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

Skalkidou A, Sergentanis TN, Gialamas SP, Georgakis MK, Psaltopoulou T, Trivella M, Siristatidis CS, Evangelou E, Petridou E

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[Intervention Review]

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

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ABSTRACT

Background

Medical treatment for subfertility principally involves the use of ovary-stimulating agents, including selective oestrogen receptor modulators (SERMs), such as clomiphene citrate, gonadotropins, gonadotropin-releasing hormone (GnRH) agonists and antagonists, as well as human chorionic gonadotropin. Ovary-stimulating drugs may act directly or indirectly upon the endometrium (lining of the womb). Nulliparity and some causes of subfertility are recognized as risk factors for endometrial cancer.

Objectives

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

Search methods

A search was performed in CENTRAL, MEDLINE (Ovid) and Embase (Ovid) databases up to July 2016, using a predefined search algorithm. A search in OpenGrey, ProQuest, ClinicalTrials.gov, ZETOC and reports of major conferences was also performed. We did not impose language and publication status restrictions.

Selection criteria

Cohort and case-control studies reporting on the association between endometrial cancer and exposure to ovary-stimulating drugs for subfertility in adult women were deemed eligible.

Data collection and analysis

Study characteristics and findings were extracted by review authors independently working in pairs. Inconsistency between studies was quantified by estimating I^2. Random-effects (RE) models were used to calculate pooled effect estimates. Separate analyses were performed, comparing treated subfertile women versus general population and/or unexposed subfertile women, to address the superimposition of subfertility as an independent risk factor for endometrial cancer.

Main results

Nineteen studies were eligible for inclusion (1,937,880 participants). Overall, the quality of evidence was very low, due to serious risk of bias and indirectness (non-randomised studies (NRS), which was reflected on the GRADE assessment.

Six eligible studies, including subfertile women, without a general population control group, found that exposure to any ovary-stimulating drug was not associated with an increased risk of endometrial cancer (RR 0.96, 95% CI 0.67 to 1.37; 156,774 participants; very low quality evidence). Fifteen eligible studies, using a general population as the control group, found an increased risk after exposure to any ovary-stimulating drug (RR 1.75, 95% CI 1.18 to 2.61; 1,762,829 participants; very low quality evidence).

Five eligible studies, confined to subfertile women (92,849 participants), reported on exposure to clomiphene citrate; the pooled studies indicated a positive association (RR 1.32; 95% CI 1.01 to 1.71; 88,618 participants; very low quality evidence), although only at high dosage (RR 1.69, 95% CI 1.07 to 2.68; two studies; 12,073 participants) and at a high number of cycles (RR 1.69, 95% CI 1.16 to 2.47; three studies; 13,757 participants). Four studies found an increased risk of endometrial cancer in subfertile women who required clomiphene citrate compared to a general population control group (RR 1.87, 95% CI 1.00 to 3.48; four studies, 19,614 participants; very low quality evidence). These data do not tell us whether the association is due to the underlying conditions requiring clomiphene or the treatment itself.

Using unexposed subfertile women as controls, exposure to gonadotropins was associated with an increased risk of endometrial cancer (RR 1.55, 95% CI 1.03 to 2.34; four studies; 17,769 participants; very low quality evidence). The respective analysis of two studies (1595 participants) versus the general population found no difference in risk (RR 2.12, 95% CI 0.79 to 5.64: very low quality evidence).

Exposure to a combination of clomiphene citrate and gonadotropins, compared to unexposed subfertile women, produced no difference in risk of endometrial cancer (RR 1.18, 95% CI 0.57 to 2.44; two studies; 6345 participants; very low quality evidence). However, when compared to the general population, an increased risk was found , suggesting that the key factor might be subfertility, rather than treatment (RR 2.99, 95% CI 1.53 to 5.86; three studies; 7789 participants; very low quality evidence).

Authors' conclusions

The synthesis of the currently available evidence does not allow us to draw robust conclusions, due to the very low quality of evidence. It seems that exposure to clomiphene citrate as an ovary-stimulating drug in subfertile women is associated with increased risk of endometrial cancer, especially at doses greater than 2000 mg and high (more than 7) number of cycles. This may largely be due to underlying risk factors in women who need treatment with clomiphene citrate, such as polycystic ovary syndrome, rather than exposure to the drug itself. The evidence regarding exposure to gonadotropins was inconclusive.

PLAIN LANGUAGE SUMMARY

Risk of endometrial cancer in subfertile women undergoing ovarian stimulation

Background

For the treatment of subfertility (delay in becoming pregnant), several medications are used to stimulate ovulation - the process of maturation and release of eggs from the ovaries. These drugs may also affect the endometrium, which is the layer of tissue lining of the womb (uterus). However, conditions that cause subfertility are known risk factors for endometrial cancer (cancer of the lining of the womb) while pregnancy and combined oral contraceptive pills have a protective effect, significantly reducing the risk of endometrial cancer. Separating causative effect of medicines used to treat subfertility from other underlying causes, which may increase the individual's risk of endometrial cancer, is therefore extremely challenging.

The aim of the review

To find out whether the medicines used to stimulate ovulation increase the risk of endometrial cancer in women who need medical help to get pregnant.

Key results

The evidence is current to July 2016. Nineteen studies, including 1,937,880 participants, were identified that compared the risk of developing cancer of the lining of the womb (endometrial cancer) in women exposed to ovary-stimulating drugs versus either subfertile women not exposed to these drugs, or women from the general population. Overall, exposure to clomiphene citrate, mainly in high dosage and in repeated cycles, may be associated with an increased risk of developing endometrial cancer later in life. The evidence about the relationship between exposure to gonadotropins and endometrial cancer was less robust. It is not possible to say whether the increased risk is due to ovulation-stimulating drug use or to the underlying cause of subfertility.

Quality of the evidence

The quality of the evidence for the findings was very low, as the included studies had severe limitations and multiple differences in the way they were conducted.

What are the conclusions?

Women who need treatment with clomiphene citrate should be aware that they are at increased risk of endometrial cancer, but this is largely due to underlying condition causing subfertility and it is not possible to assess the additional effect of clomiphene citrate, based on available data.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Exposure to any ovary-stimulating drugs for subfertility compared to untreated subfertile women and endometrial cancer risk

Patient or population: Women treated with ovary-stimulating drugs for subfertility
Intervention: Exposure to any ovary-stimulating drug for subfertility
Comparison: Untreated subfertile women

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with exposure to any ovary-stimulating drug for subfertility				
Endometrial cancer	Study population		RR 0.96 (0.67 to 1.37)	156,774 (6 observational studies)	⊕⊖⊖⊖ Very low [1,2,3]	
	111 per 100,000	109 per 100,000 (74 to 163)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

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

[1] Initial level of evidence was 'low' because of the study design (observational studies).
[2] Downgraded because of high risk of bias.
[3]Optimal information size (OIS) criterion not met (OIS = 499,938); however, the sample size was large.

Summary of findings 2. Exposure to any ovary-stimulating drugs for subfertility compared to general population and endometrial cancer risk

Patient or population: Women treated with ovary-stimulating drugs for subfertility
Intervention: Exposure to any ovary-stimulating drug for subfertility
Comparison: General population

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with exposure to any ovary-stimulating drug for subfertility				
Endometrial cancer	Study population		RR 1.75 (1.18 to 2.61)	1,762,829 (15 observational studies)	⊕⊝⊝⊝ Very low [1,2,3]	
	53 per 100,000	92 per 100,000 (62 to 138)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
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Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Initial level of evidence was 'low' because of the study design (observational studies).
[2] Downgraded because of high risk of bias.
[3] Downgraded due to inconsistency of results (significant heterogeneity) and imprecision.

Summary of findings 3. Exposure to clomiphene citrate for subfertility compared to untreated subfertile women and endometrial cancer risk

Patient or population: Women treated with ovary-stimulating drugs for subfertility
Intervention: Exposure to clomiphene citrate for subfertility
Comparison: Untreated subfertile women

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with exposure to clomiphene citrate for subfertility				
Endometrial cancer	Study population		RR 1.32 (1.01 to 1.71)	92,849 (5 observational studies)	⊕⊝⊝⊝ Very low [1,2,3]	
	524 per 100,000	691 per 100,000 (530 to 894)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

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

[1] Initial level of evidence was 'low' because of the study design (observational studies).
[2] Downgraded because of risk of bias.
[3] Optimal information size (OIS) criterion not met; however, the sample size was large.

Summary of findings 4. Exposure to clomiphene citrate for subfertility compared to general population and endometrial cancer risk

Patient or population: Women treated with ovary-stimulating drugs for subfertility
Intervention: Exposure to clomiphene citrate for subfertility
Comparison: General population

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with exposure to clomiphene citrate for subfertility				
Endometrial cancer	Study population		RR 1.87 (1.00 to 3.48)	19,614 (4 observational studies)	⊕⊖⊖⊖ Very low [1,2,3]	
	284 per 100,000	529 per 100,000 (284 to 980)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Initial level of evidence was 'low' because of the study design (observational studies).
[2] Downgraded because of risk of bias.
[3]Optimal information size (OIS) criterion not met.

Summary of findings 5. Exposure to gonadotropins for subfertility compared to untreated subfertile women and endometrial cancer risk

undefined

Patient or population: Women treated with ovary-stimulating drugs for subfertility
Intervention: Exposure to gonadotropins for subfertility
Comparison: Untreated subfertile women

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with exposure to gonadotropins for subfertility				
Endometrial cancer	Study population		RR 1.55 (1.03 to 2.34)	17,769 (4 observational studies)	⊕⊖⊖⊖ Very low [1,2,3]	
	1291 per 100,000	1987 per 100,000 (1329 to 2970)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

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

[1] Initial level of evidence was 'low' because of the study design (observational studies).
[2] Downgraded because of risk of bias in most studies and imprecise estimates in one study.
[3] Optimal information size (OIS) not met.

Summary of findings 6. Exposure to gonadotropins for subfertility compared to general population and endometrial cancer risk

Patient or population: Women treated with ovary-stimulating drugs for subfertility
Intervention: Exposure to gonadotropins for subfertility
Comparison: General population

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with exposure to gonadotropins for subfertility				
Endometrial cancer	Study population		RR 2.12 (0.79 to 5.64)	1595 (2 observational studies)	⊕⊝⊝⊝ Very low [1,2,3]	
	542 per 100,000	1148 per 100,000 (428 to 3054)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

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

[1] Initial level of evidence was 'low' because of the study design (observational studies).
[2]Downgraded because of risk of bias and imprecision.
[3] Optimal information size (OIS) not met.

Summary of findings 7. Exposure to clomiphene citrate and gonadotropins for subfertility compared to untreated subfertile women and endometrial cancer risk

Patient or population: Women treated with ovary-stimulating drugs for subfertility
Intervention: Exposure to clomiphene citrate and gonadotropins for subfertility
Comparison: Untreated subfertile women

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments

	Risk with no treatment	Risk with exposure to clomiphene citrate and gonadotropins for subfertility			
Endometrial cancer	Study population		RR 1.18 (0.57 to 2.44)	6345 (2 observational studies)	⊕⊖⊖⊖ Very low [1,2,3]
	490 per 100,000	579 per 100,000 (279 to 1196)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

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

[1] Initial level of evidence was 'low' because of the study design (observational studies).
[2] Downgraded because of risk of bias.
[3] Optimal information size (OIS) criterion not met.

Summary of findings 8. Exposure to clomiphene citrate and gonadotropins for subfertility compared to general population and endometrial cancer risk

Patient or population: Women treated with ovary-stimulating drugs for subfertility
Intervention: Exposure to clomiphene citrate and gonadotropins for subfertility
Comparison: General population 2.99 [1.53, 5.86]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with exposure to clomiphene citrate and gonadotropins for subfertility				
Endometrial cancer	Study population		RR 2.99 (1.53 to 5.86)	7789 (3 observational studies)	⊕⊖⊖⊖ Very low[1,2,3]	
	76 per 100,000	245 per 100,000 (150 to 401)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

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

[1] Initial level of evidence was 'low' because of the study design (observational studies).
[2] Downgraded because of risk of bias.
[3] Optimal information size (OIS) not met; however, the sample size was large.

Summary of findings 9. Exposure to GnRH analogues for subfertility compared to untreated subfertile women and endometrial cancer risk

Patient or population: Women treated with ovary-stimulating drugs for subfertility
Intervention: Exposure to GnRH analogues for subfertility
Comparison: Untreated subfertile women

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with exposure to GnRH analogs for subfertility				
Endometrial cancer	Study population		RR 1.21 (0.65 to 2.27)	42,558 (2 observational studies)	⊕⊖⊖⊖ Very low [1,2,3]	
	458 per 100,000	554 per 100,000 (297 to 1039)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Initial level of evidence was 'low' because of the study design (observational studies).
[2] Downgraded because of risk of bias.
[3]Optimal information size (OIS) criterion not met; however, the sample size was large

BACKGROUND

Description of the condition

Subfertility remains a key issue for modern societies in terms of the psychosocial well-being of those involved, as well as the financial and public health burden (Chambers 2007; Chambers 2013). In the UK, subfertility has been defined as failure to conceive after regular unprotected sexual intercourse for one year in the absence of known reproductive pathology (NICE 2013). The revised glossary published by the International Committee for Monitoring Assisted Reproductive Technology (ICMART), in collaboration with the World Health Organization (WHO) (Zegers-Hochschild 2009), as well as the Practice Committee of the American Society for Reproductive Medicine (ASRM 2013), also set the time interval for definition of subfertility at one year.

Subfertility has several causes, with male partners' factors prevailing in about 30% of cases and female partners' factors in 50% of cases (DH 2009). The most commonly identifiable female factors are ovulatory disorders, endometriosis (a condition characterized by painful menses and abnormal growth of endometrial tissue outside the uterus), pelvic adhesions (scar tissue), tubal blockage or other tubal abnormalities, and hyperprolactinaemia (increased blood levels of the hormone prolactin) (Fritz 2010; UpToDate 2013).

Endometrial cancer (cancer of the lining of the womb) is a common cancer. In the USA, there is a 2.8% lifetime risk of endometrial cancer. Between 2009 and 2013, the number of new cases of endometrial cancer was 25.4 per 100,000 women per year; 4.5 per 100,000 women per year will die from the disease (SEER 2016). Nulliparity is a recognised risk factor for endometrial cancer (Cetin 2008; Venn 1999), as are conditions associated with subfertility, such as polycystic ovary syndrome (a common endocrine system disorder among women of reproductive age frequently associated with high free adrogen levels and the presence of many growing follicles in the ovaries), diabetes and obesity (DiSaia 2012), and the impact of treatment for subfertility on the risk of endometrial cancer is also being explored (Siristatidis 2013). Pregnancy and use of combined oral contraceptives are known to reduce the risk of endometrial cancer, both of which are less common in women with subfertility (Cetin 2008; DiSaia 2012). These factors make differentiating causation and association extremely challenging.

Description of the intervention

Treatment for subfertility principally involves the use of fertility medication. Ovary-stimulating drugs are predominantly used for the treatment of women suffering from the ovulation disorders, WHO Group I (hypothalamic pituitary failure) and Group II (hypothalamic pituitary dysfunction, predominantly polycystic ovary syndrome) (NICE 2013). These agents can be used to induce ovulation in anovulatory women (anovulation refers to the non-release of an oocyte during a menstrual cycle), but can also be implemented for controlled ovarian stimulation in women undergoing assisted reproduction.

