convincing evidence for an increased risk of borderline tumours with clomiphene plus gonadotrophin use compared with women in the cohort unexposed to hormonal fertility treatment (Sanner 2009) (Table 1; Figure 4). The two case-control studies (Mosgaard 1998; Shushan 1996) showed no convincing evidence for an increased risk of borderline tumours with clomiphene plus gonadotrophin compared with no use in women of a similar age and variably matched for reproductive risk factors (Table 2; Figure 4).

Gonadotrophin

One cohort study showed no convincing evidence for an increased risk of borderline tumours with gonadotrophin use compared with women in the cohort unexposed to hormonal fertility treatment (Sanner 2009) (Table 1; Figure 4).

One case-control study (Shushan 1996) reported an increased risk in users of HMG (OR 9.38, 95% CI 1.66 to 52.08), however these data should be interpreted with caution due to only six of the cases ever having used HMG, generating wide confidence intervals which weaken any conclusions. One case-control study (Mosgaard 1998) showed no convincing evidence for an increased risk of borderline tumours with gonadotrophin compared with no use in women of a similar age and variably matched for reproductive risk factors (Table 2; Analysis 1.1).

One case-control study reported results separately by parity (Mosgaard 1998). Whilst risk estimates for borderline ovarian tumours were slightly lower for parous women compared with nulliparous women, there was no evidence of a real difference between these two groups for any of the drugs investigated (Table 2).

Summary of main results

Overall we found no convincing evidence of an increase in the risk of invasive ovarian tumours with fertility drug treatment. There may be an increased risk of borderline ovarian tumours in subfertile women treated with in vitro fertilisation (IVF). Studies showing an increase in the risk of ovarian cancer had a high overall risk of bias due to retrospective study design, lack of accounting for potential confounding and lack of details about fertility drug treatments given; estimates were based on a small number of cases giving rise to wide confidence intervals. Studies with more robust estimates based on a larger number of cases did not detect differences between exposed and unexposed women.

One study (Rossing 1994) reported a higher risk in women with long-term use of clomiphene citrate (12 or more cycles). This was observed in subfertile women who conceived following treatment as well in subfertile women who were refractory to therapy. The same was not shown with the use of HCG in the same cohort of patients. This study was limited by the small number of tumours, with almost half of them being borderline (5 out of 11 neoplasms), which gives strong evidence of a selection bias. Moreover, the author included two patients with granulosa cell tumour. This histological type of invasive ovarian cancer often presents with abnormalities of fertility and ovulation which may be the cause of the tumour rather than the use of ovulation-stimulating drugs.

Overall three case-control studies (Mosgaard 1998; Parazzini 1998; Shushan 1996) reported an increased risk of developing borderline ovarian cancer. In one of the studies (Shushan 1996) subfertile women treated with ovarian stimulation drugs were reported to have an increased risk of developing borderline ovarian tumours and also invasive ovarian cancer when compared to subfertile women not treated. The investigators did not provide any information on the causes of subfertility and also 36% of cases had died before contact was established, which could have caused selection bias. Another case-control study (Parazzini 1998) was based on a very small number of cases (only four) who had used fertility medications. In all three studies the higher proportion of borderline tumours may also suggest that the increased risk is attributed to the increased medical surveillance and younger age of subfertile women. The cohort study (Van Leeuwen 2011) reporting an increase in borderline ovarian tumours in subfertile women highlighted that the risk was particularly high during the first year after the IVF, which may be supported by the reported evidence that ovarian stimulation may induce growth in existing highly differentiated tumours (Brinton 2005).

DISCUSSION

Overall completeness and applicability of

evidence

The results from the cohort studies are broadly generalised to women who seek fertility treatment as on the whole the samples consisted of all women who attended fertility clinics at major hospitals within a particular time frame. Additionally, as complete case ascertainment was maximised in the majority of the non-randomised studies included, by the use of cancer registries as the source of ovarian cancer cases, this also optimised the identification and selection of the cases within a given timeframe and area. In addition, all the studies were investigating the effect of fertility drugs which are all still currently used during fertility treatment.

Quality of the evidence

A strength of our review is that almost all of the studies included the outcome taken from reliable sources (i.e. cancer registry).

We identified a few factors in the observational studies included in our review which may have biased our final conclusions. First of all, exposed and non-exposed (to the fertility drugs) groups were not always balanced and not many studies adjusted their data for important confounding factors.

Subfertile populations have lower pregnancy rates than the general population, as already proved, and low parity is an important risk factor for ovarian cancer. Risk estimates for ovarian cancer reported in cohort studies that are solely based on comparison with the general population are likely to be biased towards overestimation. In addition, nulliparity, subfertility and lack of use of oral contraceptive pill make subfertile women already at a higher risk of ovarian cancer compared to non-subfertile women. Secondly, in all the studies exposure was ascertained retrospectively and therefore they have limited information on the specific types, dosage and numbers of cycles of fertility drugs. Thirdly, the length of follow-up in some studies may be insufficient as ovarian cancer tends to develop in post-menopausal aged women, and the cancer may not have had time to develop within the time the women were followed up, reducing the number of women with ovarian cancer reported.

Moreover, we were unable to contact researchers to obtain missing data and we therefore rely on the data reported in the published article. In some cases factors relating to study quality, such as measurement of confounding variables and whether these were balanced at baseline and/or adjusted for in the analysis, the number of fertility drug cycles, dosage and type of drugs used, and the duration of subfertility, were not clearly reported.

Several cohort studies used standardised incidence ratios (SIR) to compare cancer risk in subfertile women with that in the general population. This is a statistical parameter which is difficult to interpret as it does not make a comparison between comparable women and does not take into account the influence of factors associated with subfertility that may influence the development of ovarian cancer.

Lack of blinding of investigators to case status and exposure status was also a potential source of bias, along with potential attrition bias in some studies. It is difficult gauge the impact of selective reporting bias as the studies were conducted retrospectively and participants may have been excluded from the sample, if ascertainment of exposure could not be determined. A pre-specified list of all drugs investigated was not provided by any of the studies. None of the studies included specified the histologic subtype of ovarian cancer in the cases found. Future studies should address fertility relationships for cancer histologic subtypes as there is increasing recognition of the aetiological heterogeneity of ovarian cancer ([Gates 2010](#); [Rish 1996](#)).

Potential biases in the review process

We acknowledge that publication bias may limit our conclusions and it is difficult to predict the direction in which the bias would operate. On one hand it is likely that studies with non-significant associations for particular fertility drugs remain unpublished due to perceived unimportance. On the other hand, however, there is also the chance that studies with positive associations are unpublished, although it is more likely that publication bias would be in favour of publishing positive studies.

However, we did not put any limits on our search (such as language restrictions) and we sought published and unpublished data.

We are aware that missing information limits our ability to explore the exact relationship between fertility drugs and ovarian cancer. The strength of the review could have been greatly improved if it have been possible to contact all researchers to obtain original data. Obtaining individual participant data for each study would have allowed us to perform a standard adjustment for confounding factors in all studies, if appropriate variables had been measured. Whilst this could potentially have reduced the likelihood of bias in the included studies, on the other hand it would not have resolved the major problems inherent to observational studies.

Agreements and disagreements with other studies or reviews

Our findings are in broad agreement with those in the most current systematic reviews and meta-analyses on this topic ([Kashyap 2004](#); [Li 2013](#)). These reviews included some of the studies in our review, but not those published since 2001 and not all of the cohort studies we included.

AUTHORS' CONCLUSIONS

Implications for practice

It is difficult to give clear advice about the safety of fertility treatment based on our findings, but the evidence available does not suggest that there is a clinically significant adverse effect. Current guidance recommends treatment with clomiphene citrate for a maximum of six months (NICE 2013; Nugent 1998). We found no evidence that fertility treatment with clomiphene citrate either increases or does not increase the risk of ovarian cancer. Furthermore, there was no conclusive evidence that IVF treatment utilising other fertility drugs conferred a higher risk of ovarian cancer compared with clomiphene citrate alone.

Implications for research

While it seems clear that more epidemiological research is needed, the organisation of this is problematic. The known risk factors for ovarian cancer and the rarity and later onset of incidence necessitate large, long-term prospective studies with careful selected cohorts. Whilst retrospective studies such as case-control studies are attractive (due to the low incidence of ovarian cancer, fewer participants are required to achieve adequate power) they present methodological challenges: selection of an adequate control group, retrospective collection of data on drug exposure increasing the likelihood of recall bias, and attrition bias from missing data on exposure and other important risk factors.

Collaboration between fertility services should be encouraged to facilitate sharing data. Data on drug type, dosage and duration of treatment could be collected prospectively and linked to cancer registries, which collect data on the incidence of ovarian cancer. This would provide estimates of the risk of ovarian cancer with different treatment strategies, such as mono-therapy versus multi-

therapy or high-dose versus low-dose. Information on confounding factors such as parity, oral contraception use and family history should also be collected, along with information on fertility diagnoses, types, dosages and duration of medications, and the outcome of the treatment. Ovarian cancer of different histological types and borderline ovarian tumours should be analysed separately to obtain a more reliable difference in incidence between cancer and borderline tumours.

Currently there are no recommended 'safe' limits on dose or duration of any of the other drugs used in ovarian stimulation. One important question for women and practitioners to be determined is whether clomiphene citrate alone is less likely to cause cancer compared with multi-therapy; the risks associated with to the number of IVF stimulation cycles also need to be clarified.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Brinton 2004

Methods	'Retrospective cohort study'. All women who had sought advice for infertility at 5 large reproductive endocrinology practices in the US, between 1965 to 1988. Identified from clinic records
Participants	All women with primary or secondary infertility were eligible, N = 12,193, median age 30 years exposed and 30 years for unexposed
Interventions	Fertility treatment, dosage and number of cycles reported 3277 (38.4%) received clomiphene, 866 (10.3%) received gonadotropins Clomiphene 'never use' 92,236 person-years of follow-up and 'ever use' 56,082 person-years of follow-up. Fewer than 6 cycles of clomiphene 36,298 person-years of follow-up, between 6 to 11 cycles of clomiphene with 13,621 person-years of follow-up, 12 cycles or more with 6163 person-years of follow-up. Between 1 to 900 mg of clomiphene with 19,501 person-years of follow-up, between 901 and 2250 mg of clomiphene with 17,532 person-years of follow-up and 2251 mg or more of clomiphene with more than 19,049 person-years of follow-up Gonadotropins 'never use' 133,680 person-years of follow-up and 'ever use' between 1 to 2 cycles with gonadotrophins with 6892 person-years of follow-up and for 3 cycles or more 7746 person-years of follow-up. Between 1 to 24 amps of gonadotrophins with 4861 person-years of follow-up and in 25 amps or more with 9777 person-years of follow-up
Outcomes	Ovarian cancer by histological diagnosis (see Table 2)
Notes	The median length of follow-up among participants was 18.8 years (range 1 to 34 years), with more than 80% followed for 15 or more years

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	All eligible women selected, no history of ovarian cancer at the beginning of the study and all women had at least 1 ovary
Confounding	Unclear risk	Adjusted analysis reported with important predictors adjusted for: age at first visit, race, gravidity, cause of infertility, ever breast-fed, oral contraceptive use, family history of ovarian cancer, hysterectomy, tubal ligation and years of education
Performance bias	High risk	Medical record review, no blinding of assessors to exposure status

Brinton 2004 (Continued)

Detection bias	High risk	Information on the development of cancers was obtained from questionnaires, clinic records and cancer registries. Not reported if assessors were blind to exposure status
Attrition bias	Unclear risk	Almost all the women (80% 2442/12,193) were followed for 15 or more years
Selective reporting (reporting bias)	Low risk	Results for all the fertility drugs investigated were reported

Calderon-Margalit 2009

Methods	'Retrospective cohort'. All women who gave birth 1974 to 1976 in 3 major obstetric units in Israel and included in the Jerusalem Perinatal cohort study were linked with the Israel Population Registry and Israel Cancer Registry
Participants	N = 15,426, mean age 27.5 exposed and NR for unexposed
Interventions	Fertility treatment, dosage and number of cycles not reported. Clomiphene citrate (N = 312), human menopausal gonadotrophins (N = 61), other (N = 54), unknown (N = 87). Follow-up by exposure group not reported
Outcomes	Ovarian cancer by histological diagnosis (see Table 1)
Notes	424,193 person-years follow-up (median 29 years)

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	All women in a given area with no history of ovarian cancer at the beginning of the study and with at least 1 ovary
Confounding	Unclear risk	Analysis adjusted for: age at first birth, geographic origin, social class, education, parity, mean body mass index, time to conception, ovulation disorders and mechanical treatment
Performance bias	High risk	Questionnaires, no blinding of assessors to case-control status reported
Detection bias	High risk	Cancer registry, no blinding of assessors to exposure status used

Attrition bias	Low risk	HR estimated and missing data were censored (8%)
Selective reporting (reporting bias)	Unclear risk	Unclear if all investigated fertility drugs were reported

Dor 2002

Methods	'Retrospective cohort'. All women who underwent IVF from 1981 to 1992 identified from medical records in 2 fertility clinics, Israel, and linked to Israel National Cancer Registry	
Participants	Women who received at least 1 treatment cycle. N = 5026. The mean age at first IVF treatment was 34.0 ± 6.4 years, and mean age at end of follow-up was 37.5 ± 7.1 years	
Interventions	Fertility treatment, number of cycles reported but not dosage. Between 1 to 2 cycles, 663 women, between 3 to 5 cycles, 417 women, more or equal to 6 cycles, 174 women. Length of follow-up by exposure status not reported, but cancer cases diagnosed within 1 year of IVF treatment were excluded	
Outcomes	Ovarian cancer by histological diagnosis (see Table 1)	
Notes	18,291 women-years follow-up, mean follow-up 3.6 ± 3.4 years	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	No history of ovarian cancer at the beginning of the study and with at least 1 ovary
Confounding	Unclear risk	Factors adjusted for: place of birth, type of sub-fertility, number of IVF cycles and pregnancies
Performance bias	High risk	Medical record review, no blinding of assessors to case-control status
Detection bias	High risk	Cancer registry, no blinding of assessors to exposure status
Attrition bias	High risk	73% (5026/18,291) of women were followed up (mean follow-up 3.6 ± 3.4 years). Length of follow-up by exposure status not reported
Selective reporting (reporting bias)	Unclear risk	Unclear if all investigated fertility drugs were reported

Dos Santos Silva 2009

Methods	'Retrospective cohort study'. All women with ovulatory disorders attending 2 IVF clinics from 1963 to 1999 in 2 centres in the UK. Identified from clinic records. Linked to National Health Service Central Register in England and Wales
Participants	N = 7355. Mean age 28.1 years. N = 3196 (44.5%) received fertility drugs
Interventions	Fertility drugs, no dosage and cycles reported (1976 (62%) used clomiphene and 1198 (38%) used clomiphene and HMG) Length of follow-up by exposure status not reported
Outcomes	Ovarian cancer by histological diagnosis (see Table 1)
Notes	The mean follow-up was 21.4 years (89% of the participants were followed up for at least 10 years and 14% for at least 30 years)

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	All women with ovulatory disorders and at least 1 ovary
Confounding	High risk	No adjusted analysis was reported
Performance bias	High risk	Medical notes, no blinding of assessors to case-control status
Detection bias	High risk	Cancer registry, no blinding of assessors to exposure status
Attrition bias	Low risk	7444/9152 (81.3%) followed up, 7355 analysed with complete data. Length of follow-up by exposure status not reported
Selective reporting (reporting bias)	Unclear risk	Unclear if all investigated fertility drugs were reported

Doyle 2002

Methods	'Retrospective cohort' of women who were UK residents attending 1 fertility clinic and who had received at least 1 cycle of fertility treatment from 1975 to 1989. Identified from clinic records. Linked to National Health Service Central Register in England and Wales
Participants	N = 5556, age 20 years or more at the time of treatment, resident in the UK, alive and cancer-free from 1990. Exposed group (4188, 75%) received drugs to stimulate ovulation, unexposed group did not receive drugs

Interventions	Fertility treatment, number of cycles was reported but no dosage was mentioned. Fewer than 2 cycles 20 (0.5%) women, between 2 to 4 cycles 1246 (30%) women, between 5 to 9 cycles 1770 (42%) women, more and equal to 10 cycles 1152 (28%) women. Follow-up for women who received ovarian stimulation 32,986 person-years at risk; for women with no ovarian stimulation 9753 person-years risk	
Outcomes	Ovarian cancer by histological diagnosis (see Table 1)	
Notes	Follow-up from 1990 to 1997, 43,811 person-years at risk	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	All women attending a single centre with no history of ovarian cancer at the beginning of the study and with at least 1 ovary
Confounding	Unclear risk	Factors adjusted for: age at first clinical visit, years of first clinical visit, parity, time since first treatment and age at the end of follow-up
Performance bias	High risk	Medical records, no blinding of assessors to exposure status
Detection bias	High risk	Cancer registry, no blinding of assessors to case status
Attrition bias	High risk	N = 74 women (451 person-years) excluded as follow-up restricted to 1990 onwards rather than date of first treatment. These women had died, emigrated or were diagnosed with cancer before 1990. Follow-up for women who received ovarian stimulation 32,986 person-years at risk; for women with no ovarian stimulation 9753 person-years risk
Selective reporting (reporting bias)	Low risk	All the fertility drugs investigated were reported

Franceschini 1994

Methods	'Case-control study'. Cases were 195 women with incident epithelial ovarian cancer admitted to the major teaching and general hospitals in 4 centres. Women with borderline tumours were excluded. Controls were 1339 women from the same geographical area and admitted to the same network of hospitals as cases for a wide range of acute non-neoplastic conditions. Women with hormonal or gynaecological diseases, or bilateral oophorectomy were excluded. From 1992 to 1993. Multicentre in Italy	
Participants	Age range for cases was 18 to 75 (median 55) and age range for controls was 19 to 79 years (median 56)	
Interventions	Use of 'fertility drugs', drug, dosage and number of cycles not reported	
Outcomes	Epithelial ovarian cancer by histological diagnosis (see Table 2)	
Notes	Duration of follow-up and timing of exposure not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Selection bias	High risk	All women admitted with ovarian cancer
Confounding	Unclear risk	Factors adjusted for: age, education, parity, medical diagnosis of infertility and length of attempt to first pregnancy
Performance bias	High risk	Self reported during an interview, unclear if interviewers were blinded to case-control status
Detection bias	Low risk	Epithelial ovarian cancer by histological diagnosis
Attrition bias	Unclear risk	Unclear if exclusions based on incomplete data
Selective reporting (reporting bias)	Unclear risk	Unclear if all the fertility drugs investigated were reported