Commonly used agents and their uses are listed here:

- Selective oestrogen receptor modulators (SERMs), such as tamoxifen and clomiphene citrate, make up a class of compounds that act on oestrogen receptors (Steiner 2005).These agents are used during the follicular phase (the first phase of the menstrual cycle before relase of the oocyte) to increase the serum concentration of gonadotropins, which stimulate the ovary and promote follicle (the organized aggregation of cells containing the oocyte) maturation and ovulation (Klip 2000);
- Gonadotropins (luteinising hormone (LH) and follicle-stimulating hormone (FSH) that stimulate the ovaries may be used in their recombinant form (i.e. rFSH; produced in the laboratory from DNA coming from different sources) or as human menopausal gonadotropins (hMGs), which consist of LH and FSH extracted from the urine of menopausal women (NICE 2013);
- Gonadotropin-releasing hormone (GnRH) agonists (chemicals that mimic the hormone actions) and antagonists (chemicals that inhibit the hormone actions) are nearly always used in conjunction with gonadotropins. They facilitate cycle control during in vitro fertilisation (IVF) treatment (NICE 2013); their inclusion in this review inherently encompasses their combination with hMG or FSH;
- Human chorionic gonadotropin (hCG), used intramuscularly, mimics the role of LH and induces ovulation or maturation of the oocytes (NICE 2013).

How the intervention might work

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

Specifically, fertility drugs provide the following effects.

- Selective oestrogen receptor modulators (SERMs, e.g. clomiphene citrate) are associated with a twofold to threefold increase in the mean oestradiol level, resulting in enhancement of ovulation during treated cycles, as well as an increase in progesterone levels (Dickey 1996; Sovino 2002). Clomiphene citrate might also affect the risk of endometrial cancer by interacting directly with oestrogen receptors within the uterus (Goldstein 2000; Nakamura 1997). Similarly, tamoxifen (Brown 2009; Dhaliwal 2011) has been associated with an increased risk of endometrial cancer (Swerdlow 2005).
- Treatment with hMG or FSH, as in IVF, may substantially increase the number of ovulations compared with that seen in untreated women (Klip 2000).
- hCG mimics the function of LH by initiating oocyte (female egg cell) maturation/ovulation (Klip 2000).
- GnRH modulates the endogenous pituitary release of LH and FSH and subsequent folliculogenesis (maturation of the ovarian follicle). GnRH agonists and antagonists are regularly used as an addition to the treatment of female subfertility (Jensen 2009; Klip 2000).

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

Why it is important to do this review

Exposure to fertility drugs has increased over time, and hence evaluating the long-term effects of ovulation-inducing drugs on the risk of endometrial cancer is a matter of great importance.

Over past decades, numerous studies investigating the association between fertility drugs and endometrial cancer risk have yielded conflicting or inconclusive results (Li 2013). We have recently examined the association between controlled ovarian hyperstimulation in the context of IVF and endometrial, ovarian or cervical cancer (Siristatidis 2013). In that review, we observed an association between IVF and increased risk of endometrial cancer comparing exposed women with the general population, but this association dissipated when the comparison was made versus non-exposed subfertile women. Broadening the research question, we now aim to evaluate all ovary-stimulation drugs, not just those used in the context of IVF treatment.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We considered prospective and retrospective cohort studies and case-control studies in this area. Case series, case reports and *in vitro* and animal studies were excluded.

Types of participants

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

Types of interventions

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

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

Types of outcome measures

Primary outcomes

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

Secondary outcomes

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

Search methods for identification of studies

Electronic searches

We searched CENTRAL (Issue 7, 2016), MEDLINE via Ovid (1960 to July week 3 2016) and Embase via Ovid (1980 to week 31 2016). We searched the CENTRAL database for reasons of completeness because, although this review was based on non-randomised studies (NRSs), CENTRAL contains controlled clinical trials (CCTs), interrupted time series and controlled before and after series, in addition to randomised controlled trials (RCTs).

The search terms included a combination of thesaurus-based and free-text terms. CENTRAL, MEDLINE and Embase search strategies are presented in Appendix 1, Appendix 2 and Appendix 3, respectively.

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

Searching other resources

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

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

Data collection and analysis

Selection of studies

We downloaded the search results to a special processing platform developed by Prodromos Kanavidis, a full description of which can be found in our recent publication (Siristatidis 2013).

We removed duplicates and all review coauthors were involved in selecting studies for eligibility. Review coauthors working in pairs (AS & HS, SG & TT, TS & TP) assessed the allocation of titles and abstracts, so that each allocation portion was independently assessed by two review coauthors. We were not blinded to authors' names and institutions, journal of publication or study results while assessing studies for potential inclusion.

We excluded studies that clearly did not meet the inclusion criteria. For potentially relevant studies, we obtained the full text article for further assessment. We sent letters to study authors to ask for clarification about potentially relevant studies. We resolved all disagreements by consensus.

Data extraction and management

The review authors extracted data using a predesigned Excel file before copying the data into New Reference (Review Manager 2011) for analysis. We previously had piloted the data extraction form (Appendix 4) before using it in our published report (Siristatidis 2013), which, however, focused solely on IVF. We extracted the data independently while working in pairs. We resolved all disagreements by consensus.

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

In addition, we extracted the following results, when available:

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

Assessment of risk of bias in included studies

As detailed below, RCTs were not identified, therefore the risk of bias assessment used methodology for non-randomised studies (NRSs).

The risk of bias was assessed in accordance with relevant sections of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), as well as in keeping with the rationale adopted in the most recent Cochrane review examining the association between ovarian cancer and ovary-stimulation drugs for subfertility (Rizzuto 2013). As suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 13.5.2.3), items included in the Newcastle-Ottawa scale (Wells 2011) were customised for inclusion in the detailed item-to-item list below.

The assessment of risk of bias encompassed the examination of selection bias (comparability of groups and confounding/adjustment), performance bias, detection bias, attrition bias, reporting bias, and other bias. The qualifications 'low risk', 'high risk' and 'unclear risk' were adopted for each 'risk of bias' domain, in accordance with the guidelines published by the Newcastle-Ottawa scale (Wells 2011).

Selection bias

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

Comparability of groups

- Consecutive recruitment cases (case-control studies).
- Population-based controls derived from the same population as cases (case-control studies).
- Non-exposed women drawn from the same population as the exposed cohort (cohort studies).
- Comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), obesity (all studies).

Confounding/Adjustment

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

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

Performance bias

The following features of the study design were evaluated.

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

Detection bias

The following feature was assessed.

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

Attrition bias

With respect to attrition bias, the following feature was examined.

- At least 80% of women in all groups were included in the final analysis (all studies).

Selective reporting (reporting bias)

This domain assessed the uniformity in the undertaken analyses in each study. When outcomes were reported in a prespecified way, this indicated low risk of bias. However, instances of nonreported subanalyses or models differentially implemented across various cancer types in the same study, signalled high risk of bias.

Other bias

- Length of follow-up was at least 10 years for the exposed group (Siristatidis 2013), as endometrial cancer reaches its peak incidence after the age of 55 years, whereas IVF exposure occurs mostly during the late reproductive years (cohort studies).
- Study design as a non-RCT study.

Measures of treatment effect

Both primary and secondary outcome measures were expressed as odds ratios (ORs), risk ratios (RRs), hazard ratios (HRs), standardised incidence ratios (SIRs), or incidence rate ratios (IRRs). The 95% confidence interval (CI) for log(SIR) were reconstructed via the term ± 1.96/(square root (O), where 'O' represented the observed number of events (Alder 2006). We intended to transform ORs, RRs and HRs into a single metric to reduce heterogeneity and to provide more robust estimates and analyse SIRs and IRRs separately; however, since the absolute risk of endometrial cancer is low, the four measures of association (ORs, HRs, SIRs, and IRRs) were expected to yield similar estimates of RR (Adami 2008; Larsson 2007), therefore no transformation was performed.

Unit of analysis issues

The unit of analysis was always the participant.

Dealing with missing data

The corresponding authors of 'potentially relevant' and eligible studies were contacted by email when the need arose to obtain missing data, to ask for additional information or to request methodological clarification. We did not impute missing outcome data for any of the outcomes.

Assessment of heterogeneity

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

Assessment of reporting biases

As we included more than 10 studies in the review, we assessed publication bias using Egger's formal statistical test ((Egger 1997); *Cochrane Handbook for Systematic Reviews of Interventions*, Section 10.4.3.1, (Higgins 2011) at the 90% level, and a funnel plot was constructed. We intended to also use an Egger's modified test (Harbord's test) to assess possible small-study effect biases (Harbord 2006), however the low number of included studies precluded this opportunity.

Data synthesis

Our intention was to carry out meta-analyses separately for RCTs in accordance with the intention-to-treat principle and for any non-randomised studies (cohort and case-control studies); however, no RCTs were identified for inclusion.

We used RE models to present an analysis, where at least two relevant studies had to exist (DerSimonian 1986). We also calculated separate pooled effect estimates for each risk ratio (RR) measures (and OR, HR, SIR, IRR). As mentioned before, the four relative measures were expected to yield similar estimates . As we described earlier, when possible, subgroup analyses by type of effect estimate were performed.

Our intention was to perform sensitivity analyses by type of measure, yet this was not feasible due to the small number of included studies. Separate analyses were carried out for the different reference populations available (general population of women and subfertile women who did not receive fertility treatment).

'Summary of findings' tables

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group system was used to build 'Summary of findings' tables as suggested by the Cochrane Handbook for Systematic Reviews of Interventions (Schunemann 2011). This included comparisons of risk of endometrial cancer in women exposed to any ovary-stimulating drug (clomiphene citrate, gonadotropins, combination of clomiphene citrate and gonadotropins, and GnRH analogues) versus untreated subfertile women or women of the general population.

The quality of evidence was very low for all comparisons. The observational nature of the included studies resulted in an initial rating of 'low' quality of evidence, which was further downgraded mostly because of the high risk of bias, and, in some comparisons, because of imprecision or inconsistency or both.

Subgroup analysis and investigation of heterogeneity

According to data availability, the various therapeutic agents were evaluated by drug subtype (SERMs, gonadotropins, GnRH agonists and antagonists, hCG) and as individual drugs. Subgroup analyses were also performed for each ovary-stimulation agent by type of effect measures. Separate analyses were performed by:

- gravidity and/or parity;
- age groups;
- causes of subfertility;
- histological type of cancer;
- dosage (low: 1000 mg or less; medium: 1000 to 2000 mg; high: 2000 mg or more of clomiphene citrate)
- number of cycles (low: 1 to 3; medium: 4 to 6; high: 7 or more);
- number of oocytes (0 to 3; 3 to 6; 6 to 10; 10 or more oocytes)
- studies including or excluding events during the first year of follow-up (Siristatidis 2013).

Although we intended to perform meta-regression analyses to adjust for mutual confounding, the small number of studies precluded any meaningful analysis.

We did not need to statistically adjust for multiple analyses, as such adjustments pertain to multiple comparisons, which were not relevant in the context of our study (Sergentanis 2014; Siristatidis 2013).

Sensitivity analysis

As mentioned earlier, sensitivity analysis for each type of effect measure was not employed, as there were insufficient numbers of available studies. Similarly, sensitivity analyses based on the risk of bias assessment, although planned, were not carried out because of the high risk of bias in all of the examined studies. Sensitivity analyses were only performed for studies with mean or median follow-up 10 years or more in the exposed cohort.

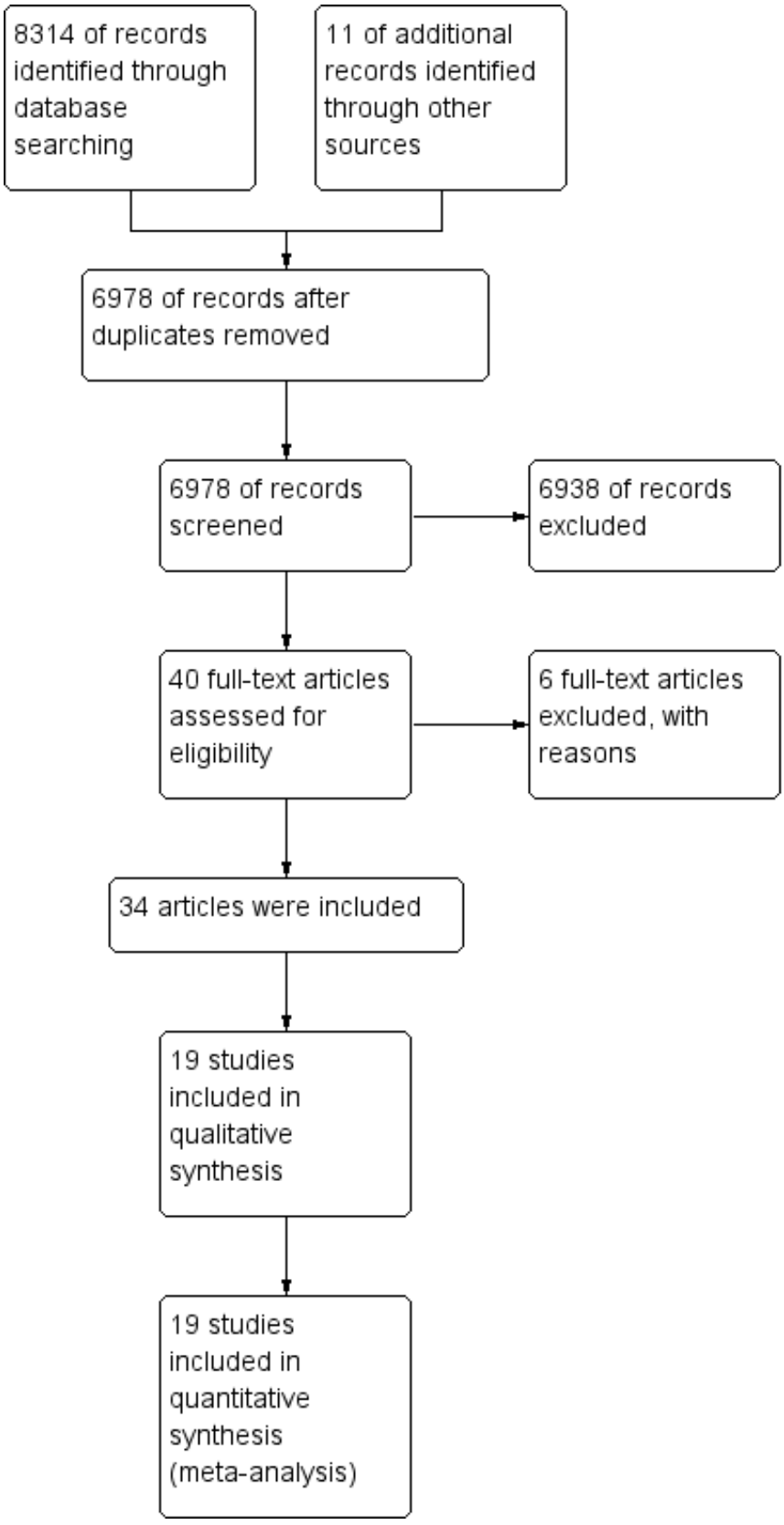
RESULTS

Description of studies

Results of the search

Searching of all databases resulted in 8314 records: 3716 were retrieved from Medline; 4090 from Embase; and 508 from CENTRAL. Handsearch of references of relevant articles yielded 11 additional relevant studies. No relevant articles were identified by search of the grey literature. Removal of 1336 duplicates yielded 6978 unique records. After reading titles and abstracts, 40 articles were deemed potentially eligible, for which full text was obtained for further scrutiny. Of these, six studies were excluded (Characteristics of excluded studies). Thirty-four articles corresponding to 19 studies were included. There were no studies meeting eligibility criteria that required translation. All the articles had an abstract in the English language. The selection of study process is graphically represented in a PRISMA Flow Diagram (Figure 1).

Figure 1. PRISMA Flow Diagram



Included studies

Nineteen studies (Benshushan 2001; Brinton 2013a; Brinton 2013b; Calderon-Margalit 2009; Dor 2002; Dos Santos Silva 2009; Doyle 2002; Jensen 2009; Kessous 2016; Klip 2004; Kristiansson 2007; Lerner-Geva 2012; Luke 2015; Parazzini 2001; Parazzini 2010; Potashnik 1999; Reigstad 2015; Venn 1999; Yli-Kuha 2012) were included; Characteristics of included studies are presented in the respective section of the review.

One study was conducted in Australia (Venn 1999), one in Denmark (Jensen 2009), one in Finland (Yli-Kuha 2012), two in Italy (Parazzini 2001; Parazzini 2010), one in Netherlands (Klip 2004), one in Norway (Reigstad 2015), one in Sweden (Kristiansson 2007), two in the UK (Dos Santos Silva 2009; Doyle 2002), seven in Israel (Benshushan 2001; Brinton 2013a; Calderon-Margalit 2009; Dor 2002; Kessous 2016; Lerner-Geva 2012; ; Potashnik 1999), and two in USA (Brinton 2013b; Luke 2015). Thirteen studies were multi-centre (Benshushan 2001; Brinton 2013a; Brinton 2013b; Dor 2002; Jensen 2009; Klip 2004; Kristiansson 2007; Luke 2015; Parazzini 2001; Parazzini 2010; Reigstad 2015; Venn 1999; Yli-Kuha 2012), whereas six were single-centre (Calderon-Margalit 2009; Dos Santos Silva 2009; Doyle 2002; Kessous 2016; Lerner-Geva 2012; Potashnik 1999).

Sixteen of the studies were of retrospective cohort design (Brinton 2013a; Brinton 2013b; Calderon-Margalit 2009; Dor 2002; Dos Santos Silva 2009; Doyle 2002; Jensen 2009; Kessous 2016; Klip 2004; Kristiansson 2007; Lerner-Geva 2012; Luke 2015; Potashnik 1999; Reigstad 2015; Venn 1999; Yli-Kuha 2012). Of these, eight studies identified women from IVF centres or reproductive endocrinology practices (Brinton 2013b; Dor 2002; Dos Santos Silva 2009; Doyle 2002; Klip 2004; Lerner-Geva 2012; Potashnik 1999; Venn 1999), and five from registries (Brinton 2013a; Jensen 2009; Kristiansson 2007; Luke 2015; Reigstad 2015). One study identified its population from major obstetric units in West Jerusalem (Calderon-Margalit 2009) and another from the reimbursements for drugs or drug combinations that are specific to these subfertility treatments (Yli-Kuha 2012). Lastly, one study recruited consecutive women who delivered at the sole hospital in Negev, Israel, serving the entire population (Kessous 2016). Comparison of the risk of endometrial cancer in subfertile women receiving ovarian-stimulating drugs treatment to that of untreated subfertile women, general population, or both was made by three (Brinton 2013a; Brinton 2013b; Jensen 2009), eight (Calderon-Margalit 2009; Dor 2002; Kessous 2016; Kristiansson 2007; Luke 2015; Potashnik 1999; Reigstad 2015; Yli-Kuha 2012), and five studies (Dos Santos Silva 2009; Doyle 2002; Klip 2004; Lerner-Geva 2012; Venn 1999), respectively. Duration of follow-up was more than 10 years for 10 studies (Brinton 2013b; Calderon-Margalit 2009; Dos Santos Silva 2009; Doyle 2002; Jensen 2009; Kessous 2016; Klip 2004; Lerner-Geva 2012; Potashnik 1999; Reigstad 2015) and less than 10 years in six studies (Brinton 2013a; Dor 2002; Kristiansson 2007; Luke 2015; Venn 1999; Yli-Kuha 2012). All studies were conducted between 1949 and 2011.

Three studies were of case-control design (Benshushan 2001; Parazzini 2001; Parazzini 2010), two of which included controls retrieved from the same hospitals as cases (Parazzini 2001; Parazzini 2010), and one compared cases derived from a nationwide cancer registry with population-based controls (Benshushan 2001). All studies were conducted between 1965 and 2006.

Studies used clomiphene citrate, gonadotropins (human menopausal gonadotrophin (hMG) or human chorionic gonadotropin (hCG), and gonadotropin-releasing hormone (GnRH) agonists, alone or in combination, as ovarian-stimulating drugs, except for seven studies that did not provide data on the specific medications used (Dor 2002; Klip 2004; Kristiansson 2007; Parazzini 2001; Parazzini 2010; Reigstad 2015; Yli-Kuha 2012). Twelve studies reported neither the drug doses nor the number of cycles used for subfertility treatment (Benshushan 2001; Calderon-Margalit 2009; Dor 2002; Doyle 2002; Kessous 2016; Kristiansson 2007; Lerner-Geva 2012; Luke 2015; Parazzini 2001; Parazzini 2010; Reigstad 2015; Yli-Kuha 2012), while three studies only provided data on the number of fertility treatment cycles, but not the medicine dosages used (Brinton 2013a; Jensen 2009; Venn 1999).

No relevant studies of tamoxifen as an ovary-stimulating drug for subfertility were identified. No studies were retrieved evaluating the association between ovarian-stimulating drugs and endometrial hyperplasia.

Excluded studies

Excluded studies, along with the reason for their exclusion, are presented in the Characteristics of excluded studies section. One study was excluded because data on endometrial cancer were not stated (Klemetti 2005); notification failure email was received after sending an email requesting data to three authors of this study, including the corresponding author. Similarly, three studies were excluded, as they did not include data on exposure to ovarian stimulation drugs (Brinton 1989; ; DeMichele 2008; Yang 2015). Specifically, no response was received to our email addressed to the authors of the study by DeMichele et al. (DeMichele 2008); no data were made available for the studies by Brinton et al (Brinton 1989).), following our detailed communication with Dr. Louise Brinton. Regarding the eligibility of the pooled study by Yang et al. (Yang 2015), the authors were contacted in order to provide the results of the analyses pertaining to subfertility treatments. However, the authors did not provide any additional information, due to the considerably limited number of cases with subfertility treatment information. In one study (Holody-Zareba 2014) tamoxifen was used exclusively for breast cancer treatment. Lastly, in one study, clomiphene citrate was used specifically for treatment of polycystic ovary syndrome (Wild 2000).

Risk of bias in included studies

Risk of bias of included studies is presented in the Characteristics of included studies section. Figure 2 depicts the assessment of the bias domains of each included study, while Figure 3 provides a graphical representation. No studies were found to be of low risk for bias, primarily because none of the studies was an RCT.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

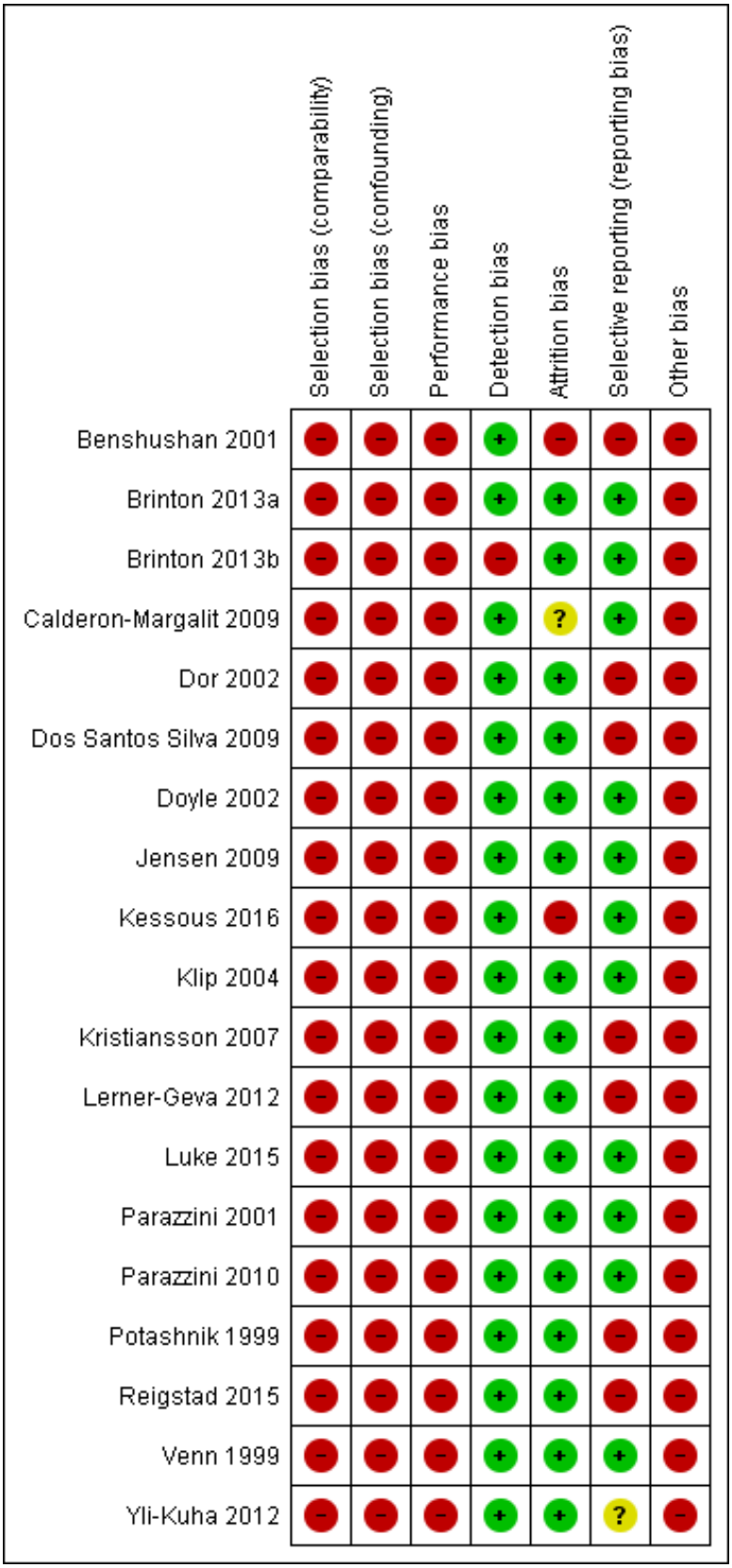
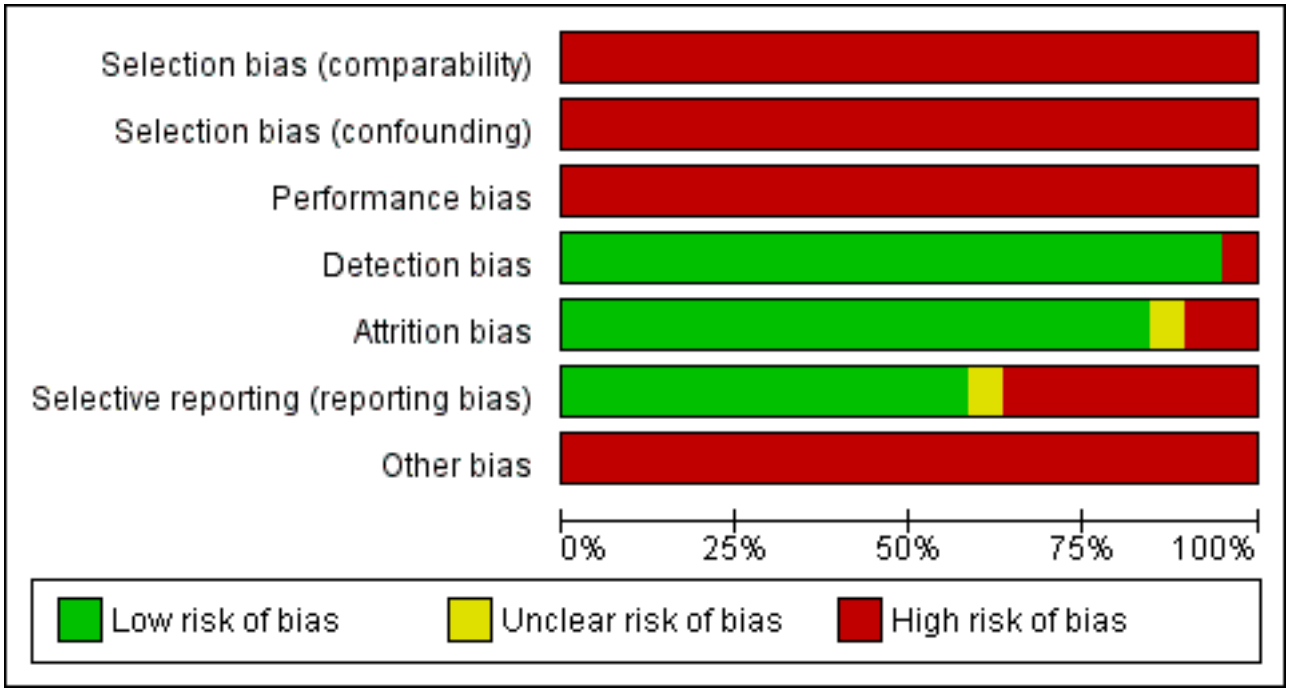


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

In all cohort studies, non-exposed women were drawn from the same population as the exposed cohort; furthermore, all cohort studies, but six (Dos Santos Silva 2009; Jensen 2009; Kessous 2016; Lerner-Geva 2012; Luke 2015; Potashnik 1999), guaranteed that no women had a history of endometrial cancer at the beginning of follow-up. However, none of the studies guaranteed the comparability of intervention and control group in terms of PCOS, diabetes mellitus, obesity and cause of subfertility, rendering them all at high risk of selection bias

Population controls matched for age and geographical region were selected in one study (Benshushan 2001), whereas in the remaining two case-control studies (Parazzini 2001; Parazzini 2010), controls constituted women hospitalised for non-neoplastic ailments. Nevertheless, in all case-control studies, cases were histologically confirmed and consecutively recruited from a secure source. Similarly to the cohort studies, no comparability among the cases and controls on PCOS, diabetes mellitus, obesity and cause of infertility was ensured,

Regarding adjustment for confounding factors among cohort studies, in one study (Kristiansson 2007), only incidence rate ratios (IRRs) were calculated based on crude estimates and, in another one (Kessous 2016), relative risks (RRs) were calculated on the basis of crude numbers. Six studies (Dor 2002; Dos Santos Silva 2009; Lerner-Geva 2012; Luke 2015: Potashnik 1999; Venn 1999) reported Standardized Incidence Ratios (SIRs) inherently adjusted just for age and calendar time. Apart from age, two studies adjusted for body mass Index (BMI) (Brinton 2013a; Calderon-Margalit 2009) and one for smoking (Brinton 2013a). Regarding parity, two studies adjusted for parity at exit (after last ovulation-induction cycle) (Brinton 2013a; Doyle 2002), whereas two studies (Jensen 2009; Reigstad 2015) controlled both for parity at the beginning of follow-up and additional births during the follow-up period. On the other hand, one study (Brinton 2013b) adjusted for gravidity. Moreover, three studies (Brinton 2013a; Calderon-Margalit 2009; Yli-Kuha 2012) adjusted for socioeconomic status, one study (Yli-Kuha 2012) for marital status and another one (Calderon-Margalit 2009) for family size, ovulatory disorders and geographic origin. Finally, adjustment for year of first visit in the fertility clinic was performed in three studies (Brinton 2013b; Doyle 2002; Jensen 2009).