Jensen 2009

Methods	'Nested case-control study'. Women with subfertility problems and referred to all Danish private fertility clinics or hospitals 1963 to 1998, and all women with ICD diagnosis of infertility from the national patient registry (a nationwide register of virtually all discharges for somatic conditions from Danish hospitals since 1977). Linked to civil registration database to obtain date of migration or death. Linked to Danish cancer registry and Danish registry of pathology for ovarian cancer diagnosis. Cases were women with ovarian cancer by 30 June 2006. Controls were randomly selected in 4 age strata and 5 strata according to year of entry to cohort	
Participants	Cohort comprised N = 54, 449 women with primary or secondary infertility, N = 176 cases; 1360 controls. Median age at first evaluation of infertility was 30 years (range 16 to 55) and median age at the end of follow-up was 47 (range 18 to 81) years	
Interventions	Fertility drugs, number of cycles reported for each drug but dosage not reported. Gonadotrophins 1 to 4 cycles 18/130, 5 to 9 cycles 7/46 women, more or equal to 10 cycles 1/8. Clomiphene citrate from 1 to 4 cycles 35/226 women, 5 to 9 cycles 15/117 women, more or equal to 10 cycles 8/74 women. HCG between 1 to 4 cycles 31/232 women, 5 to 9 cycles 13/121 women and more or equal to 10 cycles 5/60 women. GnRH between 1 to 4 cycles 14/100 women, 5 to 9 cycles 1/10 women and more or equal to 10 cycles 0 women. Duration of follow-up by fertility drug not reported	
Outcomes	Ovarian cancer by histological diagnosis (see Table 1)	
Notes	95% of women (54,362) were followed up for a median of 16.0 years (range 0.0 to 42.6 years) , with 25% followed for more than 23 years. 957,454 person-years of observation	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	All women with infertility treated at either a private clinic or public hospital or with a diagnosis of infertility on national disease registry. No history of ovarian cancer at the beginning of the study and with at least 1 ovary
Confounding	Unclear risk	Factors adjusted for: parity, number of births, maternal age at birth of first child and maternal age at birth of last child
Performance bias	High risk	Medical records, no blinding of assessors to case-control status
Detection bias	High risk	Cancer registry, no blinding of assessors to exposure status
Attrition bias	Low risk	95% of women had similar length of follow-up

Jensen 2009 (Continued)

Selective reporting (reporting bias)	Low risk	All the fertility drugs investigated were reported
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Kallen 2011

Methods	Retrospective cohort, Sweden, multicentre
Participants	All women who gave birth following IVF treatment during 1982-2007, identified from all IVF clinics in Sweden and Swedish Medical Birth Register (24,058). A control group comprised 95,775 women recorded in Medical Birth Register. The mean age at first delivery after IVF was 40.3 years
Interventions	There was no clear report of the number of IVF cycles, dosage and type of fertility drugs used
Outcomes	Ovarian cancer by histological diagnosis, Swedish Cancer Registry
Notes	Average follow-up time was 8.3 years for IVF women

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	All eligible women selected, no history of ovarian cancer at the beginning of the study and all women had at least 1 ovary
Confounding	Unclear risk	Adjustment was made in the analysis for maternal age and year of birth, smoking and parity
Performance bias	High risk	Medical record review, no blinding of assessors to case-control status
Detection bias	Unclear risk	Cancer registry, no blinding of assessors to exposure status
Attrition bias	High risk	75% (24,058/95,775) of women were followed up (mean follow-up time 8.3 years)
Selective reporting (reporting bias)	Unclear risk	Dosage, number of IVF cycles and type of drugs used were not reported

Kurta 2012

Methods	Retrospective case-control study. Multicentre in USA
Participants	Participants were residents in Western Pennsylvania, Eastern Ohio and Western New York state participating in the Hormones and Ovarian cancer Prediction study (national population-based study). All cases were histologically confirmed to have primary epithelial ovarian cancers diagnosed between 2003 and 2008. Eligible women were at least 25 years old and were within 9 months of initial diagnosis at the time of recruitment. A total of 155 cases. 290 controls were frequency matched to cases (about 2:1) by 5-year age group and telephone area code through random digit dialling. Women who had undergone a bilateral oophorectomy were ineligible. Trained interviewers collected questionnaire data that included detailed reproductive, gynaecologic and medical histories as well as information about lifestyle and family medical history. Mean age for cases and controls was not reported
Interventions	Fertility drugs used were: raloxifene, danazol, unknown hormone pills, bromocriptine, progesterone and metformin. Fertility drugs doses was not reported. The majority used fertility drugs for less than 12 months (66.7%); mean duration was 11.4 months (range 1 to 134 months). Among the cases 105/155 (67%) were not exposed to fertility drugs and 50/155 (32%) were exposed. Among the controls 192/290 (66%) were not exposed to fertility drugs and 98/290 (34%) were exposed to fertility drugs
Outcomes	Invasive epithelial ovarian cancer by histological diagnosis
Notes	Duration of exposure was not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	High risk	Only live cases included and women who had a confirmed histological diagnosis and returned a questionnaire about exposure
Confounding	Low risk	Matched for age at the time of the diagnosis and area of residence. Factors adjusted for age, race, education, tubal ligation, age at menarche, duration of oral contraceptive use, number of live births, duration of breast-feeding, perineal talc use and family history of breast/ or ovarian cancers
Performance bias	High risk	Self reported by questionnaire of exposure status. Unclear if blinding of assessors to case-control status was used
Detection bias	High risk	Cancer registry, no blinding of assessors to exposure status

Attrition bias	Low risk	71% (902/1270) of the total cases eligible returned the questionnaire. 97% (1802/1844) of the controls participated to the study
Selective reporting (reporting bias)	Low risk	Results for all the drugs investigated were reported

Lerner-Geva 2003

Methods	'Retrospective cohort'. All infertile women who attended 1 IVF clinic and who received at least 1 treatment cycle in Israel from 1984 to 1992 identified from the medical records. Linked to the Israel National Cancer Registry	
Participants	N = 1082 with 7002 person-years follow-up. The mean age at the first IVF treatment was 32.7 ± 4.8 years, and the mean age at the end of the follow-up 38.7 ± 5.2 years	
Interventions	Fertility drug not reported. 650 women received 1 to 2 cycles of treatment, 323 received 3 to 5 cycles and 109 received more than 6 cycles	
Outcomes	Ovarian cancer by histological diagnosis (see Table 1)	
Notes	Mean years of follow-up 6.5 ± 2.2	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Unclear risk	No history of ovarian cancer at the beginning of the study and with at least 1 ovary. Women with cancer diagnosed within 1 year of IVF treatment excluded from analyses
Confounding	Unclear risk	Factors adjusted for: continent of birth, type of infertility, diagnosis of infertility, number of IVF cycles and treatment outcome (pregnancy or not)
Performance bias	High risk	Medical records, no blinding of assessors to case-control status
Detection bias	High risk	Cancer registry, no blinding of assessors to exposure status
Attrition bias	Unclear risk	85% (1082/7002) of women were followed up
Selective reporting (reporting bias)	Unclear risk	Unclear whether all the fertility drugs investigated and reported

Lerner-Geva 2012

Methods	Retrospective cohort, Israel 1964-1974, only 1 centre
Participants	2431 subfertile women treated at the Sheba Medical Center compared to the general population
Interventions	Fertility treatment with clomiphene (N = 884), clomiphene and HMG (N = 238) and with HMG (N = 159)
Outcomes	Ovarian cancer by histological diagnosis
Notes	Mean age at the end of the follow-up 62.7 +/- 8.1 years. 88,181 person-years follow-up (over 30 years follow-up)

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	All women coming to the infertility centre where the study was started. All women had no history of ovarian cancer at the beginning of the study and at least 1 ovary
Confounding	Unclear risk	Adjusted analysis was not reported
Performance bias	High risk	Medical notes review, no blinding of assessors to exposure status
Detection bias	High risk	Information on the development of cancer was obtained from a cancer registry. Not reported whether assessors were blind to exposure status
Attrition bias	Low risk	Almost all the women (94%) were followed up (2431/2575) throughout the time
Selective reporting (reporting bias)	Unclear risk	Type of drugs used was reported. There was no information about dosage of drugs used and number of cycles

Modan 1998

Methods	'Retrospective cohort' of women diagnosed with infertility 1964 to 1974 and who had visited the clinic more than once (2 centres in Israel) identified from medical records. Linked to Israel Cancer Registry
Participants	Women with primary or secondary infertility. N = 2496. Mean age at entry was 28.7, mean age at the end of the follow-up was 50.0

Modan 1998 (Continued)

Interventions	Fertility treatment, 908 women with clomiphene citrate, 242 women with clomiphene citrate + HMG, 159 women with HMG. No dosage or number of cycles were reported. Women received at least 1 cycle of fertility drugs. Duration of follow-up by exposure group not reported	
Outcomes	Ovarian cancer by histological diagnosis (see Table 1)	
Notes	54,413 person-years follow-up, mean follow-up 21.4 years	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	No history of ovarian cancer at the beginning of the study and with at least 1 ovary
Confounding	High risk	Adjusted analysis not reported
Performance bias	High risk	Medical records, no blinding of assessors to case-control status
Detection bias	High risk	Cancer registry, no blinding of assessors to exposure status
Attrition bias	Unclear risk	96% of women followed (2496/54,413)
Selective reporting (reporting bias)	Unclear risk	Unclear if all investigated fertility drugs were reported

Mosgaard 1997

Methods	'Prospective case-control study'. Cases were all women with a first diagnosis of ovarian cancer 1989 to 1994 selected from the Danish Cancer Registry with histological diagnosis and who returned a completed questionnaire with exposure data (N = 684). A random sample of 3 controls per case were selected from the National Person Register, matched by area of residence, age at time of cancer diagnosis, with at least 1 ovary and completed questionnaire from 1989 to 1994. Multicentre in Denmark, but number of centres not reported	
Participants	N = 1721 women. Mean age for cases = 47.2 (range 18 to 59). Mean age for controls = 46 (range 19 to 59)	
Interventions	Fertility drugs, dosage and number of cycles not reported. 28/684 (20.7%) cases were exposed to infertility drugs and 58/1721 (23.8%) controls were exposed to fertility drugs	
Outcomes	Invasive epithelial and non-epithelial ovarian cancer by histologic diagnosis (see Table 2)	
Notes	Duration of exposure not reported	

Mosgaard 1997 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Selection bias	High risk	Only live cases included and women who had a confirmed histological diagnosis and returned a questionnaire about exposure
Confounding	Unclear risk	Matched for age at time of diagnosis and area of residence. Factors adjusted for: age, menarche, parity, age at first birth, duration of infertility, other causes of infertility, use of oral contraceptive pill, use of intrauterine devices, menopausal status, age at menopause, use of hormonal replacement therapy, age at sterilisation, history of cancer and family history for cancer, smoking and body mass index
Performance bias	High risk	Self reported exposure status. Unclear if blinding of assessors to case-control status was used
Detection bias	High risk	Cancer registry, no blinding of assessors to exposure status
Attrition bias	Unclear risk	88% questionnaires returned for cases, 79.8% for controls. 80.7% of questionnaires for the cases were valid for analysis and 97% of the questionnaires were valid for the controls
Selective reporting (reporting bias)	Unclear risk	Unclear if all investigated fertility drugs were reported