With respect to case-control studies, one study controlled only for age (Benshushan 2001) through the matching process, whereas both of the remaining studies (Parazzini 2001; Parazzini 2010) adjusted also for parity, BMI, oral contraceptive use, hormone replacement treatment use, and education. The latter study (Parazzini 2010) additionally adjusted for age at menarche, menopausal status, study centre, and calendar period of interview.

None of the included studies provided appropriate adjustment for age at menopause, alcohol intake and diabetes mellitus, rendering them all at a high risk of bias.

Blinding

None of the studies was blinded regarding the administration of allocated interventions; therefore, all studies were rated as high risk for performance bias. In fifteen of the cohort studies (Brinton 2013a; Brinton 2013b; Dor 2002; Dos Santos Silva 2009; Doyle 2002; Jensen 2009; Kessous 2016: Klip 2004; Kristiansson 2007; Lerner-Geva 2012; Luke 2015; Potashnik 1999; Reigstad 2015; Venn 1999; Yli-Kuha 2012), exposure to ovary-stimulation drugs was ascertained by a secure source, namely, medical records, whereas in one study (Calderon-Margalit 2009), exposure was ascertained by an interview using a structured questionnaire, yet interviewers were not blinded to presence of endometrial cancer. Similarly, information on exposure in all case-control studies was collected

by trained interviewers using structured questionnaires, without being blinded to case-control status.

Regarding ascertainment of outcome, it was performed by record linkage in all cohort studies but one (Brinton 2013b). In one study (Brinton 2013b), information on the outcome of approximately12% of participants was based on questionnaires and no blinding process was reported. Regarding case-control studies (Benshushan 2001; Parazzini 2001; Parazzini 2010), identification of endometrial cancer cases was also registry-based.

Incomplete outcome data

The majority of cohort studies reported a completeness of follow-up of at least 80%, which was considered adequate a priori, therefore, these studies were considered at low risk for attrition bias. In one study (Kessous 2016), outcome data were derived from a local hospital and not from a registry, therefore implying attrition bias. In one study (Calderon-Margalit 2009), despite accounting completeness of follow-up among its strengths, no quantification of completeness was provided, therefore the risk of attrition bias was considered unclear. Among case-control studies, the proportion of nonparticipants was considerably low (< 5%) in two studies (Parazzini 2001; Parazzini 2010), whereas in one study (Benshushan 2001) this proportion reached 60%, so this study was judged as being at high risk for attrition bias.

Selective reporting

Two studies (Dor 2002; Potashnik 1999) were considered at high risk for selective reporting bias, as the first one (Dor 2002) did not report results by cause of subfertility, number of IVF cycles, and treatment outcome, while the latter (Potashnik 1999) provided results by cause of subfertility only for breast cancer. In another study (Yli-Kuha 2012), it was unclear whether analyses by specific ovulation induction drug could be performed. Furthermore, in four studies (Benshushan 2001; Dos Santos Silva 2009; Kristiansson 2007; Lerner-Geva 2012), selective reporting of results of statistical models was observed. Specifically, one study (Lerner-Geva 2012) reported selectively the results of the multivariate regression models, another one (Kristiansson 2007) did not provide the endometrial cancer-specific Standarized Incidence Ratios and Poisson regression results. Likewise, one study (Dos Santos Silva 2009) did not present Cox regression models results and one study (Benshushan 2001) did not report on multivariate logistic regression models' results for the use of subfertility drugs or clomiphene citrate. Finally, one study (Reigstad 2015) did not provide results of stratified analyses for endometrial cancer.

Other potential sources of bias

Only 10 out of the 16 included cohort studies had an adequate length of follow-up (> 10 years) (Brinton 2013b; Calderon-Margalit 2009; Dos Santos Silva 2009; Doyle 2002; Jensen 2009; Kessous 2016: Klip 2004; Lerner-Geva 2012; Potashnik 1999; Reigstad 2015).

Effects of interventions

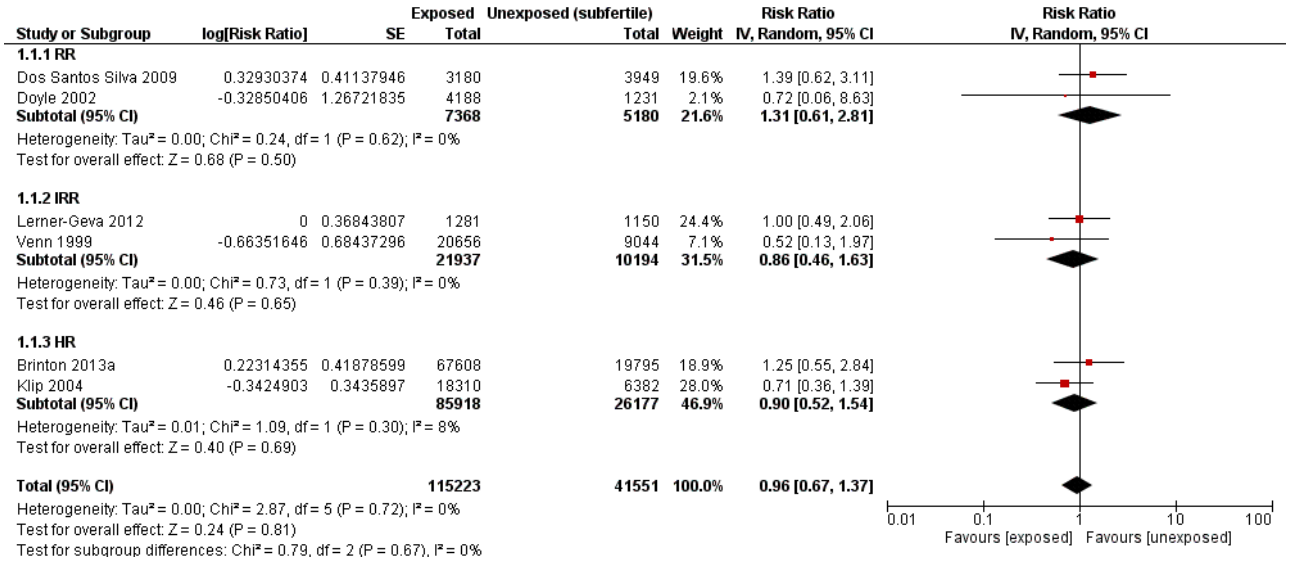
See: **Summary of findings for the main comparison** Exposure to any ovary-stimulating drugs for subfertility compared to untreated subfertile women and endometrial cancer risk; **Summary of findings 2** Exposure to any ovary-stimulating drugs for subfertility compared to general population and endometrial cancer risk; **Summary of findings 3** Exposure to clomiphene citrate for subfertility compared to untreated subfertile women and endometrial cancer risk; **Summary of findings 4** Exposure to clomiphene citrate for subfertility compared to general population and endometrial cancer risk; **Summary of findings 5** Exposure to gonadotropins for subfertility compared to untreated subfertile women and endometrial cancer risk; **Summary of findings 6** Exposure to gonadotropins for subfertility compared to general population and endometrial cancer risk; **Summary of findings 7** Exposure to clomiphene citrate and gonadotropins for subfertility compared to untreated subfertile women and endometrial cancer risk; **Summary of findings 8** Exposure to clomiphene citrate and gonadotropins for subfertility compared to general population and endometrial cancer risk; **Summary of findings 9** Exposure to GnRH analogues for subfertility compared to untreated subfertile women and endometrial cancer risk

Any subfertility drug

Any drug: studies versus unexposed subfertile women

Meta-analysis of six studies, which included 156,774 participants with unexposed subfertile women as the control group (Brinton 2013a; Dos Santos Silva 2009; Doyle 2002; Klip 2004; Lerner-Geva 2012; Venn 1999) indicated that exposure to any subfertility drug was not associated with the risk of endometrial cancer (pooled RR 0.96, 95% CI 0.67 to 1.37, I^2 = 0%; 6 studies,156,774 participants; quality of evidence: very low, Analysis 1.1, Figure 4, Summary of findings for the main comparison).

Figure 4. Forest plot of comparison: 2 Exposure to any drug; comparison group: subfertile; any, outcome: 2.1 Endometrial cancer; subgroup by effect estimate.

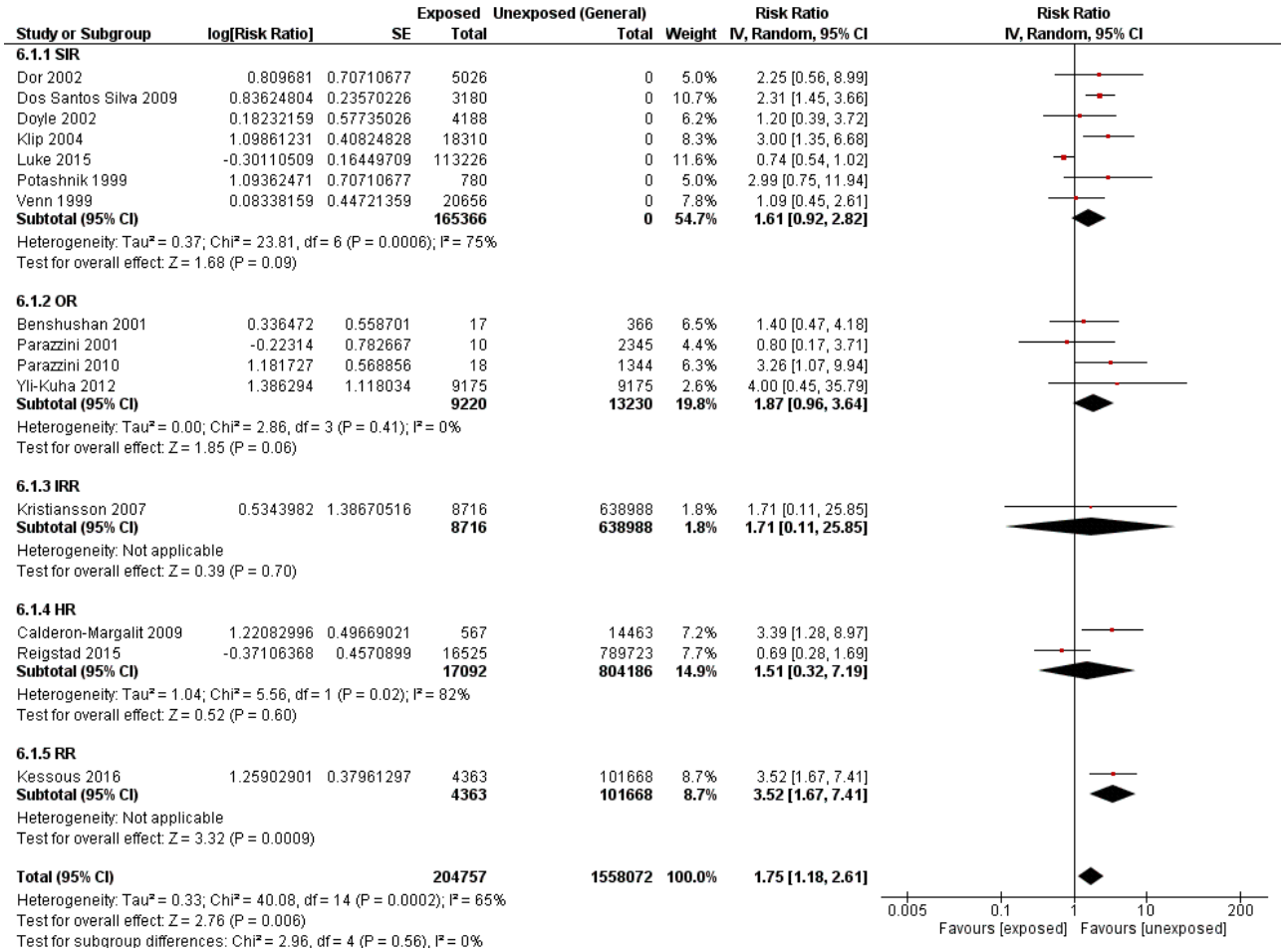


Analyses by parity (pooled RR 1.00, 95% CI 0.05 to 18.85, I^2 = 64% for parous (Analysis 2.1) and pooled RR 0.76, 95% CI 0.35 to 1.67, I^2 = 0% for nulliparous women (Analysis 3.1), and number of cycles (pooled RR 0.82, 95% CI 0.11 to 6.17, I^2 = 71% for low numbers (Analysis 4.1) and pooled RR 0.86, 95% CI: 0.46 to 1.59, I^2 = 0% for medium numbers (Analysis 5.1) in two studies (Brinton 2013a; Klip 2004) confirmed the null pattern.

Any drug: studies versus the general population

Conversely, meta-analysis of 15 studies, including 1,762,829 participants, (Benshushan 2001; Calderon-Margalit 2009; Dor 2002; Dos Santos Silva 2009; Doyle 2002; Kessous 2016; Klip 2004; Kristiansson 2007; Luke 2015; Parazzini 2001; Parazzini 2010; Potashnik 1999; Reigstad 2015; Venn 1999; Yli-Kuha 2012) adopting the general population as reference, suggested an increased risk of endometrial cancer associated with exposure to any subfertility drug (pooled RR 1.75, 95% CI 1.18 to 2.61, I^2 = 65%; 15 studies, 1,762,829 participants; quality of evidence: very low, Analysis 6.1, Figure 5, Summary of findings 2).

Figure 5. Forest plot of comparison: 6 Exposure to any drug; comparison group: general population; any, outcome: 6.1 Endometrial cancer; subgroup by effect estimate.



Analyses by number of cycles, (pooled RR 2.33, 95% CI 0.93 to 5.87, 2 studies, I^2 = 21% for low numbers (Analysis 7.1); pooled RR 3.39, 95% CI 0.77 to 14.87, 2 studies, I^2 = 46% for medium numbers (Analysis 8.1), including two studies (Klip 2004; Venn 1999), did not demonstrate a significant effect with a high level of inconsistency. Analyses by number of oocytes (two studies, Klip 2004; Venn 1999) found an association with risk of endometrial cancer for ten or more retrieved oocytes (0 to 3 oocytes retrieved: pooled RR 2.95, 95% CI 0.47 to 18.57, 2 studies, I^2 = 58% (Analysis 9.1); more than 10 oocytes retrieved: pooled RR 6.93, 95% CI 2.24 to 21.50, 2 studies, I^2 = 0% (Analysis 10.1).

Clomiphene citrate

Clomiphene citrate: studies versus unexposed subfertile women

Using unexposed subfertile women as controls, five studies (Brinton 2013a; Brinton 2013b; Dos Santos Silva 2009; Jensen 2009; Lerner-Geva 2012), reported on the association between exposure to clomiphene citrate and risk of endometrial cancer; meta-analysis indicated an increased risk (pooled RR 1.32, 95% CI 1.01 to 1.71,I^2 = 0%; 5 studies, 92,849 participants; quality of evidence: very low (Analysis 11.1, Summary of findings 3).

Analyses by dosage pointed to an association only at high dosage (pooled RR 1.69, 95% CI 1.07 to 2.68, I^2 = 0% (Analysis 14.1), whereas the analyses pertaining to low dosage (pooled RR 1.30, 95% CI 0.78 to 2.17, I^2 = 0% (Analysis 12.1) and medium dosage (pooled RR 1.27, 95% CI 0.76 to 2.13, I^2 = 0% (Analysis 13.1), including two studies (Brinton 2013a; Dos Santos Silva 2009) did not yield an association.

The analysis by number of cycles (three studies, Brinton 2013b; Dos Santos Silva 2009; Jensen 2009) was in accordance with that pertaining to dosage, as the effect was evident in women receiving a high number of cycles (pooled RR 1.69, 95% CI 1.16 to 2.47, I^2 = 0% (Analysis 16.1) but not in those exposed to a medium number of cycles (pooled RR 1.22, 95% CI 0.87 to 1.73, I^2 = 0% (Analysis 15.1).

Analyses by parity in two studies (Brinton 2013a; Jensen 2009) did not yield any associations (pooled RR 1.68, 95% CI 0.82 to 3.43, I^2 = 0% for parous women (Analysis 17.1); pooled RR 1.01, 95% CI 0.51 to 2.01, I^2 = 29% for nulliparous women (Analysis 18.1).

Clomiphene citrate: studies versus the general population

Four studies, encompassing 19,614 participants (Benshushan 2001; Calderon-Margalit 2009; Dos Santos Silva 2009; Lerner-Geva 2012), reported on exposure to clomiphene citrate compared to a general population reference group; the meta-analysis yielded a pooled RR

1.87 and 95% CI 1.00 to 3.48, I^2 = 46%; 4 studies, 19,614 participants; with high risk of bias and very low quality of evidence (Analysis 19.1, Summary of findings 4).

Analyses by dosage, including two studies (Dos Santos Silva 2009; Potashnik 1999), suggested an association at high dosage (pooled RR 5.48, 95% CI 2.28 to 13.17, I^2 = 17% (Analysis 21.1), whereas the analysis pertaining to low dosage (pooled RR 1.52, 95% CI 0.48 to 4.78, I^2 = 2% (Analysis 20.1) did not yield any association.

Analysis by number of cycles, based on two studies (Dos Santos Silva 2009; Potashnik 1999), found that there may be an effect in women receiving a high number of cycles (7 or more) (pooled RR 4.17, 95% CI 1.35 to 12.94, I^2 = 0% (Analysis 23.1) but there was no difference in women who had received three cycles or fewer (pooled RR 1.82, 95% CI 0.56 to 5.90, I^2 = 6% (Analysis 22.1). .

Gonadotropins

Analysis of four studies, with unexposed subfertile women as the control group (Brinton 2013b; Dos Santos Silva 2009; Jensen 2009; Lerner-Geva 2012), found that exposure to gonadotropins may be associated with increased risk of endometrial cancer (pooled RR 1.55, 95% CI 1.03 to 2.34, I^2 = 0%; 4 studies, 17,769 participants; quality of evidence: very low (Analysis 24.1, Summary of findings 5). This finding was mainly associated with one study (Jensen 2009). Analysis of the two studies (1595 participants) assessing risk against the general population (Dos Santos Silva 2009; Lerner-Geva 2012) demonstrated no difference (pooled RR 2.12, 95% CI 0.79 to 5.64, I^2 = 0%; 2 studies, 1595 participants; quality of evidence: very low (Analysis 27.1, Summary of findings 6).No consistent dose-response pattern arose from the subanalyses by number of cycles with subfertile women as the control group (two studies, Brinton 2013b; Jensen 2009); medium number of cycles (pooled RR 1.61, 95% CI 1.00 to 2.60, I^2 = 0% (Analysis 25.1); high number of cycles (pooled RR 1.90, 95% CI 0.80 to 4.52, I^2 = 0% (Analysis 26.1).

Combination of clomiphene citrate and gonadotropins

The analysis of two studies (Dos Santos Silva 2009; Lerner-Geva 2012) with unexposed subfertile women as controls (6,345 participants) indicated no association between the combination of clomiphene citrate with gonadotropins on the risk of endometrial cancer (pooled RR 1.18, 95% CI 0.57 to 2.44, I^2 = 0%; 2 studies, 6345; quality of evidence: very low (Analysis 28.1, Summary of findings 7). The respective analysis of three studies (Dos Santos Silva 2009; Lerner-Geva 2012; Venn 1999) versus the general population (3 studies, 7,789 participants) suggested there was a positive association (pooled RR 2.99, 95% CI 1.53 to 5.86, I^2 = 44%, quality of evidence: very low (Analysis 29.1, Summary of findings 8).

GnRH

Meta-analysis of two studies, with 42,558 participants (Brinton 2013a; Jensen 2009), reporting on the risk of endometrial cancer after exposure to GnRH (vs subfertile women) found no difference in the risk of endometrial cancer, either at the overall analysis (pooled RR 1.21, 95% CI: 0.65 to 2.27, I^2 = 0%, 2 studies, 42,558 participants; quality of evidence: very low (Analysis 30.1, Summary of findings 9) or at the analyses (two studies, Brinton 2013a; Jensen 2009) by parity (pooled RR 2.88, 95% CI 0.95 to 8.71, I^2 = 0% for parous women (Analysis 31.1) and pooled RR 0.75, 95% CI 0.34 to 1.63, I^2 = 0% for nulliparous women (Analysis 32.1).

Sensitivity analyses

Where possible, sensitivity analyses were conducted excluding studies with inadequate follow-up periods in the exposed cohort (mean or median < 10 years). In the analysis of any subfertility drug among the subfertile population, the results remained unchanged after exclusion of studies with inadequate follow-up (Brinton 2013a; Venn 1999) (pooled RR 0.95, 95% CI 0.63 to 1.44, 2 studies, I^2 = 0% (Analysis 33.1). Similarly, the robustness of the findings for the general population was replicated in sensitivity analysis of the five studies (Calderon-Margalit 2009; Dos Santos Silva 2009; Doyle 2002 ;Kessous 2016; Potashnik 1999) with long enough follow-up (pooled RR 2.52, 95% CI 1.80 to 3.53, I^2 = 0% (Analysis 34.1). Consistent with the respective overall analyses were also the findings for subfertile women in the sensitivity analyses for exposure to clomiphene (pooled RR 1.35, 95% CI 1.03 to 1.78, 4 studies (exclusion of Brinton 2013a), I^2 = 0% (Analysis 35.1) and gonadotropins (pooled RR 1.82, 95% CI 1.01 to 3.27, 3 studies (exclusion of Brinton 2013a), I^2 = 0% (Analysis 37.1), as well as for the analysis versus the general population regarding clomiphene (pooled RR 2.08, 95% CI 1.01 to 4.28, 3 studies (exclusion of Benshushan 2001), I^2 = 58% (Analysis 36.1) and the combination of clomiphene citrate and gonadotropins (pooled RR 3.58, 95% CI 1.82 to 7.06, 2 studies (exclusion of Venn 1999), I^2 = 44% (Analysis 38.1).

DISCUSSION

Summary of main results

We examined the effect of ovarian-stimulating drugs for subfertility on the risk of endometrial cancer. All included studies were non-randomised: therefore, the quality of the evidence was very low and downgrading was apparent in the GRADE assessment. Similarly to the two previous meta-analyses by our team (Siristatidis 2013; Sergentanis 2014), studies adopting the general population, in contrast to subfertile women, as the control group, yielded different results. Indeed, results of studies examining comparisons versus the general population were affected by the superimposed effect of subfertility (Siristatidis 2013; Sergentanis 2014), the latter representing a well established risk factor for endometrial cancer (Cetin 2008).

The quality of the evidence was very low due to serious risk of bias and indirectness by GRADE assessment. All studies were at high risk of bias due to the non-randomised design and bias due to confounders was not taken into account in the studies. The clinical bias should also be emphasized, as the groups were often markedly different and had different underlying risks of endometrial cancer.

The six studies with unexposed subfertile women used as the control group did not suggest an association between exposure to any drug and risk of endometrial cancer (RR 0.96, 95% CI 0.67 to 1.37, 156,774 participants; Analysis 1.1, Figure 4). Drug-specific analyses of the five available studies, found an association between exposure to clomiphene citrate and risk of endometrial cancer (RR 1.32, 95% CI 1.01 to 1.71, 92,849 participants; Analysis 11.1), especially at high doses (RR 1.69, 95% CI 1.07 to 2.68; Analysis 14.1) and high number of cycles (RR 1.69, 95% CI 1.16 to 2.47; Analysis 16.1), but it was not possible to separate the effect of clomiphene from the underlying condition leading to the need for multiple cycles or high doses from the evidence available. There was no consistent association between gonadotrophin exposure and risk of endometrial cancer, when unexposed subfertile women were

used as the control group (RR 1.55, 95% CI 1.03 to 2.34, 4 studies, 17,769 participants; Analysis 24.1), nor was there a consistent dose-response effect (Analysis 25.1; Analysis 26.1).

Clomiphene citrate, one of the most widely used agents to treat subfertility, directly interacts with the oestrogen receptors in the endometrium (Nakamura 1997; Goldstein 2000) as a selective oestrogen receptor modulator, with chemical properties similar to tamoxifen (Sovino 2002), which has been associated with an increased risk of endometrial cancer (Hu 2015). The dose-response effects may suggest a causative effect (Hill 1965). However, high doses of clomiphene citrate are very likely to have been preferentially prescribed to women with PCOS, which is a known risk factor for endometrial cancer (Dos Santos Silva 2009).

Studies comparing subfertile women treated with fertility drugs compared to a general population inherently introduced significant bias, especially since nulliparity is a known risk factor for endometrial cancer, whereas pregnancy has a protective effect. Meta-analyses from these studies comparing exposure to any subfertility agent versus the general population demonstrated a 1.8-fold increased risk of endometrial cancer (RR 1.75, 95% CI 1.18 to 2.61, 15 studies, 1,762,829 participants; Analysis 6.1). Higher numbers of retrieved oocytes (RR 6.93, 95% CI 2.24 to 21.50; Analysis 10.1) did appear to be associated with an increased risk of endometrial cancer, although the data were based on a highly selected, small number of women, as was the association between the high number of clomiphene cycles (RR 4.17, 95% CI 1.35 to 12.94; Analysis 23.1) or high doses of clomiphene (RR 5.48, 95% CI 2.28 to 13.17; Analysis 21.1).

Overall completeness and applicability of evidence

The included studies based their exposed groups on women who attended subfertility clinics at major hospitals. Most studies relied upon cancer registries for completeness of case ascertainment. The results may demonstrate a possible association between the requirement for treatment with some fertility medications, especially at high doses or high number of cycles, and an increased risk of endometrial cancer, compared to women who do not require treatment. However, the evidence cannot say whether this a causative effect or merely reflects an increased incidence of known risk factors for endometrial cancer in women who require fertility treatment (e.g. nulliparity, PCOS, obesity).

Quality of the evidence

Overall, the quality of the evidence was derived from non-randomised studies and was rated as very low according to GRADE methodology (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8; Summary of findings 9), mostly on account of the studies being at very high risk of bias. Moderate inconsistency was highlighted in only two comparisons (I^2 > 40%, Analysis 19.1; Analysis 29.1). Furthermore, all comparisons suffered from serious indirectness, mostly on account of differences in the studied populations and the presence, as well as causes, of underlying subfertility.

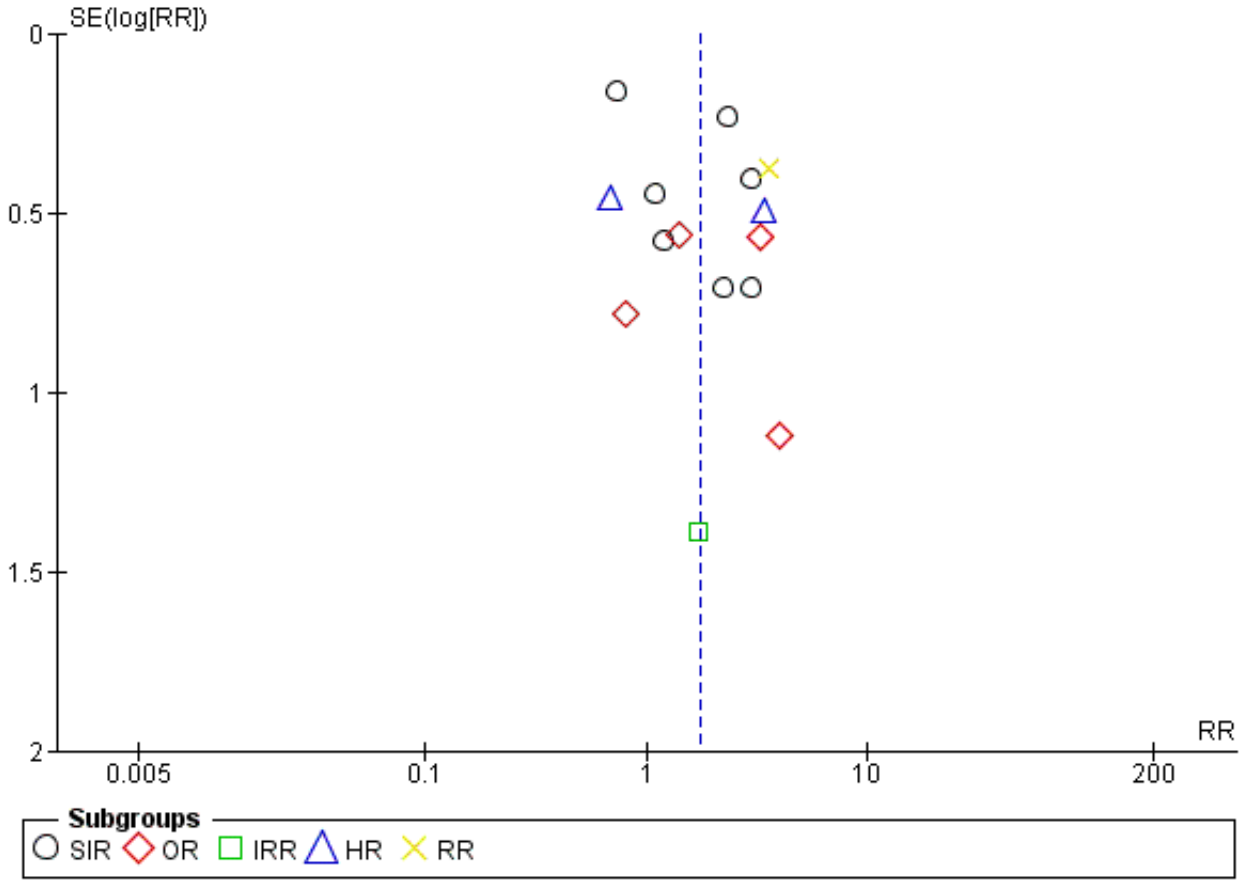
A variety of limitations in the individual studies may have further interfered with the quality of evidence. Specifically, the lack of adjustment for meaningful confounding factors, as well as the relatively short follow-up periods of study subjects in relation to peak incidence of endometrial cancer, should be highlighted. . Only 10 (Brinton 2013b; Calderon-Margalit 2009; Dos Santos Silva 2009; Doyle 2002; Jensen 2009; Kessous 2016: Klip 2004; Lerner-Geva 2012; Potashnik 1999; Reigstad 2015) out of the 16 included cohort studies (Brinton 2013a; Brinton 2013b; Calderon-Margalit 2009; Dor 2002; Dos Santos Silva 2009; Doyle 2002; Jensen 2009; Kessous 2016: Klip 2004; Kristiansson 2007; Lerner-Geva 2012; Luke 2015: Potashnik 1999; Reigstad 2015; Venn 1999; Yli-Kuha 2012) encompassed a follow-up period longer than 10 years among exposed women. Both PCOS and obesity, which predispose to development of endometrial cancer at a young age, are known causes of subfertility and therefore may have skewed the detection of young endometrial cancers in the cohorts, under-reporting the overall risk of endometrial cancer in the control groups. However, these findings were replicated in sensitivity analyses, which excluded studies with short follow-up. The fact that studies were registry-based may have minimized attrition and detection bias.