Mosgaard 1998

Methods	'Case-control study'. All Danish women < 60 years with histologically confirmed borderline ovarian tumours identified from the Danish Cancer Registry 1989 to 1994 with histological diagnosis and who returned a completed questionnaire with exposure data (N = 263). Random sample of 3 controls per case were selected from the National Person Register, matched by area of residence, age at time of cancer diagnosis and completed a questionnaire. National study in Denmark from 1989 to 1994
Participants	N = 1721 women with at least 1 ovary. Mean age for cases 43.6 (range 22 to 59). Mean age for controls 46 (range 19 to 59)
Interventions	Fertility drugs, dosage and number of cycles not reported
Outcomes	Borderline ovarian cancer by histologic diagnosis (see Table 2)

Mosgaard 1998 (Continued)

Notes	Duration of exposure not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Selection bias	High risk	Live cases only and women who responded to questionnaire on exposure
Confounding	Unclear risk	Case and controls were matched for age at time of diagnosis, area of residence. Factors adjusted for: parity, use of oral contraceptive pill, menopause, use of hormonal replacement therapy and smoking
Performance bias	High risk	Self reported (type of treatment - oral/injections) with some checks with the fertility clinics for confirmation. No blinding of assessors to case-control status
Detection bias	High risk	Cancer registry, no blinding of assessors to exposure status
Attrition bias	Unclear risk	87.8% questionnaires were returned and they were all selected for cases to analyse; 79.8% questionnaires were returned for controls and all were used for analysis
Selective reporting (reporting bias)	Unclear risk	Unclear if all investigated fertility drugs were reported

Parazzini 1997

Methods	'Case-control study'. Cases were women < 75 years diagnosed with invasive ovarian cancer within 1 year of interview and admitted to a major teaching or general hospital in Milan, Italy from 1983 to 1991. Controls were women admitted to the same hospitals where the cases were identified with acute non-gynaecological, non-hormonal or non-neoplastic conditions
Participants	N = 971 cases, age 22 to 74 (median 54 years). N = 2758 controls, age 23 to 74 (median 52 years)
Interventions	Fertility drugs, number of cycles reported but not dosage used per cycle. Fewer than or equal to 6 cycles 1/971 cases and 3/2758 controls. More than or equal to 6 cycles 4/971 cases and 7/2758 controls
Outcomes	Invasive epithelial ovarian cancer by histological diagnosis (see Table 2)

Parazzini 1997 (Continued)

Notes	Duration of exposure per number of cycles reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Selection bias	Unclear risk	Cases and controls were recruited from the same geographic area
Confounding	Unclear risk	Factors adjusted for: age, education, parity, oral contraceptive use, difficulties in conception
Performance bias	High risk	Questionnaires, no blinding of assessors to case-control status used
Detection bias	High risk	How the cases were ascertained was not reported and blinding of assessors to exposure status was used
Attrition bias	Low risk	Case and controls assessed for exposure and outcome at the same time when admitted to hospital
Selective reporting (reporting bias)	Unclear risk	Unclear if all the fertility drugs used were investigated

Parazzini 1998

Methods	'Case-control study'. Cases were women with histologically confirmed borderline ovarian tumours admitted to 1 hospital in Milan, Italy. Controls were women admitted to hospitals serving the same catchment area as the cases lived in with acute non-gynaecological, non-hormonal, non-neoplastic conditions from 1986 to 1991	
Participants	N = 93 cases, age 23 to 64 years. N = 273 controls, age 24 to 64 years	
Interventions	Fertility drugs, dosage and number of cycles not reported. 4/93 (4.3%) cases and 0/273 controls exposed to fertility drugs	
Outcomes	Borderline ovarian cancer by histological diagnosis (see Table 2)	
Notes	States that cases in this report were not included in previous articles on relationship between fertility drugs and ovarian cancer	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Parazzini 1998 (Continued)

Selection bias	Unclear risk	Cases and controls were recruited from the same geographic area
Confounding	Unclear risk	Factors adjusted for: age, education, parity, oral contraceptive use and difficulty in conception
Performance bias	High risk	Face-to-face interview. Blinding unclear
Detection bias	High risk	How the cases were ascertained was not reported and no binding of assessors to exposure status
Attrition bias	Unclear risk	Case and controls assessed for exposure and outcome at the same time when admitted to hospital
Selective reporting (reporting bias)	Unclear risk	Unclear whether all the fertility drugs used and investigated

Parazzini 2001

Methods	'Case-control study'. Cases were women with incident histologically confirmed ovarian cancer admitted to the major teaching and general hospitals in 4 geographic regions in Italy (women with borderline tumours were excluded) from 1992 to 1999. Controls were women from the same geographical area and admitted to the same network of hospitals as the cases for a wide range of acute non-neoplastic conditions (women with hormonal or gynaecological diseases, or bilateral oophorectomy were excluded)	
Participants	N = 1031 cases, median age 56, range 18 to 79 years; N = 2411 controls, median age 57, range 17 to 79 years	
Interventions	Fertility drugs, dosage and number of cycles not reported. 15/1031 (1.5%) cases were exposed to fertility drugs and 26/2411 (1.1%) controls were exposed to fertility drugs	
Outcomes	Epithelial ovarian cancer by histological diagnosis (see Table 2)	
Notes	Length of exposure not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Selection bias	Unclear risk	Cases and controls were recruited from the same geographic area

Parazzini 2001 (Continued)

Confounding	Unclear risk	Factors adjusted for: age, education, menopausal status, age at menopause, parity, spontaneous miscarriages, termination of pregnancy, oral contraceptive use, family history for ovarian cancer and history of infertility
Performance bias	High risk	Structured interviewer-administered questionnaire and checked with medical records. Unclear if blinding of assessors to case-control status was used
Detection bias	High risk	How the cases were ascertained has not been specified and it is unclear if blinding of assessors to exposure status was used
Attrition bias	Unclear risk	Case and controls assessed for exposure and outcome at the same time as admitted to hospital
Selective reporting (reporting bias)	Unclear risk	Unclear if all fertility drugs used were investigated

Potashnik 1999

Methods	'Retrospective cohort'. All women with infertility attending 1 fertility clinic (Soroka University Hospital), Israel, 1960 to 1984. Identified from medical records. Linked to the National Cancer Registry	
Participants	Women with at least 2 recorded visits to the clinic. N = 1197. Mean age at first visit 27.5 ± 5.4 years, mean age at the end of the follow-up 44.8 ± 6.4 years for cohort. Mean age for exposed at first visit 27.5 ± 5.1 , mean age at the end of follow-up for exposed 27.7 ± 5.8 years, mean age at the first visit for unexposed 27.7 ± 5.8 , at the end of the follow-up 44.8 ± 7.1 years for unexposed	
Interventions	Infertility treatment, 0 with clomiphene citrate, 531/780 treated with clomiphene citrate + HMG, 6/780 treated with HMG. 780 (65.2%) exposed to fertility drugs. Duration of follow-up for women exposed to fertility drugs 18.0 ± 4.9 years, non-exposed 17.6 ± 5.9 years	
Outcomes	Ovarian cancer by histological diagnosis recorded on the National Cancer Registry (see Table 1)	
Notes	21,407 person-years follow-up. Mean follow-up 17.9 ± 5.3 years	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Potashnik 1999 (Continued)

Selection bias	Low risk	All women with infertility that attended a particular clinic. No person had ovarian cancer at the start of the study and with at least 1 ovary
Confounding	Unclear risk	Factors adjusted for: age and ethnic origin
Performance bias	High risk	Medical records, no blinding of assessors to case-control status
Detection bias	High risk	Cancer registry, no blinding of assessors to exposure status
Attrition bias	Unclear risk	Case ascertainment 90% to 95% complete. Missing data by exposure group not reported
Selective reporting (reporting bias)	Unclear risk	Unclear if all fertility drugs used were investigated

Rossing 1994

Methods	'Nested case-control study'. The cohort (N = 3837) comprised women undergoing fertility treatment at participating clinics in Seattle, US from 1974 to 1985. Cases were women with ovarian cancer after enrolment in the study until 1992 identified from cancer registry. Controls were a random selection of women from the cohort stratified by age at enrolment 3:1 for each case within each strata	
Participants	Women that had made at least 2 clinic visits and lived in an area covered by the cancer surveillance system. Mean age of women at enrolment 29.7 years	
Interventions	Clomiphene dosage and number of cycles not reported	
Outcomes	Ovarian cancer by histological diagnosis recorded in cancer surveillance system (see Table 1)	
Notes	43,438 person-years of observation	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	No person had ovarian cancer at the start of the study and with at least 1 ovary
Confounding	Unclear risk	Adjusted analysis presented, but factors adjusted for not reported
Performance bias	High risk	Medical records, no blinding of assessors to case-control status

Rossing 1994 (Continued)

Detection bias	High risk	Cancer registry, no blinding of assessors to exposure status
Attrition bias	Unclear risk	74.2% of the controls were eligible to be interviewed
Selective reporting (reporting bias)	Unclear risk	Unclear if all investigated fertility drugs were reported

Rossing 2004

Methods	'Population-based case-control study'. From 1994 to 1998 in 3 regions (Atlanta, Georgia; Detroit, Michigan; Seattle, Washington) in the US (cancer registry - local US born, with no history of breast cancer (to match the controls)). Cases identified from cancer registry. Controls randomly selected from the Women's Contraceptive and Reproductive Experiences (CARE) study of breast cancer (English speaking women born in the US, white/black, in 5 geographic regions), age 35 to 64 at reference date	
Participants	N = 378 cases; N = 1637 controls. Age range between 35 and 54 for cases and 35 and 64 for controls	
Interventions	Fertility drugs, dosage and cycles not reported	
Outcomes	Epithelial, non-epithelial and borderline ovarian cancer by histological diagnosis (see Table 2)	
Notes	Controls were more likely to have Black ethnicity 27.1% versus 13.5%. Length of follow-up from exposure not reported	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Unclear risk	Only women still alive were selected as cases; controls were matched on geographic area and age
Confounding	Unclear risk	Factors adjusted for: study site, race, age, marital status, education, cigarette smoking, age at menarche, oral contraceptive use in months
Performance bias	High risk	Information obtained through face-to-face interview and not medical records. Interviewers were not blinded to case-control status
Detection bias	High risk	Cancer registry

Rossing 2004 (Continued)

Attrition bias	Unclear risk	Length of follow-up from exposure not reported
Selective reporting (reporting bias)	Unclear risk	Unclear if all the fertility drugs used were investigated

Sanner 2009

Methods	'Retrospective cohort'. Women with infertility or infertility-associated disorders attending 3 university hospital fertility clinics in Sweden from 1961 to 1975. Linked to Swedish Cancer Register	
Participants	N = 2768, median age 27 (16 to 45) exposed. N = 1615 (58%) unexposed who did not receive hormonal treatment. Median age 27 (16 to 45)	
Interventions	Fertility treatment, 389 (34%) with clomiphene citrate; 325 (28%) gonadotrophins and 439 (38%) with clomiphene citrate + HMG. The median follow-up time for the cohort was 33 years (range 1 to 47 years). Duration of follow-up by exposure group was not reported	
Outcomes	Primary invasive epithelial or borderline ovarian cancer by histological diagnosis obtained from National Cancer Registry (see Table 1)	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	All women with at least 1 ovary and no history of ovarian cancer
Confounding	High risk	No adjusted analysis reported
Performance bias	High risk	Medical record review at the IVF clinics. Any exposure outside the IVF clinics included was unknown. No blinding of assessors to case-control status reported
Detection bias	High risk	Cancer registry, no blinding of assessors to exposure status was reported
Attrition bias	Unclear risk	81% of women were followed up
Selective reporting (reporting bias)	Low risk	All the fertility drugs used were reported

Shushan 1996

Methods	'Population-based case-control study' in Israel. Cases were women with invasive and borderline epithelial ovarian cancer reported to registry from 1990 to 1993. Cases were selected from National Cancer Registry (only included living cases). Controls were randomly selected from same telephone dialling code (matched for geographic area)
Participants	N = 164 cases with invasive cancer; N = 36 cases with borderline cancer, N = 408 controls
Interventions	Fertility drugs, dosage and number of cycles were not reported
Outcomes	Primary invasive epithelial or borderline ovarian cancer by histological diagnosis from Israel Cancer Registry (see Table 2)
Notes	Length of follow-up post-exposure not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Unclear risk	Only women still alive were selected as cases; controls were matched on geographic area and age
Confounding	Unclear risk	Factors adjusted for: age, parity, BMI, region of birth, education, family history, interviewer
Performance bias	High risk	Self reported during an interview, interviewer not blind to case-control status
Detection bias	High risk	Cancer registry
Attrition bias	Unclear risk	200/287 (70%) of living selected cases interviewed. Length of follow-up post-exposure not reported
Selective reporting (reporting bias)	Unclear risk	Unclear if other fertility drugs investigated but not reported

Van Leeuwen 2011

Methods	Historical cohort (OMEGA), Netherlands, multicentre (12 hospitals)
Participants	Subfertile women who received at least 1 IVF cycle with ovarian stimulation (19,861) 1983-1995. The control group comprised subfertile women not treated with IVF (6604) selected from the 4 IVF clinics with a computerised registry of all subfertile women evaluated 1980-1995 before IVF was a routine procedure. Mean age of IVF-treated women was 47.5 and for women who did not receive IVF was 49.4 years

Interventions	In the IVF group 32.9% of women had 1 to 2 stimulated IVF cycles, 32.8% had 3 to 4 cycles and 17.5% received 5 or more cycles. Clomiphene/HMG or FSH/HMG stimulation protocols were used until 1988-1989, whereas stimulation with GnRH agonists became more common after 1990 (from 20% in 1986 to about 90% after 1990). From 1984 to 1994, the number of ampoules of gonadotrophins strongly increased	
Outcomes	Ovarian cancer including borderline ovarian tumours by histological diagnosis; linkage with national cancer registry	
Notes	Median duration of follow-up was for the exposed 14.3 years and for the non-exposed 16.4 years	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Selection bias	Unclear risk	All women in a given area with no history of ovarian cancer at the beginning of the study and with at least 1 ovary. Women in cohort who did not receive IVF were slightly older and had a slightly longer median duration of follow-up than women who did receive IVF
Confounding	High risk	Analysis was adjusted for age at the end of the follow-up, endometriosis, tubal problems and parity
Performance bias	Unclear risk	Information based on medical records and for women without medical record data, information was added from health questionnaire
Detection bias	Unclear risk	Cancer registry; no blinding of assessors to exposure status used
Attrition bias	High risk	Analytic cohort 19,146 IVF treated, 6006 non-IVF treated. 67.3% responded and consented to future record linkage, 4.3% responders refused, 28.2% non-responders, 0.2% were deceased at initial approach of IVF group. 40.7% responded and consented to future record linkage, 3.1% responders refused, 55.4% non-responders, 0.9% were deceased at initial approach of non-IVF group
Selective reporting (reporting bias)	Unclear risk	10,343/19,146 (54%) at 10 years follow-up and 7621/19,146 (40%) at more than 15 years of follow-up

Venn 1999

Methods	'Retrospective cohort'. Women who registered with at least 1 of 10 participating clinics in Australia before 1994. 30% before 1986, 70% 1986 to 1996. Linked to cancer registry
Participants	Women who received at least 1 IVF treatment. N = 29,700, median age 31 (range 18 to 50) in exposed, median 30 (range 18 to 53) in unexposed
Interventions	Fertility treatment used, 1182 (6.9%) with clomiphene citrate, 6543 (38.2%) with clomiphene citrate + HMG, 1464 (8.5%) with HMG, 11,153 (65%) with HMG + GnRH agonist, 1771 (8.6%) with other treatments NR. Dosage NR. 6346 (37.0%) with 1 cycle, 3712 (21.6%) with 2 cycles, 5157 (30.1%) between 3 and 5 cycles, 1933 (11.3%) more than 6 cycles. 134,240 person-years follow-up in exposed, 96,794 person-years in unexposed. Median follow-up in exposed 7 (range < 1 to 21) years; in unexposed median 10 (< 1 to 22) years
Outcomes	Invasive ovarian cancer by histological diagnosis from the Victoria Cancer Registry (see Table 1)
Notes	80% of the cohort sample was followed up until 1996

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	No person had ovarian cancer at the start of the study and had at least 1 ovary
Confounding	High risk	No adjusted analysis reported and groups were not matched or balanced for confounding factors at baseline
Performance bias	High risk	Medical records; no blinding of assessors to case-control status
Detection bias	High risk	Cancer registry; no blinding of assessors to exposure status
Attrition bias	Low risk	81% exposed and 72% unexposed were followed up
Selective reporting (reporting bias)	Low risk	All the drugs used were reported

Yli-Kuha 2012

Methods	Retrospective cohort, Finland 1996-1998, single centre
Participants	Subfertile women (N = 9175) who purchased drugs for IVF between 1996-1998 and their age and residence-matched controls randomly selected from the general population register (N = 9175)

Interventions	Fertility treatment but dosage, number of cycles and type of drugs used was not reported	
Outcomes	Ovarian cancer by histological diagnosis, Finnish cancer registry	
Notes	Mean follow-up time for exposed subfertile women was 7 years and 9 months	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	All women in a given area with no history of ovarian cancer at the beginning of the study and with at least 1 ovary
Confounding	Unclear risk	Cases were age and residence matched with controls and further adjusted for socioeconomic position and marital status
Performance bias	High risk	Medical record review, no blinding of assessors to exposure status
Detection bias	Unclear risk	Information on the development of the cancers was obtained from the medical notes and cancer registry. Not reported if assessors were blind to exposure status
Attrition bias	Low risk	All women (9175) were followed up for 7 years and 9 months
Selective reporting (reporting bias)	Unclear risk	The fertility drugs used were not reported

amp: ampoule

BMI: body mass index

FSH: follicle-stimulating hormone

GnRH: gonadotrophin-releasing hormone

HCG: human chorionic gonadotrophin

HMG: human menopausal gonadotrophin

HR: hazard ratio

ICD: International Classification of Diseases

IVF: in vitro fertilisation

NR: not reported

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

Study	Reason for exclusion
Adami 1994	General article about risk factors for ovarian cancer
Adelson 1993	General article
Al-Shawaf 2005	Review article
Albrektsen 1996	Case-control study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer
Althuis 2005	General article in infertility and risk of ovarian cancer
Anderson 1996	Case report
Artini 1997	Case series (fewer than 30 patients)
Attia 2006	General article on infertility and risk of ovarian cancer
Ayhan 2004	General article on infertility
Badawy 2009	General article on infertility and risk of ovarian cancer
Balasch 1994	Case series (fewer than 30 patients)
Bandera 2005	General article on infertility and risk of ovarian cancer
Bayar 2006	Case report
Bose 2008	General article on infertility and risk of ovarian cancer
Brekelmans 2003	Review article
Brinton 1996	General article on infertility and risk of ovarian cancer
Brinton 1997	General article on infertility
Brinton 2007	Review article
Brinton 2012	Review of some observational studies investigating risk of ovarian cancer and use of infertility drugs
Bristow 1996	Review article
Bristow 1996	Review article
Burger 2004	Review article

(Continued)