Potential biases in the review process

This systematic review was limited to observational, non-randomised studies. It was unable to demonstrate causation, merely association, although RCTs in this area are nearly impossible, since it would be ethically challenging to restrict fertility treatment to women requiring it. The meta-analysis used a publication-based approach and obtaining individual participant data for each study was not possible, which could have allowed adjustment for confounding factors across included studies.

On the positive side, we adopted clear definitions of exposures and outcome and we adhered to procedures that minimized extraction, recording and retrieval bias, by carefully searching for 'grey' literature; furthermore, no language restriction was adopted. No evidence of publication bias was documented in the only analysis with more than ten study arms, namely that referring to any subfertility drug, with general population women as the reference group (Analysis 6.1), as shown in Figure 6 and verified by Egger's test (P = 0.102).

Figure 6. Funnel plot of comparison: 6 Exposure to any drug; comparison group: general population; any, outcome: 6.1 Endometrial cancer; subgroup by effect estimate.



One other source of bias in the review was due to multiple analyses, without adjustment for multiple analyses (Jakobsen 2014a, Jakobsen 2014b, Jakobsen 2016).

Agreements and disagreements with other studies or reviews

In general, there is a paucity of publications on the association of exposure to subfertility drugs and endometrial cancer. This meta-analysis is in agreement with the previous systematic review by our team (Siristatidis 2013), which focused exclusively on the context of IVF . Specifically, in that study, risk of endometrial cancer was increased among women undergoing controlled ovarian hyperstimulation for IVF versus the general population (RR 2.04, 95% CI 1.22 to 3.43); on the other hand, no difference in risk was found versus untreated subfertile women (RR 0.45, 95% CI 0.18 to 1.14).

Another meta-analysis based on six studies did not find an association between fertility treatment and risk of uterine cancer (Saso 2015).

AUTHORS' CONCLUSIONS

Implications for practice

The available data was of very low quality and at significant risk of bias, since it is known that subfertile women have risk factors for endometrial cancer that are independent of treatment for subfertility. It seems that the exposure to clomiphene citrate as an ovary-stimulating drug in subfertile women may be associated with an increased risk of endometrial cancer, especially at higher doses (more than 2000 mg) and higher number of cycles (7 or more cycles). Evidence regarding exposure to gonadotropins is even less conclusive. It is therefore difficult to give any certainty about the safety of subfertility treatments. Contemporary guidelines already recommend treatment with clomiphene citrate as the first line of treatment for up to 12 months only for women with World Health Organization Group II ovulation disorders (hypothalamic pituitary dysfunction), such as PCOS (NICE 2013). These data should not prevent women from seeking treatment of subfertility, but they should be aware of their underlying increased risk of endometrial cancer and adopt lifestyle changes to reduce their risk, such as weight loss and adequate endometrial protection with progesterones, should they have oligomenorrhoea due to PCOS.

Implications for research

This systematic review points to the need for register-based studies with the potential to span longer follow-up periods, to provide detailed subfertility treatment history and adjustment for confounding factors, so as to avoid the additive effect of subfertility. Detailed analyses concerning histotypes, dose-response effects and the potentially modifying role of parity, gravidity or age at first exposure seem warranted. Endometrial cancer is recognized as being a heterogenous disease, with different aetiologies for type I and type II tumours. Given that no studies have been undertaken assessing differences in the associations for ovary-stimulating drugs between these two major groupings of tumours, future studies should bear this in mind.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Benshushan 2001

Methods	Case-control.
Participants	Histologically confirmed endometrial cancer cases (n = 128) diagnosed between 1989 and 1992, born between 1929 and 1957, and alive at the time of the interview were identified from a nationwide cancer registry. Controls (n = 255) were obtained by random telephone selection within the same area codes and interviewed during the same period as the cases. Thus, cases and controls were matched for geographic area. Eligibility for the control group was based on date of birth in the identical range to that of the cases. Women who had undergone hysterectomy were excluded as controls.
Interventions	Subfertility hormones, clomiphene citrate. Ascertainment of exposure was based on personal interviews exclusively.
Outcomes	Histologically confirmed endometrial cancer.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Quote: "Cases of endometrial cancer were identified from the Israel Cancer Registry". Comment: Cases were recruited consecutively. Quote: "Controls were obtained by telephoning randomly selected numbers within the same area codes as those of the cases. Cases and controls were matched for geographic area by the sampling procedure". Comment: Population-based controls. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity ensured.
Selection bias (confounding)	High risk	Quote: "Eligibility for the control group was based on date of birth in the identical range to that of the cases" Comment: Analyses controlling only for age.
Performance bias	High risk	Comment: Ascertainment of exposure was based on personal interviews exclusively; blindness of interviewers not reported.
Detection bias	Low risk	Quote: "Cases of endometrial cancer were identified from the Israel Cancer Registry". Comment: Assessors of cancer status were blinded to exposure status.
Attrition bias	High risk	Quote: "Non-response bias is large, 60%, which raises doubts for whether the study group is representative. However, a comparison between cases and

Benshushan 2001 *(Continued)*

		those who did not participate in the study shows that the age, area of residency and histology in the two groups were not different". Commnent: Non-response rate was considerably high among cases.
Selective reporting (reporting bias)	High risk	Comment: Multivariate logistic regression models' results not reported for use of subfertility drugs or clomiphene citrate.
Other bias	High risk	Comment: Non-RCT study.

Brinton 2013a

Methods	Retrospective cohort.
Participants	Cohort of 87,418 women who received treatment or were registered with fertility problems on or after September 25; 1994 were retrieved from a registry. Women were diagnosed as having problems conceiving, having undergone fertility treatments in either the hospital or community clinics, or having purchased medications for fertility problems. Excluded were 6 women who exited before or on the same day as entry and 9 who were diagnosed with cancer before entry into the cohort, leaving 87,403 eligible study subjects. Of these, 67,608 were exposed to fertility treatments. Mean follow-up, 8.1 years.
Interventions	Exposure to any fertility treatment, any IVF, number of IVF cycles, clomiphene citrate, gonadotropin-releasing hormone analogues, or progestogen.
Outcomes	Histologically confirmed endometrial cancer, retrieved from nationwide cancer registry. Medical records were also examined to assure completeness of information on malignant tumour diagnoses. Incident cases in total cohort, 41; in exposed cohort, 34.
Notes	Subfertility indication was classified into 6 non-mutually exclusive categories: 1) male subfertility, 2) anovulation, 3) mechanical causes, 4) polycystic ovary syndrome, 5) endometriosis, and 6) pituitary-hypothalamic problems.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias (comparability)	High risk	Quote: "We considered ineligible for study six women who exited before or on the same day as entry (one due to death) and nine who were diagnosed with cancer before entry into the cohort". Comment: Outcome not likely to be present at start. Quote: "Information on whether the patient had been exposed to any fertility treatment was classified according to whether she ever had IVF treatment". Comment: Non-exposed drawn from the same population as the exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "Adjusted for age at entry, body mass index, smoking, parity at exit, and socioeconomic status". Comment: Analyses inadequately controlling for potential confounders.

Brinton 2013a *(Continued)*

Performance bias	High risk	Quote: "From the women's electronic medical records (EMR), we attempted to obtain information on demographic factors (date of birth, district of residence, enumeration area), potential cancer risk factors (parity status at cohort entry, parity status at cohort exit, number of children at exit, weight, height, ever smoked cigarettes, and infertility indication), and fertility treatments". Comment: Exposure to ovary-stimulation drugs was ascertained by medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "After appropriate Institutional Review Board clearances, we linked our study population with the Israel Cancer Registry (ICR)". Comment: Outcome was ascertained by record linkage.
Attrition bias	Low risk	Quote: "The coverage of solid tumours in the registry is > 90% nationwide" Comment: Follow-up was expected to be rather complete.
Selective reporting (reporting bias)	Low risk	Comment: All of the study's prespecified (primary and secondary) outcomes that were of interest in the review have been reported in the prespecified way.
Other bias	High risk	Quote: "Mean 8.1 years of follow-up, SD 3.8". Comment: The length of follow-up was considered inadequate. Comment: Non-RCT study

Brinton 2013b

Methods	Retrospective cohort.
Participants	Cohort of 12193 women ≥ 18 years old, who had sought advice for subfertility between 1965 and 1988 at 5 reproductive endocrinology practices in Boston, MA; Chicago, IL; Detroit, MI; Palo Alto, CA, and New York City, NY. Participants with either primary or secondary subfertility were eligible, but those evaluated for reversal of a tubal ligation were not. An initial follow-up was pursued during 1998 to 2001 and a second in 2010. After excluding the 1319 participants who requested no additional follow-up, 8 who were enrolled twice, 6 found to be < 18 years of age, 1 who requested removal from the study and 1 with a missing date of birth, outcome information through 2010 was available for 10018 participants. Excluded from analysis were 15 participants with missing information on a cancer diagnosis date, 111 with < 1 year of follow-up and 60 with a hysterectomy during the first year of follow-up, leaving 9832 analytic study subjects, of whom 3933 were exposed to fertility treatments. Mean follow-up, 26.4 years.
Interventions	Ever use of clomiphene citrate or gonadotropins. Information on clomiphene citrate and gonadotropins included age at first use, treatment cycles, and total cumulative dosage.
Outcomes	Endometrial cancer. Follow-up procedures included searches for deaths and updated addresses through several publicly available and proprietary databases. Attempts were made to mail a short questionnaire, focusing on the development of cancers and cancer risk factors that might have changed over time, to located subjects who did not expressly indicate that they wanted no further follow-up. In addition, linkages against cancer registries in the 14 states in which the majority of participants resided were completed. For the 12.4% of participants who resided outside these states, outcome information was dependent on completed questionnaires, with attempts to validate any self-reports of cancers by requesting records from the participant's treating physicians. Incident cases in total cohort, 118; in exposed cohort, 52.

Brinton 2013b *(Continued)*

Notes	Causes of subfertility were endometriosis, anovulation, tubal disease/pelvic adhesions, male factor, cervical disorder, uterine disorder.

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Quote: "We excluded from analysis 15 patients with missing information on a cancer diagnosis date, 111 with 1 year of follow-up and 60 with a hysterectomy during the first year of follow-up". Comment: Outcome not likely to be present at start. Comment: Non-exposed drawn from the same population as the exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "Adjustment for potential confounding factors, [were] obtained using Cox proportional hazards regression with age as the time metric [...] Table III: HRs adjusted for study site, calendar year of the first clinic visit and reproductive status at the first clinic visit". Comment: Analyses inadequately controlling for potential confounders.
Performance bias	High risk	Quote: "Trained staff abstracted data regarding the infertility workup (all procedures and tests), medications prescribed, menstrual and reproductive histories, and other factors that might affect health. Information on the clinical workup was used to define causes of infertility, as previously described". Comment: Exposure to ovary-stimulation drugs was ascertained by medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	High risk	Quote: "In addition to information on cancers identified through death records and completed questionnaires, we completed linkages against cancer registries in the 14 states in which the majority of patients resided. For the 12.4% of patients who resided outside these states, outcome information was dependent on completed questionnaires, with attempts to validate any self-reports of cancers by requesting records from the patients' treating physicians". Comment: Outcome was ascertained both by record linkage and questionnaires. No blinding process was reported.
Attrition bias	Low risk	Quote: "Nonetheless, our loss to follow-up of 7.7% was quite low given the observation time". Comment: Follow-up is considered to be rather complete.
Selective reporting (reporting bias)	Low risk	Comment: All of the study's prespecified (primary and secondary) outcomes that were of interest in the review have been reported in the prespecified way.
Other bias	High risk	Quote: "An average of 26.4 years of follow-up". Comment: Length of follow-up was considered adequate. Comment: Non-RCT study.

Calderon-Margalit 2009

Methods	Retrospective cohort.
Participants	Between 1974 and 1976, 15,426 mothers were interviewed in the hospital on the first or second day after giving birth, including 98% of births occurring in the 3 major obstetric units in West Jerusalem and covering 91% of all births in the area at the time. The questionnaire collected information on obstetric and gynaecologic history, time to conception, and whether the couple had sought advice for subfertility, including mechanical treatments such as tubal insufflation. Women were asked whether they had received medical treatment for induction of ovulation prior to the index pregnancy. Linkage to the Israel Population Registry permitted tracing and ascertainment of vital status for 15047 mothers. Excluded were 17 mothers diagnosed with cancer prior to their first birth in the postpartum subcohort, leaving 15,030 analytic study subjects, of which 567 were exposed to fertility treatments. Median follow-up, 29 years.
Interventions	Any fertility treatment, clomiphene citrate. Information on dosages, number of fertility cycles, and age at first fertility cycle was not available.
Outcomes	Endometrial cancer. Information on cancer incidence until 2004 was obtained by linkage with the nationwide Israel Cancer Registry. Incident cases in total cohort, 44; in exposed cohort, 5.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Quote: "We excluded from this study 17 mothers who were diagnosed with cancer prior to their first birth in the postpartum subcohort". Comment: Outcome not likely to be present at start. Comment: Non-exposed drawn from the same population as exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "Controlling for age, socioeconomic status, geographic origin, body mass index, family size, and ovulatory disorders did not materially change this association". Comment: Analyses inadequately controlling for potential confounders.
Performance bias	High risk	Quote: "Between November 1974 and December 1976, 15,426 mothers were interviewed in the hospital on the first or second day after giving birth. This postpartum subcohort included 98% of births occurring in the 3 major obstetric units in West Jerusalem and covered 91% of all births in the area at the time. The questionnaire collected information on obstetric and gynaecologic history, time to conception, and whether the couple had sought advice for infertility, including mechanical treatments such as tubal insufflation. Women were asked whether they had received medical treatment for induction of ovulation prior to the index pregnancy". Comment: Exposure was ascertained by questionnaires; blindness of interviewer not stated

Calderon-Margalit 2009 *(Continued)*

Detection bias	Low risk	Quote: "Information on cancer incidence as of December 31, 2004, was obtained by linking the ascertained cohort with the Israel Cancer Registry, which receives notification of all malignancies diagnosed throughout the country". Comment: Outcome was ascertained by record linkage
Attrition bias	Unclear risk	Quote: "The strengths of this study included the design of the within-cohort comparison and the completeness of follow-up data on cancer incidence". Comment: Although completeness of follow-up was accounted among the strengths, no quantification was provided.
Selective reporting (reporting bias)	Low risk	Comment: All of the study's prespecified (primary and secondary) outcomes that were of interest in the review have been reported in the prespecified way.
Other bias	High risk	Quote: "During 424,193 person-years of follow-up (median, 29), 1,215 women developed cancer (median age at diagnosis, 49.4 years)". Comment: Length of follow-up was considered adequate. Comment: Non-RCT study.