Cetin 2008	Review article
Chene 2009	General article on infertility and risk of ovarian cancer
Clinton 1997	General article on infertility and risk of ovarian cancer
Cohen 1993	General article on infertility and risk of ovarian cancer
Cramer 1998	Cohort study about other risk factors (no infertility or infertility drugs included) for ovarian cancer
Crosbie 2005	Review article
Croughan-Minihane 2001	Unpublished data. Abstract not fully informative about risk calculated by authors
Cusido 2007	Case-control study evaluating risk of borderline ovarian cancer. Controls were women treated for benign ovarian pathology requiring surgery. Crude estimates only presented, no attempt at controlling for confounding. No details on how ovarian cancer was confirmed
Demiroglu 2006	Review article on infertility and ovarian cancer
Devesa 2010	Review article on infertility and risk of ovarian cancer
Dos Santos 2002	Case series (fewer than 30 patients)
Duckitt 1998	General article on infertility and risk of ovarian cancer
Duska 1996	Review article
Franceschini 1991	Pooled analysis of 3 European case-control studies
Franco 2000	Case series (fewer than 30 patients)
Gadducci 2004	Review article
Gadducci 2013	Review of some observational studies investigating risk of ovarian cancer and use of infertility drugs
Genc 2011	General article on infertility and risk of ovarian cancer
Glud 1998	Review article
Goldberg 1992	Case series (fewer than 30 patients)
Goodman 2001	Research article
Goshen 1998	Review article
Gwinn 1990	Case-control study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer

(Continued)

Hankinson 1995	Cohort study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer
Harris 1992	Collaborative analysis of 12 US case-control studies
He 2012	Review of some observational studies investigating risk of ovarian cancer and use of infertility drugs
Helzlsouer 1995	General article on infertility and risk of ovarian cancer
Horn-Ross 1992	Collaborative analysis of 12 US case-control studies
Jensen 2007	Cohort study on reproductive factors and risk of breast cancer
Jensen 2008	Cohort study about reproductive factors (no infertility or infertility drugs included) and risk of breast cancer
Kashyap 2003	Review article
Kaufman 1995	Review article
Kelly 2003	General article on infertility and risk of ovarian cancer
King 1994	General article on infertility and ovarian cancer
Klip 2000	General article on infertility
Klip 2001	Cohort study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer
Konishi 1999	Review article
Kristiansson 2007	General article on infertility and risk of ovarian cancer
Kurian 2004	Review article
La Vecchia C 2011	General article on infertility and risk of ovarian cancer
Land 1993	Review article
Lerner-Geva 2010	Review article
Lerner-Geva 2004	Review article
Lerner-Geva 2006	Cohort study on reproductive factors and risk of breast cancer
Li 2013	Meta-analysis of only some of the cohort studies published on the risk of ovarian cancer in women treated with ovulation stimulation drugs

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Lopes 1993	General article on infertility and ovarian cancer
Mandai 2007	Review article
McGuire 2004	General article on infertility and risk of ovarian cancer
McSorley 2009	General article on infertility and risk of ovarian cancer
Menon 2009	Article on sensitivity and specificity of possible ovarian cancer screening
Miao 2006	General article on infertility/article in Chinese (abstract in English)
Modugno 2001	Case-control study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer
Negri 1991	Pooled analysis of case-control studies
Ness 2000	Pooled analysis of case-control studies
Ness 2003	Review article
Ness 2011	General article on the risk of ovarian cancer
Nieto 2001	General article on infertility and risk of ovarian cancer
Oktay 2010	Review article on infertility and risk of ovarian cancer
Ozcan 2009	Review article on infertility and risk of ovarian cancer
Ozdemir 2005	Research article
Parazzini 2004	General article on infertility and risk of ovarian cancer
Paulson 1996	Review article
Persson 1995	General article on infertility/article in Swedish (abstract in English)
Purdie 1995	Case-control study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer
Riman 1998	General article on infertility and ovarian cancer
Riman 2002	Case-control study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer
Rish 1996	Case-control study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer

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Rodriguez 1998	Reported only risk of ovarian cancer in infertile women but not treated with ovarian stimulating drugs
Ron 1995	Review article
Rosemberg 1994	Case-control study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer
Rosen 1997	General article on infertility
Rosenblatt 1993	Case-control study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer
Rossing 1996	Cohort study about reproductive factors (no infertility or infertility drugs included) and risk of breast cancer
Schildkraut 1996	General article on infertility and risk of ovarian cancer
Shoham 1994	Review article
Siristatidis 2013	A meta-analysis on risk of ovarian cancer and women treated with ovarian stimulating drugs for infertility
Smith 2001	General article on infertility and ovarian cancer
So 2008	General article on infertility and ovarian cancer
Soegaard 2007	Case-control study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer
Spirtas 1993	General article on infertility and ovarian cancer
Stein 1997	General article on infertility and ovarian cancer
Tarlatzis 1995	Review article
Trifonov 2000	Article in Bulgarian/review article
Unkila-Kallio 1997	Case series (fewer than 30 patients)
Unkila-Kallio 2000	Cohort study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer
Venn 2003	Review article
Venn 1995	Sub-set of larger cohort described in Venn 1999
Venn 1997	Review article

(Continued)

Venn 2001	Cohort study about reproductive factors (no infertility or infertility drugs included) and risk of ovarian cancer
Vlahos 2010	Review article
Wakeley 2000	Review article
Whittemore 1994	Commentary/letter
Willemssen 1993	Case series (fewer than 30 patients)
Zreik 2008	Review article

DATA AND ANALYSES

Comparison 1. Infertility drugs versus no infertility drug

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Borderline ovarian cancer	5		Odds Ratio (Fixed, 95% CI)	Totals not selected
1.1 Any infertility drug	4		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Clomiphene	3		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Clomiphene + gonadotrophin	3		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Gonadotrophin	3		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Invasive ovarian cancer	16		Odds Ratio (Fixed, 95% CI)	Totals not selected
2.1 Any infertility drug	12		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Clomiphene	8		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Clomiphene + gonadotrophin	6		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Gonadotrophin	6		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 GnRH	1		Odds Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Infertility drugs versus no infertility drug, Outcome 1 Borderline ovarian cancer.

Review: Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility

Comparison: 1 Infertility drugs versus no infertility drug

Outcome: 1 Borderline ovarian cancer

(1) nulliparous and multiparous women

(2) multiparous subgroup of women

(3) nulliparous subgroup women

(4) multiparous subgroup women

(5) nulliparous subgroup women

(6) multiparous subgroup women

(7) nulliparous subgroup women

Analysis 1.2. Comparison 1 Infertility drugs versus no infertility drug, Outcome 2 Invasive ovarian cancer.

Review: Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility

Comparison: 1 Infertility drugs versus no infertility drug

Outcome: 2 Invasive ovarian cancer

(Continued ...)

(... Continued)

- (1) multiparous subgroup of women
- (2) nulliparous subgroup of women
- (3) multiparous subgroup of women
- (4) nulliparous subgroup of women
- (5) multiparous subgroup of women
- (6) nulliparous subgroup of women
- (7) nulliparous subgroup women
- (8) multiparous subgroup women
- (9) nulliparous subgroup women
- (10) multiparous subgroup women
- (11) multiparous subgroup women
- (12) nulliparous subgroup women
- (13) nulliparous subgroup women
- (14) multiparous subgroup women

ADDITIONAL TABLES

Table 1. Cohort studies

Cohort studies							
Study	Ovarian cancer type	Total number of exposed cases versus unexposed	Drug, dose and number of cycles	Crude estimate (95% CI)	Adjusted estimate RR (95% CI)	Factors adjusted for	Standardised incidence ratio (SIR)
Modan 1998	Invasive	1309 versus 1187	Fertility drugs	-	-	-	1.6 (0.8 to 2.9)
			Clomiphene citrate/HMG	-	-	-	Not calculated
			Clomiphene citrate	-	-	-	2.7 (0.97 to 5.8)
			HMG	-	-	-	Not calculated
Potashnik 1999	Invasive	780/417	Fertility drugs	-	-	-	0.91 (0.10 to 3.27)

Table 1. Cohort studies (Continued)

Venn 1999	Invasive	20,656 versus 9044	Fertility drugs	-	-	-	Any drug: 0.88 (0.42 to 1.84) 1 to 2 cycles IVF: 1.26 (0.41 to 3.90) 3 to 5 cycles: 0.71 (0.10 to 5.03) > 6 cycles: 2.00 (0.3 to 14.2)
			Clomiphene citrate	-	-	-	2.46 (0.35 to 17.5)
			Clomiphene citrate + HMG	-	-	-	0.77 (0.19 to 3.07)
			HMG	-	-	-	1.14 (0.16 to 8.10)
			HMG + GnRH	-	-	-	0.48 (0.07 to 3.38)
Doyle 2002	Invasive	4188 versus 1231	Fertility drugs	-	Hazard rate ratio 0.59 (0.12 to 3.00)	Age at first clinical visit, years of first clinical visit, parity, time since first treatment and age at the end of follow-up	-
Dor 2002	Invasive	1254 versus 3772	Fertility drugs	-	-	-	1 to 2 IVF cycles: 0.98 (0.45 to 1.86) 3 to 5 IVF cycles: 1.21 (0.52 to 2.39) > 6 cycles: 0 (0 to 1.20)
Lerner-Geva 2003	Invasive	1082 versus 5920	Fertility drugs	-	-	-	5.0 (1.02 to 14.6)

Table 1. Cohort studies (Continued)

Brinton 2004	Invasive	4143 NR	versus	Clomiphene citrate	Rate ratio 0.82 (0.4 to 1. 5)	1 to 900 mg rate ratio: 0.94 (0.4 to 2.3) 901 to 2250 mg: 0.71 (0.2 to 2.0) > or equal to 2251 mg: 0.80 (0.3 to 2.1) < 6 cycles: 0. 85 (0.4 to 1.7) 6 to 11 cycles: 0.44 (0.1 to 1. 9) > or equal to 12 cycles: 1.54 (0.5 to 5.1)	Age, calendar time, area of residence, par- ity at first visit	-
				Go- nadotrophins	Rate ratio 1. 09 (0.4 to 2.8)	Dosage (amps) 1 to 24: rate ratio 1.36 (0.3 to 5. 7) > or equal to 25: 0.96 (0.3 to 3.1) 1 to 2 cycles: 0. 95 (0.2 to 3.9) > or equal 3 cycles: 1.21 (0. 4 to 3.9)	Age, calendar time, area of residence, par- ity at first visit	-
				Go- nadotrophins + clomiphene citrate	-	Rate ratio 1.02 (0.3 to 2. 8)	Age, calendar time, area of residence, par- ity at first visit	-
Calderon- Margalit 2009	Invasive	929 versus 14, 463		Fertility drugs	HR 0.61 (0.08 to 4.42)		Age	-
				Clomiphene citrate	HR 0.98 (0.14 to 7.11)		Age	-
Sanner 2009	Invasive	1153 versus 1615		Fertility drugs	-	-	-	1.19 (0.54 to 2.25)
	Borderline			Fertility drugs	-	-	-	2.62 (1.35 to 4.58)

Table 1. Cohort studies (Continued)

	Invasive		Go-nadotrophins	RR 3.55 (1.23 to 10.24)	5.21 (1.67 to 16.20) (a) 5.28 (1.70 to 16.47) (b)	a) Age and indication b) Pregnancy during follow-up	2.29 (0.84 to 4.97)
	Borderline		Go-nadotrophins	RR 0.95 (0.11 to 8.11)	1.11 (0.12 to 10.17) (a) 1.12 (0.12 to 10.32) (b)	a) Age and indication b) Pregnancy during follow-up	1.88 (0.05 to 10.45)
	Invasive		Clomiphene citrate	RR 1.12 (0.24 to 5.29)	1.52 (0.3 to 17.79) (a) 1.57 (0.32, 7.62) (b)	a) Age and indication b) Pregnancy during follow-up	0.92 (0.11 to 3.32)
	Borderline		Clomiphene citrate	RR 2.70 (0.64 to 11.28)	3.06 (0.69 to 13.68) (a) 3.25 (0.72 to 14.51) (b)	a) Age and indication b) Pregnancy during follow-up	4.59 (0.95 to 13.42)
	Invasive		Clomiphene citrate + go-nadotrophins	RR 0.48 (0.06 to 3.80)	0.72 (0.09 to 6.00) (a) 0.74 (0.09 to 6.22) (b)	a) Age and indication b) Pregnancy during follow-up	0.36 (0.01 to 2.00)
	Borderline		Clomiphene citrate + go-nadotrophins	RR 2.28 (0.55 to 9.54)	2.70 (0.58 to 12.65) (a) 2.90 (0.62 to 13.55) (b)	a) Age and indication b) Pregnancy during follow-up	3.99 (0.82 to 11.67)
Dos Santos Silva 2009	Invasive	3194 versus 3976	Fertility drugs	-	1.42 (0.53 to 3.99)	Age, calendar time, area of residence, parity at first visit	1.10 (0.57 to 1.93)
Kallen 2011	Invasive	24,058/1,394,061	Fertility drugs	-	2.09 (1.39 to 3.12)	Year of delivery after IVF, age and smoking	

Table 1. Cohort studies (Continued)

Van Leeuwen 2011	Invasive	19,146/6006	Fertility drugs	-	-	-	1.35 (0.91 to 1.92) Excluding the first year: 1.30 (0.86 to 1.88)
			HMG/FSH	-	-	-	1 to 40 ampoules: 1.25 (0.41 to 2.93) 41 to 80: 1.21 (0.39 to 2.83) > 81: 1.58 (0.68 to 3.11)
			IVF	-	1.14 (0.54 to 2.41) (a) 1.51 (0.65 to 3.54) (b) 2.26 (0.78 to 6.55) (c)	a) Age, endometriosis b) > 1 year follow-up c) > 10 years follow-up	1 to 2 cycles: 1.35 (0.68 to 2.42) 3 to 4 cycles: 1.19 (0.57 to 2.18) > 5 cycles: 1.41 (0.57 to 2.90)
	Borderline		Fertility drugs	-	-	-	1.93 (1.31 to 2.73) Excluding the first year: 1.76 (1.16 to 2.56)
			HMG/FSH	-	-	-	1 to 40 ampoules: 1.75 (0.57 to 4.08) 41 to 80: 2.03 (0.74 to 4.42) > 81: 1.69 (0.62 to 3.69)
			IVF	-	6.38 (2.05 to 19.84) (a) 4.23 (1.25 to 14.33) (b) 2.26 (0.46 to 11.05) (c)	a) For age, tubal problems and parity b) > 1 year follow-up c) > 10 years	1 to 2 cycles: 1.70 (0.97 to 3.74) 3 to 4 cycles: 1.99 (1.22 to 4.14) > 5 cycles: 1.45 (0.47 to 3.38)

Table 1. Cohort studies (Continued)

Yli-Kuha 2012	Invasive	9175/9175	IVF	-	2.75 (0.69 to 9.63)	Adjusted for marital status and socioeconomic position	-
	Borderline				2.25 (0.59 to 8.68) excluding first year after treatment	Adjusted for marital status and socioeconomic position	-
Lerner-Geva 2012	Invasive	2431/NR	Clomiphene citrate	-	-	-	1.33 (0.57 to 2.63)
			Clomiphene citrate + HMG	-	-	-	NR
			HMG	-	-	-	0.74 (0.01 to 4.12)

FSH: follicle-stimulating hormone

GnRH: gonadotrophin releasing hormone

HCG: human chorionic gonadotrophin

HMG: human menopause gonadotrophin

HR: hazard ratio

IVF: in vitro fertilisation

NR: not reported

RR: risk/rate ratio

Table 2. Case-control studies

Case-control studies							
Study	Ovarian cancer type	Total number of cancer cases/controls	Drug	Crude OR (95% CI)	Adjusted odds ratio (95% CI)	Factor adjusted for	
Rossing 1994	Invasive/ borderline	135 / NR	Clomiphene citrate	Rate ratio 11.00 (1.50 to 80.67)	Rate ratio > 1 year 11 (1.5 to 8.2)	Parity	

Table 2. Case-control studies (Continued)

				-	Rate ratio > 1 year 7.2 (1.2 to 43.9)	Age
				-	Rate ratio < 1 year 0.7 (0.1 to 4.6)	Age
				-	Rate ratio < 1 year 0.8 (0.1 to 5.7)	Parity
			HCG	-	Rate ratio 1.0 (0.2 to 4.1)	Age
				-	Rate ratio 1.0 (0.2 to 4.3)	Parity
Franceschini 1994	Invasive	195 / 1339	Fertility drugs	0.8 (0.2 to 3.7)	0.7 (0.2 to 3.7)	Age, area of residence, education, number of pregnancies, use of OCP
Sushan 1996	Invasive	68 / 77	Fertility drugs	1.78 (0.97 to 3.27)	1.31 (0.63 to 2.74)	Age, parity, BMI, region of birth, education, family history, interviewer
	Borderline	26 / 77	Fertility drugs	5.03 (2.04 to 12.22)	3.52 (1.23 to 10.09)	Age, parity, BMI, region of birth, education, family history, interviewer
	Invasive		Clomiphene citrate	1.32 (0.57 to 3.01)	0.88 (0.33 to 2.34)	Age, parity, BMI, region of birth, education, family history, interviewer
	Borderline		Clomiphene citrate	1.62 (0.25 to 7.87)	1.28 (0.25 to 6.87)	Age, parity, BMI, region of birth,

Table 2. Case-control studies (Continued)

						education, family history, interviewer
	Invasive		HMG	3.95 (1.33 to 12.2)	3.19 (0.86 to 11.82)	Age, parity, BMI, region of birth, education, family history, interviewer
	Borderline		HMG	14.58 (3.82 to 55.91)	9.38 (1.66 to 52.08)	Age, parity, BMI, region of birth, education, family history, interviewer
	Invasive		HMG/ clomiphene citrate	1.97 (1.03 to 3.77)	1.42 (0.65 to 3.12)	Age, parity, BMI, region of birth, education, family history, interviewer
	Borderline		HMG/ clomiphene citrate	4.86 (1.81 to 12.79)	3.08 (0.98 to 9.69)	Age, parity, BMI, region of birth, education, family history, interviewer
Parazzini 1997	Invasive	971 / 2758	Fertility drugs	0.5 (0.1 to 3.6) Nulliparous 0.6 (0.1 to 3.5)	1.1 (0.4 to 3.3) < 6 cycles 0.7 (0.1 to 7.9) > 6 cycles 1.0 (0.2 to 3.8)	Age, education, OCP, parity
Mosgaard 1997	Invasive	684 / 1721	Fertility drugs	Nulliparous 0.80 (0.92 to 5.58) Parous 0.62 (0.29 to 1.82)	Nulliparous 0.83 (0.35 to 2.01) Parous 0.56 (0.24 to 1.29)	Age, residence, use of OCP, menopausal status, previous cancer, family history, HRT, BMI
			Clomiphene citrate	Nulliparous 0.69 (0.23 to 1.96) Parous 0.91 (0.4	Nulliparous 0.67 (0.23 to 1.96) Parous	Age, residence, use of OCP, menopausal status, previ-