Dor 2002

Methods	Retrospective cohort.
Participants	Cohort of 5026 women who received at least one treatment cycle from 1981 to 1992 at 2 IVF units operated by the same physicians, who used similar treatment protocols, in Israel. Participants were identified by meticulous review of the medical records of the units since their foundation. Mean follow-up, 3.6 years.
Interventions	IVF treatment with three main ovarian hyperstimulation protocols: combined treatment with clomiphene citrate followed by human menopausal gonadotropin, FSH and LH; human menopausal gonadotropin; gonadotropin-releasing hormone analogue, followed by human menopausal gonadotropin. Human chorionic gonadotropin was administered when the appropriate ovarian response was achieved.
Outcomes	Histopathologically confirmed endometrial cancer. The study cohort computer file was linked to the nationwide Israel Cancer Registry to identify cancer cases through 1996 and observed cases were compared to expected cases calculated from the general population. Incident cases in the cohort, 2.
Notes	Causes of subfertility were mechanical, ovulatory, male factor.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias (comparability)	High risk	Quote: "Cases of cancer that were diagnosed within 1 year of initiation of IVF treatment were excluded from analysis to allow a minimal latency period between exposure and development of cancer". Comment: Outcome not likely to be present at start.

Dor 2002 *(Continued)*

		Quote: "Expected cases of cancer were computed on the basis of age, sex, place of birth, and year-specific national cancer incidence rates". Comment: Non-exposed drawn from the same population as the exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "Standardized incidence ratios (SIRs) were computed as a ratio of observed to expected cases of cancer, along with estimated 95% CIs. Expected cases of cancer were computed on the basis of age, sex, place of birth, and year-specific national cancer incidence rates". Comment: Analyses adjusted only for age.
Performance bias	High risk	Quote: "Patients were identified by meticulous review of the medical records of the units since their foundation". Comment: Exposure to ovary-stimulation drugs was ascertained by a secure source, namely, medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "The study cohort computer file was linked to the Israel National Cancer Registry to identify cancer cases through December 1996". Comment: Ascertainment of outcome by record linkage.
Attrition bias	Low risk	Quote: "Depending on the cancer site, cancer ascertainment during internal verifications through the Israel Cancer Registry was found to be 90% to 95% complete". Comment: Follow-up was expected to be rather complete.
Selective reporting (reporting bias)	High risk	Comment: Analyses on endometrial cancer by type of subfertility, number of IVF cycles, and treatment outcome not reported.
Other bias	High risk	Quote: "mean follow-up, 3.6 ± 3.4". Comment: Inadequate length of follow-up (< 10 years). Comment: Non-RCT study.

Dos Santos Silva 2009

Methods	Retrospective cohort.
Participants	Cohort of 9152 study subjects were identified through 2 case series of women who attended reproductive endocrinology practices in 2 hospitals in London. Of these, 7444 were traced and flagged through national registry to ascertain their vital status, and to obtain information on site-specific cancer incidence, cause-specific mortality and migrations. Eighty-nine subjects were excluded because flagging was considered to be unreliable (n = 8), they were no longer National Health Service patients at the time they joined the cohort (n = 79), or they had subsequently undergone a sex change operation (n = 2). Further excluding women with missing information on treatment resulted in the inclusion of 7129 women, of which 3180 were exposed to fertility treatment. Mean follow-up, 21.4 years.

Dos Santos Silva 2009 *(Continued)*

Interventions	Only clomiphene citrate, only gonadotropins, both clomiphene citrate and gonadotropins. Data on dosages, number of fertility treatment cycles, and years since time at first fertility treatment was available.
Outcomes	Endometrial cancer. Incident cases in total cohort, 30; in exposed cohort, 18.
Notes	Causes of subfertility included polycystic ovarian syndrome, male factor, thyroid disease, anovulation, irregular ovulation, amenorrhoea, weight-related ovulatory disorders, hyperprolactinaemia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Comment: Exclusion of endometrial cancer cases at the beginning of the study was not reported. Comment: Non-exposed women drawn from the same population as exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "Two approaches were used to compare study groups within the cohort. In the first, the risk of dying from a particular cause, or of developing a certain site-specific cancer, among patients 'exposed' to a given characteristic (e.g. treatment type) relative to the risk among those 'unexposed' was estimated as the ratio between the two corresponding SMRs, or SIRs, to take into account calendar period and age effects". Comment: Analyses adjusted only for age.
Performance bias	High risk	Quote: "From the meticulous clinical notes kept by the founders of these case series, a trained abstractor extracted and computerised relevant data, including information on signs and symptoms at presentation, final diagnosis, treatments prescribed (with number of cycles and dose) and their outcome. Hospital records (mainly on microfilms) and computer databases were also reviewed". Comment: Exposure to ovary-stimulation drugs was ascertained by medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "Study subjects were followed through the National Health Service Central Register (NHSCR) in England and Wales to ascertain their vital status, and to obtain information on site-specific cancer incidence, cause-specific mortality and migrations". Comment: Outcome was ascertained by record linkage.
Attrition bias	Low risk	Quote: "Weaknesses of our study include the fact that follow-up was possible only for 80% of the original cohort; however, there was no evidence that those untraced through the NHSCR differed from those who were traced". Comment: Completeness of follow-up was considered adequate.
Selective reporting (reporting bias)	High risk	Comment: Results of Cox regression models not reported for endometrial cancer.
Other bias	High risk	Quote from Table 1: "Mean follow-up of 21.4 years".

Dos Santos Silva 2009 *(Continued)*

	Comment: Length of follow-up was considered adequate. Comment: Non-RCT study.

Doyle 2002

Methods	Retrospective cohort.
Participants	Women attending a large subfertility clinic in London, UK, who had at least 1 cycle of subfertility treatment between 1975 and 1989, were resident in the UK, and aged ≥ 20 years at the time of treatment, were included. Due to uncompleted clinical records regarding death, emigration, or cancer diagnosis before 1990, cancer incidence was investigated from 1990 onwards in 5556 women known to be alive, cancer-free and still resident in the UK on January 1, 1990. Women were followed up until cancer registration, death, emigration or December 31, 1997, whichever was earliest. There were no data on ovarian stimulation for 137 women, resulting in a cohort of 5419 women of which 4188 were exposed to ovarian stimulation. Median follow-up, 15.5 years.
Interventions	Clomiphene citrate, human menopausal gonadotropin or both, and, from 1985 onwards, gonadotropin-releasing hormone agonist.
Outcomes	Endometrial cancer cases, identified through the National Health Service Central Registry in Southport, UK. Incident cases in total cohort, 4; in exposed cohort, 3.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Quote: "Restricting the follow-up period to 1990 onwards rather than date of first treatment onwards resulted on the exclusion of 74 women who had died, immigrated or been diagnosed with cancer before 1990". Comment: Outcome not likely to be present at start. Quote: "The women were divided in two groups: those who had received drugs to stimulate ovulation and who had not". Comment: Non-exposed drawn from the same population as exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "Cox proportional hazards models used adjusting for age, calendar year, parity following last treatment cycle and year of first clinical visit". Comment: Analyses inadequately controlling for potential confounding factors.
Performance bias	High risk	Comment: Exposure to ovary-stimulation drugs was ascertained by medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "Details of all women in the cohort were submitted for tracing to the National Health Service Central Register (NHSCR) in Southport, UK, who provided ongoing notifications of emigrations, deaths and cancer registrations".

Doyle 2002 *(Continued)*

		Comment: Outcome was ascertained by record linkage.
Attrition bias	Low risk	Quote: "33 women (0.9%) were lost to follow-up". Comment: Follow-up was considered to be complete.
Selective reporting (reporting bias)	Low risk	Comment: All of the study's prespecified (primary and secondary) outcomes that were of interest in the review have been reported in the prespecified way.
Other bias	High risk	Quote: "By the end of the follow-up a median of 15.5 years had elapsed since first clinic visit". Comment: Length of follow-up was considered adequate. Comment: Non-RCT study

Jensen 2009

Methods	Case-cohort.
Participants	The cohort comprised 54,449 women with subfertility problems referred to Danish hospitals or private fertility clinics between 1965 and 1998, as well as recorded in the nationwide National Patient Registry. Through linkage of the cohort to the population-based civil registration system, 87 women with invalid civil registry numbers were excluded, leaving an analytic cohort of 54,362 women. The cohort was followed for endometrial cancer occurrence from the date of the first subfertility evaluation to the date of emigration, death, or hysterectomy or June 30, 2006, whichever occurred first. At the time of linkage, 101 women had been diagnosed with endometrial cancer during the follow-up period. For comparison, a subcohort of 1360 women was randomly selected from the subfertility cohort. Hospital files and medical records on all subfertility-related medical visits were collected. For 18 cases, records could not be found, leaving 83 women with endometrial cancer for analysis. In the subcohort, 78 women for whom the hospital files could not be found, 8 women for whom a diagnosis of subfertility could not be confirmed, and 33 women for whom the cause of subfertility was previous sterilization were excluded, leaving 1241 women. Two of the subcohort members were diagnosed with endometrial cancer during the follow-up period; therefore, they were included both as cases and as members of the subcohort in the analyses. Median follow-up, 16 years.
Interventions	Gonadotropins, clomiphene citrate, human chorionic gonadotropin, gonadotropin-releasing hormone analogs. Information on number and duration of fertility treatment cycles, and, for a minority of the women, dosage of fertility drugs, was available.
Outcomes	Endometrial cancer cases identified through cohort linkage to the nationwide Danish Cancer Registry and the Danish Registry of Pathology from January 1, 2004, onward, because the Danish Cancer Registry was updated only until December 31, 2003, at the time of analysis.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias (comparability)	High risk	Comment: Exclusion of endometrial cancer cases at the beginning of the study was not reported. Comment: Non-exposed women drawn from the same population as exposed cohort.

Jensen 2009 *(Continued)*

		Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "All analyses were stratified according to calendar year and age at start of follow-up. Rate ratios were adjusted for parity (nulliparous/parous) and number of additional births (linear)". Comment: Analyses inadequately controlled for potential confounding factors.
Performance bias	High risk	Quote: "We collected hospital files and medical records on all infertility-related medical visits for all infertile women in whom uterine cancer developed and for members of the subcohort". Comment: Exposure to ovary-stimulation drugs was ascertained by medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "Information on uterine cancer status was obtained through cohort linkage to the Danish Cancer Registry and the Danish Registry of Pathology". Comment: Outcome was ascertained by record linkage.
Attrition bias	Low risk	Quote: "Losses to follow-up were virtually absent in our study as a result of the precise linkage between our cohort and the Danish population-based registers, and uterine cancer diagnoses were completely ascertained through linkage with the Danish Cancer Registry and the Danish Registry of Pathology". Comment: Follow-up was considered complete.
Selective reporting (reporting bias)	Low risk	Comment: All of the study's prespecified (primary and secondary) outcomes that were of interest in the review have been reported in the prespecified way.
Other bias	High risk	Quote: "The median length of follow-up was 16.0 years". Comment: Length of follow-up was considered adequate. Comment: Non-RCT study.

Kessous 2016

Methods	Retrospective cohort.
Participants	A population-based cohort of consecutive participants who delivered between 1988 to 2013 in the sole hospital of a region in Israel. Participants with known genetic predisposition for malignancy or known female malignancies before or during the index pregnancy were excluded from the study. A total of 106,031 subjects met the inclusion criteria. Follow-up period was until 2013 and for this study a retrospective follow-up of hospitalizations due to female malignancies up to 26 years after the index birth was performed. Mean follow-up, 11.6 years.
Interventions	Any fertility drugs (IVF treatment or ovulation induction).
Outcomes	Endometrial cancer cases identified via linkage to a computerised hospitalisation database. Hospitalisation for the disease during the study period was considered an event. Incident cases in total cohort, 61; in exposed cohort, 8.
Notes	
Risk of bias	

Kessous 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Quote:"Patients with known genetic predisposition for malignancy or known female malignancies before or during the index pregnancy were excluded from the study". Comment: Outcome not likely to be present at start. Quote: "The studied population was composed of consecutive patients who delivered between the years 1988–2013". Comment: Non-exposed drawn from the same population as the exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "Statistical significance was calculated using the Chi-square test for differences in qualitative variables". Quote: "Cox proportional hazard models were used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for long-term risk of female malignancies". Comment: Analyses inadequately controlled for potential confounding factors.
Performance bias	High risk	Comment: Exposure to ovary-stimulation drugs was ascertained by medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "The first hospitalization for female malignancies including ovarian cancer, uterine cancer, cervical cancer and breast cancer at Soroka University Medical Center was considered an event. The exact ICD codes for each type of the female malignancies are presented in the 'Appendix'. Comment: Outcome was ascertained by record linkage.
Attrition bias	High risk	Quote: "However, the ascertainment of malignancies diagnosed in patients that were treated in another hospital could not be accomplished. It is therefore possible that some patients were missed". Comment: Completeness of follow-up was considered inadequate.
Selective reporting (reporting bias)	Low risk	All of the study's prespecified (primary and secondary) outcomes that were of interest in the review have been reported in theprespecified way.
Other bias	High risk	Quote: "Patients had a mean follow-up duration of more than a decade (11.6 years)". Comment: The length of follow-up was considered adequate. Comment: Non-RCT study

Klip 2004

Methods	Retrospective cohort.
Participants	The study cohort consisted of 26,428 women diagnosed with subfertility problems between 1980 and 1995 in all 12 IVF hospitals in the Netherlands, with known date of birth, and > 18 years at the time of first visit to the fertility clinic. Women that emigrated, were lost to follow-up, refused to participate, were diagnosed with cancer before entering the cohort, or had unknown date of first IVF treatment or privacy issues were excluded, leaving 24,692 in the analytic cohort, 18,310 and 6382 in the exposed and

Klip 2004 *(Continued)*

	unexposed group, respectively. Attempt was made to frequency match the control group according to the distribution of the subfertility diagnoses in the IVF group. All cohort members received a risk factor questionnaire, and subfertility data were collected from their medical records. Median follow-up, 5.2 years in exposed; 8.0 years in unexposed group.
Interventions	At least one IVF treatment cycle with ovarian stimulation. Information on date, type of IVF treatment, dosages and type of fertility drugs used in each phase of the menstrual cycle (human menopausal gonadotropin, follicle-stimulating hormone, clomiphene citrate, human chorionic gonadotropin, progesterone and luteal phase support) was available.
Outcomes	Endometrial cancer identified through record linkage to the population-based Netherlands Cancer Registry for the period 1989 to 1997. Incident cases in total cohort, 12; in exposed cohort, 6.
Notes	Subfertile women were unable to achieve conception after 1 or more years of frequent unprotected intercourse. The cause of subfertility was medically verified and classified as tubal factor, male factor, ovarian disorder (including ovulation disorder, polycystic ovary syndrome, premature menopause), cervical factor, uterine abnormality, endometriosis, or unexplained.

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Quote: "The following women were excluded from all analyses: 80 women diagnosed with cancer before entering the cohort (including two women with breast cancer and six women with ovarian cancer)". Comment: Outcome not likely to be present at start. "The unexposed group consisted of 6,588 women whose subfertility was diagnosed in the four participating clinics that had a computerised registry of all subfertile women evaluated after 1980. We extensively checked whether women in the unexposed group received IVF in other hospitals". Comment: Non-exposed drawn from the same population as the exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	"Standardised Incidence Ratio (SIR), defined as the ratio of the observed (O) and expected (E) number of cancers in the study population. Expected numbers were calculated by applying the person-year distribution in the cohort to sex-, age- and calendar period-specific reference data from the NCR, Hazard Ratios adjusted for age at the end of follow-up". Comment: Analyses adjusted only for age.
Performance bias	High risk	Quote: "Research assistants specifically trained for data collection in this study abstracted detailed information from the medical records of 13,216 women in the cohort". Comment: Exposure to ovary-stimulation drugs was ascertained by a secure source, namely, medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "The study outcome, cancer incidence, was assessed through record linkage with the NCR for the period 1989-1997 and through the health questionnaire survey (including medical verification of self-reported tumours) for the periods before 1989 and after 1997".