Table 2. Case-control studies (Continued)

				to 3.06)	1.11 (0.4 to 3.06)	ous cancer, family history, HRT, BMI
			Clomiphene citrate + HCG	Nulliparous 1.99 Parous 0.24	Nulliparous 1.12 (0.32 to 3.96) Parous 0.56 (0.12 to 2.7)	Age, residence, use of OCP, menopausal status, previous cancer, family history, HRT, BMI
			HMG + HCG	Nulliparous 1.06 Parous 0.54	Nulliparous 0.82 (0.18 to 3.71), Parous 0.5 (0.10 to 2.47)	Age, residence, use of OCP, menopausal status, previous cancer, family history, HRT, BMI
Parazzini 1998	Borderline	92 / 273	Fertility drugs	27.5 (1.5 to 51.60)	-	-
Mosgaard 1998	Borderline	231 / 1721	Fertility drugs	2.27 (1.30 to 3.96) Nulliparous 1.5 Parous 1.5	2.19 (1.24 to 3.85)	Age and residence
			Clomiphene citrate	Nulliparous 0.71 Parous 1.76	Nulliparous 0.80 (0.19 to 3.38) Parous 1.93 (0.56 to 6.59)	Age, residence, use of OCP, use of HRT, smoking
			Clomiphene citrate + HCG	Nulliparous 5.20 Parous 1.42	Nulliparous 3.01 (0.73 to 12.33) Multiparous 1.54 (0.30 to 7.81)	Age, residence, use of OCP, use of HRT, smoking
			HCG + HMG	Nulliparous 1.95 Parous 1.57	Nulliparous 0.91 (0.14 to 6.13) Parous 1.43 (0.28 to 7.19)	Age, residence, use of OCP, use of HRT, smoking
Parazzini 2001	Invasive	1031 / 2411	Fertility drugs	1.3 (0.7 to 2.5) Nulliparous 0.6 (0.7 to 2.5)	-	-

Table 2. Case-control studies (Continued)

				Parous 1.9 (0.7 to 2.5)		
Rossing 2004	Invasive	378 / 1634	Fertility drugs	-	Nulliparous 1.0 (0.4 to 2.8) Parous 0.8 (0.4 to 1.5)	Age, race, study site, duration of use of OCP (parous - also number of births)
			Clomiphene cit- rate	-	Nulliparous 1.2 (0.4 to 3.5) Parous 0.8 (0.4 to 1.6)	Age, race, study site, duration of use of OCP (parous - also number of births)
			HMG/ clomiphene cit- rate/ gonadotrophins	-	Nulliparous 1.0 (0.4 to 3.0); Parous 0.8 (0.4 to 1.6)	Age, race, study site, duration of use of OCP (parous - also number of births)
Jensen 2009	Invasive	626 / 615	Clomiphene cit- rate	Rate ratio 1.28 (0.79 to 2.07)	Rate ratio: 1.14 (0.79 to 1. 64) 1 to 4 cycles: 1. 27 (0.83 to 1.94) 5 to 9 cycles: 1. 03 (0.57 to 1.86) Equal or > 10 cy- cles: 0.92 (0.42 to 2.02)	Age, parity
			Gonadotrophins	Rate ratio 0.85 (0.44 to 1.64)	Rate ratio: 0.83 (0.50 to 1. 37) 1 to 4 cycles: 0. 74 (0.41 to 1.33) 5 to 9 cycles: 1. 09 (0.49 to 2.44) Equal or > 10 cy- cles: 0.96 (0.09 to 10.30)	Age, parity
			HCG	Rate ratio 0.95 (0.57 to 1.58)	Rate ratio: 0.89 (0.62 to 1. 29)	Age, parity

Table 2. Case-control studies (Continued)

					1 to 4 cycles: 0.96 (0.62 to 1.48) 5 to 9 cycles: 0.86 (0.47 to 1.57) Equal or > 10 cycles: 0.70 (0.28 to 1.80)	
			GnRH	Rate ratio 0.71 (0.32 to 1.54)	Rate ratio: 0.80 (0.42 to 1.51) 1 to 4 cycles: 0.81 (0.42 to 1.56) 5 to 9 cycles: 0.68 (0.09 to 5.38)	Age, parity
Kurta 2012	Invasive	155 / 290	Fertility drugs	1.87 (0.53 to 6.65) < 6 months: 0.92 (0.48 to 1.74) > 6 months: 0.75 (0.42 to 1.34)	0.57 (0.31 to 1.05) parous 0.47 (0.09 to 2.53) nulliparous	-
			Clomiphene citrate	0.87 (0.49 to 1.56)	-	-
			Gonadotrophins	0.51 (0.20 to 1.32)	-	-
			Gonadotrophins + Clomiphene citrate	0.94 (0.37 to 2.42)	-	-

BMI: body mass index

CI: confidence interval

GnRH: gonadotrophin-releasing hormone

HCG: human chorionic gonadotrophin

HMG: human menopausal gonadotrophin

HRT: hormone replacement therapy

IUD: intrauterine device

NR: not reported

OCP: oral contraceptive pill

OR: odds ratio

APPENDICES

Appendix 1. CENTRAL search strategy

- #1 Mesh descriptor: [Ovarian Neoplasms] explode all trees
- #2 ovar* near/5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*)
- #3 #1 or #2
- #4 Mesh descriptor: [Ovulation Induction] explode all trees
- #5 Mesh descriptor: [Fertility Agents] explode all trees
- #6 (fertil* or infertil*) near/5 (agent* or drug*)
- #7 (stimul* or induc*) near/5 (ovar* or ovul*)
- #8 MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees
- #9 SERM or (selective next (estrogen or oestrogen) next receptor next modulator*) or clomiphene or chloramiphene or clomid* or clomifen* or tamoxifen
- #10 Mesh descriptor: [Gonadotropins] explode all trees
- #11 gonadotropin-releasing hormone
- #12 Mesh descriptor: [Gonadotropin-Releasing-Hormone] explode all trees
- ##13gonadotropin* or (luteinizing hormone*) or (follicle stimulating hormone*) or LH or FSH or hMG or hCG or GnRH*
- #14 Mesh descriptor: [Growth Hormone] explode all trees
- #15 Mesh descriptor: [Insulin-Like Growth Factor 1] explode all trees
- #16 (growth hormone*) or (insulin near/5 (growth factor)) or GH or IGF
- #17 Mesh descriptor: [Reproductive Techniques, Assisted] explode all trees
- #18 (assist* near/5 reproduct*) or ART or (in vitro near/5 fertili*) or IVF
- #19 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
- #20 #3 and #19

Appendix 2. MEDLINE search strategy

- 1 exp Ovarian Neoplasms/
- 2 (ovar* adj5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*)).mp.
- 3 1 or 2
- 4 exp Ovulation Induction/
- 5 exp Fertility Agents/
- 6 ((fertil* or infertil*) adj5 (agent* or drug*)).mp.
- 7 ((stimul* or induc*) adj5 (ovar* or ovul*)).mp.
- 8 exp Selective Estrogen Receptor Modulators/ or (selective adj (estrogen or oestrogen) adj receptor adj modulator*).mp.
- 9 (SERM* or clomiphene or chloramiphene or clomid* or clomifen* or tamoxifen).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 exp Growth Hormone/
- 14 Insulin-Like Growth Factor I/
- 15 (growth hormone* or (insulin adj5 growth factor) or GH or IGF).mp.
- 16 exp Reproductive Techniques, Assisted/
- 17 ((assist* adj5 reproduct*) or ART or (in vitro adj5 fertili*) or IVF).mp.
- 18 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
- 19 3 and 18
- 20 randomized controlled trial.pt.
- 21 controlled clinical trial.pt.
- 22 randomized.ab.
- 23 placebo.ab.
- 24 drug therapy.fs.
- 25 randomly.ab.

26 trial.ab.
 27 groups.ab.
 28 exp Cohort Studies/
 29 cohort*.mp.
 30 exp Case-Control Studies/
 31 (case* and control*).mp.
 32 (case* and series).mp.
 33 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
 34 19 and 33
 35 exp animals/ not humans.sh.
 36 34 not 35
 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 3. EMBASE search strategy

1 exp ovary tumor/
 2 (ovar* adj5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*)).mp.
 3 1 or 2
 4 exp ovulation induction/
 5 exp fertility promoting agent/
 6 (((fertil* or infertil*) adj5 (agent* or drug*)) or ((stimul* or induc*) adj5 (ovar* or ovul*))).mp.
 7 selective estrogen receptor modulator/ or (selective adj (estrogen or oestrogen) adj receptor adj modulator*).mp.
 8 (SERM* or clomiphene or chloramiphene or clomid* or clomifen* or tamoxifen).mp.
 9 exp gonadotropin/
 10 gonadorelin/
 11 (gonadotropin* or luteinizing hormone* or follicle stimulating hormone* or LH or FSH or hMG or hCG or GnRH*).mp.
 12 growth hormone/
 13 somatomedin/
 14 (growth hormone* or (insulin adj5 growth factor) or GH or IGF).mp.
 15 exp infertility therapy/
 16 ((assist* adj5 reproduct*) or ART or (in vitro adj5 fertili*) or IVF).mp.
 17 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
 18 3 and 17
 19 exp controlled clinical trial/
 20 crossover procedure/
 21 double-blind procedure/
 22 randomized controlled trial/
 23 single-blind procedure/
 24 random*.mp.
 25 factorial*.mp.
 26 (crossover* or cross over* or cross-over*).mp.
 27 placebo*.mp.
 28 (double* adj blind*).mp.
 29 (singl* adj blind*).mp.
 30 assign*.mp.
 31 allocat*.mp.
 32 volunteer*.mp.
 33 exp cohort analysis/
 34 cohort*.mp.
 35 retrospective study/

36 prospective study/
 37 prospective study/
 38 (case* and (control* or series)).mp.
 39 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 or 37 or 38
 40 18 and 39
 41 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
 42 40 not 41
 key:
 [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

WHAT'S NEW

Last assessed as up-to-date: 29 July 2013.

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 8, 2013

Date	Event	Description
11 February 2015	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

IR and LS selected studies and contributed to the writing of the text. IR, RB and LS extracted data. RB reviewed drafts and suggested revisions. LS performed statistical analysis. All the authors approved the final version.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Ipswich Hospital NHS Trust, UK.

The staff at the library helped us in searching and providing articles

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We decided to add the following fertility medications to the review: selective oestrogen receptor modulator (SERM); gonadotrophin-releasing hormone agonist (GnRH-AG); gonadotrophin-releasing hormone antagonist (GnRH-A); growth hormone.

INDEX TERMS

Medical Subject Headings (MeSH)

Case-Control Studies; Cohort Studies; Fertility Agents, Female [*adverse effects]; Ovarian Neoplasms [*chemically induced; pathology]; Ovulation Induction [*methods]

MeSH check words

Female; Humans