Klip 2004 *(Continued)*

		Comment: Ascertainment of outcome by record linkage.
Attrition bias	Low risk	Quote from Table 1: "Loss to follow-up: 1.9%" Comment: Follow-up was expected to be rather complete.
Selective reporting (reporting bias)	Low risk	Comment: All of the study's prespecified (primary and secondary) outcomes that were of interest in the review have been reported in the prespecified way.
Other bias	High risk	Quote from Table 2: "a median follow-up duration of 16.9 years". Comment: Inadequate length of follow-up (< 10 years). Comment: Non-RCT study

Kristiansson 2007

Methods	Retrospective cohort.
Participants	The cohort consisted of 647,704 women 21 to 43 years of age, born in Sweden, and registered with a first pregnancy (IVF or non-IVF), from 1981 to 2001 in the nationwide Medical Birth Registry. In this cohort, 8716 women received IVF treatment, of whom 7645 had IVF for their first delivery, whereas 1071 had had a previous delivery without IVF treatment. Women with live birth following pregnancy achieved by IVF treatment in a stimulated cycle, without or with intracytoplasmic sperm injection, were allocated to the IVF group. Women with live birth without such treatment (not in the register of IVF treatment) were allocated to the non-IVF group. Women with IVF treatment with ovum transfer in a natural cycle or frozen–thawed embryo transfer and women diagnosed with an invasive tumour before the first conception leading to birth were excluded. Women with repeated pregnancies following in vitro fertilization were not taken into account, because the number of cases among women with multiple pregnancies were too few. The categorization of exposure was IVF or non-IVF where IVF could be multiple IVF pregnancies. Mean follow-up in the exposed group, 6.2 years; in the non-exposed, 7.8 years.
Interventions	IVF treatment.
Outcomes	Endometrial cancer. Cases were ascertained by record linkage to the National Cancer Registry in Sweden. Incident cases in cohort, 79; in exposed cohort, 1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Quote: "Women diagnosed with an invasive tumour before the first conception leading to birth were also excluded." Comment: Outcome not likely to be present at start. Quote: "Women with live birth without such treatment (not in the register of IVF treatment) were allocated to the non-IVF group". Comment: Non-exposed drawn from the same population as the exposed cohort.

Kristiansson 2007 *(Continued)*

		Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Comment: Analyses were not adjusted for any potential confounding factors.
Performance bias	High risk	Quote: "The Swedish National Board of Health and Welfare is responsible for official statistics about deliveries, assisted reproduction, cancer incidence and causes of death. Data on all deliveries in Sweden from 1973 are reported to the Swedish Medical Birth Registry, which contains individual data collected during pregnancy, delivery and the neonatal period". Comment: Exposure to ovary-stimulation drugs was ascertained by a secure source, namely, medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "Tumour cases were ascertained by record linkage in National Cancer Registry". Comment: Outcome was ascertained by record linkage.
Attrition bias	Low risk	Quote: "Tumour cases were ascertained by record linkage in National Cancer Registry. The overall reporting to the registry is estimated to be 96% of all diagnosed cases". Comment: Follow-up was expected to be rather complete.
Selective reporting (reporting bias)	High risk	Comment: Standardized Incidence Ratios and Poisson regression results not reported for endometrial cancer.
Other bias	High risk	Quote from Table 1: "Average number of person-years/woman: 6.4". Comment: Length of follow-up was considered inadequate (< 10 years). Comment: Non-RCT study.

Lerner-Geva 2012

Methods	Retrospective cohort.
Participants	The cohort was comprised of 2431 subfertile women between 1964 and 1974, identified by reviewing the medical records of a subfertility clinic in Israel, at their first clinic visit, of whom 1281 women were exposed to fertility treatment. Mean follow-up, 33.8 years.
Interventions	At least 1 cycle of human menopausal gonadotropin, clomiphene citrate, or both.
Outcomes	Histopathologically confirmed endometrial cancer identified through linkage to the nationwide Israel Cancer Registry through 2005. Incident cases in total cohort, 30; in exposed cohort, 17.
Notes	Participants with primary or secondary subfertility were Included.. Participants with a diagnosis of anovulatory cycles, amenorrhoea, oligomenorrhoea, or irregular periods were classified as having hormonal subfertility. Participants were classified as having mechanical subfertility if hysterosalpingography and/or laparoscopy demonstrated a mechanical problem, and there was evidence for normal ovulation by biphasic body basal temperature and/or urinary pregnanediol levels of above 5 mg/24-hours

Lerner-Geva 2012 *(Continued)*

during the expected luteal phase. Ovulating participants with no mechanical problems, whose partner had repeated abnormal semen analysis, were included in the male subfertility group. Participants who did not fulfil any of the above stated criteria were defined as unexplained subfertility.

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Comment: Exclusion of endometrial cancer cases at the beginning of the study was not reported. Quote: "Patients were identified by reviewing the infertility clinic's medical records. Patients were considered as unexposed if they did not have ovulation induction treatment defined as at least one cycle of human menopausal gonadotrophin (hMG) or clomiphene citrate (CC) or both". Comment: Non-exposed drawn from the same population as the exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	"Standardized incidence ratio (SIR) was calculated as the ratio between observed and expected cancer cases according to the general population cancer rates matched for sex, age and continent of birth". Comment: Analyses adjusted only for age.
Performance bias	High risk	Quote: "Patients were identified by reviewing the infertility clinic's medical records. Patients were considered to have had ovulation induction treatment if they received at least one cycle of human menopausal gonadotrophin (hMG) or clomiphene citrate (CC) or both". Comment: Exposure to ovary-stimulation drugs was ascertained by a secure source, namely, medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "The study cohort file was linked to the Israel Cancer Registry to identify cancer cases through 31 December 2005". Comment: Ascertainment of outcome by record linkage.
Attrition bias	Low risk	Quote: "Depending on the cancer site, cancer ascertainment through the Israel Cancer Registry was found to be 90–95% complete". Follow-up was expected to be rather complete.
Selective reporting (reporting bias)	High risk	Comment: Selective reporting of multivariate regression models results.
Other bias	High risk	Quote from Table 1: "Mean years of follow-up: 33.8 years". Comment: Length of follow-up was considered to be adequate. Comment: Non-RCT study.

Luke 2015

Methods	Retrospective cohort.
Participants	Cohort of 113,226 New York, Texas, and Illinois residents, who were treated with ART between 2004 and 2009 and whose cycles were reported to the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System, were linked to their respective state population-based cancer registries. Women identified as having a cancer diagnosis before ART and through 6 months after initiation of ART therapy were excluded from this analysis; similarly, women with an ''unknown primary site'' malignancy were also excluded. Follow-up periods after date of last treatment were until December 2010 for New York, and December 2012 for Texas and Illinois; for women, who were diagnosed with cancer, the follow-up period was censored at the time of diagnosis. Mean follow-up, 4.87 years.
Interventions	ART treatment.
Outcomes	Endometrial cancer cases identified through linkage to the state cancer registries. Incident cases in cohort, 49.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Quote: "Standardized incidence ratio (SIR) and the 95% confidence interval (CI) were calculated for the observed/expected ratios for all women and for women without prior ART, both with and without the ART diagnosis of "Other", because that diagnosis may include a history of prior cancer". Comment: Outcome not likely to be present at start. Quote: "The SART CORS database contains comprehensive data from more than 90% of all clinics providing assisted reproductive technology in the United States (http://www.sart.org). Data were collected and verified by SART". Comment: Non-exposed drawn from the same population as the exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "Standardized incidence ratio (SIR) and the 95% confidence interval (CI) were calculated for the observed/expected ratios". Comment: Analyses inadequately controlled for potential confounding factors.
Performance bias	High risk	Quote: "Approximately 10% of the reporting clinics are audited each year by the CDC and SART to validate the accuracy of the reported data". Comment: Exposure to ovary-stimulation drugs was ascertained by medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "Each of the three state cancer registries then linked reported cancers for each woman in the data file". Comment: Outcome was ascertained by record linkage.
Attrition bias	Low risk	Quote: "New York, Texas, and Illinois maintain population-based cancer registries that have consistently received gold certification by the North American Association of Central Cancer Registries". Comment: Completeness of follow-up was considered adequate.
Selective reporting (reporting bias)	Low risk	All of the study's prespecified (primary and secondary) outcomes that were of interest in the review have been reported in the prespecified way.

Luke 2015 *(Continued)*

Other bias	High risk	Quote: "We observed no evidence of increased risk of cancers after nearly 5 years of follow-up" Comment: The length of follow-up was considered inadequate. Comment: Non-RCT study.

Parazzini 2001

Methods	Case-control.
Participants	Cases were 568 women aged < 75 years, with histologically confirmed endometrial cancer, diagnosed within the year that preceded the interview, and who had been admitted to the National Cancer Institute and to the Ospedale Maggiore (which includes the four largest teaching and general hospitals in the greater Milan area, in Italy). Controls included 1787 women residing in the same area, and admitted for acute non-neoplastic, non-gynaecological conditions to the same network of hospitals as cases.
Interventions	Any fertility drugs.
Outcomes	Endometrial cancer.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Quote: "The cases that were studied were 568 women below the age of 75 (range, 28 to 74 years; median, 61 years) with histologically confirmed endometrial cancer". Comment: Cases were recruited consecutively. Quote: "Controls were women admitted for acute non-neoplastic, non-gynaecological conditions at the same hospital network". Comment: Hospital-based controls. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "Multiple logistic regression models including terms for age, education, parity, BMI, oral contraceptives, hormone replacement therapy use". Comment: Analyses inadequately controlling for potential confounding factors.
Performance bias	High risk	Quote: Information was collected by trained interviewers with a standard questionnaire". Comment: Exposure to ovary-stimulation drugs ascertained by structured questionnaires, both for cases and controls; blindness of interviewer not stated.
Detection bias	Low risk	Quote: "The cases that were studied were 568 women below the age of 75 with histologically confirmed endometrial cancer that was diagnosed within the year that preceded the interview who had been admitted to the National Cancer Institute and to the Ospedale Maggiore".

Parazzini 2001 *(Continued)*

		Comment: Assessors of cancer status were blinded to exposure status.
Attrition bias	Low risk	Quote: "Less than 2% of the identified cases and controls refused to be interviewed". Comment: Adequate participation rate in final analyses.
Selective reporting (reporting bias)	Low risk	Comment: All of the study's prespecified (primary and secondary) outcomes that were of interest in the review have been reported in the prespecified way.
Other bias	High risk	Non-RCT study.

Parazzini 2010

Methods	Case-control.
Participants	Cases and controls were identified by trained interviewers through regular visits to selected medical wards of the major hospitals of three Italian areas between 1992 to 2006. Cases were 454 women with incident, histologically confirmed endometrial cancer, and no earlier diagnosis of cancer. Controls were 908 women admitted to the same network of hospitals as cases for a wide spectrum of non-neoplastic acute illnesses. Women admitted for gynaecological or hormone-related conditions or any medical conditions associated with long-term dietary changes as well as women with a history of hysterectomy were excluded from the control group. Controls were admitted for trauma, orthopaedic disorders, acute surgical conditions, and miscellaneous other illnesses, including eye, nose, ear, skin, or dental disorders.
Interventions	Any fertility drugs. The data were collected by trained interviewers during the hospital stay using a structured questionnaire and included age at start and duration of treatment.
Outcomes	Endometrial cancer.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Quote: "Cases were 454 women with incident, histologically confirmed endometrial cancer, and no earlier diagnosis of cancer". Comment: Cases were recruited consecutively. Quote: "Women admitted for gynaecological or hormone-related conditions or any medical conditions associated with long-term dietary changes were not eligible as controls. Women with a history of hysterectomy were excluded from the control group". Comment: Hospital-based controls. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "Conditional logistic regression models, conditioned for matching variables (centre and quinquennia of age) and adjusted for calendar period of interview, education, body mass index, age at menarche, menopausal status, parity, oral contraceptive and hormone replacement therapy use".

Parazzini 2010 *(Continued)*

		Comment: Analyses inadequately controlling for potential confounding factors.
Performance bias	High risk	Quote: "Information was collected by trained interviewers with a standard questionnaire". Comment: Exposure to ovary-stimulation drugs ascertained by structured questionnaires, both for cases and controls; blindness of interviewer not stated.
Detection bias	Low risk	Quote: "Cases were 454 women (median age 60 years; range 18– 79) with incident, histologically confirmed endometrial cancer, and no earlier diagnosis of cancer". Comment: Assessors of cancer status were blinded to exposure status.
Attrition bias	Low risk	Quote: "Fewer than 5% of the cases and controls approached refused to be interviewed". Comment: Adequate participation rate in final analyses.
Selective reporting (reporting bias)	Low risk	Comment: All of the study's prespecified (primary and secondary) outcomes that were of interest in the review have been reported in the prespecified way.
Other bias	High risk	Non-RCT study.

Potashnik 1999

Methods	Retrospective cohort.
Participants	The study cohort included 1197 subfertile women attending a subfertility clinic in Beer-Sheba, Israel, between 1960 and 1984, of whom 780 were exposed to fertility treatment. Mean follow-up, 17.9 years.
Interventions	Any drug; clomiphene citrate. Data on dosages and number of cycles were available.
Outcomes	Histologically confirmed endometrial cancer was retrieved by linkage of the cohort to the Israel National Cancer Registry through 1994. Incident cases in total cohort, 2; in exposed cohort, 2.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Comment: Exclusion of endometrial cancer cases at the beginning of the study was not reported. Comment: Non-exposed women drawn from the same population as exposed cohort. Quote: "No statistically significant differences were found between the exposed and unexposed groups regarding all types of infertility, ethnic origin, and age at first visit". Comment: No comparability on diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.

Potashnik 1999 *(Continued)*

Selection bias (confounding)	High risk	Quote: "The standardized incidence ratio was computed as the ratio of observed to expected numbers of cases with 95% confidence interval (CI) estimates". Comment: Analyses inadequately controlling for potential confounding factors.
Performance bias	High risk	Comment: Exposure to ovary-stimulation drugs was ascertained by medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "The study cohort computer file was linked to the Israel National Cancer Registry to identify cancer cases". Comment: Outcome was ascertained by record linkage
Attrition bias	Low risk	Quote: "Cancer ascertainment during internal verifications was found to be 90%–95% complete" Comment: Follow-up was expected to be rather complete.
Selective reporting (reporting bias)	High risk	Comment: Analyses on endometrial cancer by type of subfertility not reported.
Other bias	High risk	Quote: "The mean (+/-SD) duration of follow-up for the study population was 17.9+/-5.3 years".. Comment: Length of follow-up was considered adequate. Comment: Non-RCT study.

Reigstad 2015

Methods	Retrospective cohort.
Participants	The cohort consisted of 806,248 women, born in Norway, and registered with a first pregnancy (IVF or non-IVF), from 1984 to 2010 in the Medical Birth Registry of Norway. In this cohort, 16,525 women gave birth to a child following assisted reproductive technology (ART). Women who had at least one pregnancy initiated by ART (IVF, ICSI, a combination of the two or any other kind of treatment) were classified as ART women, and women who had no registered ART pregnancies were classified as non-ART. Subjects who delivered after emigrating from Norway, and those with a cancer prior to the start of follow-up were excluded. The categorization of exposure was ART or non-ART where ART could be multiple ART pregnancies. Median follow-up in the exposed group, 7.3 years; in the non-exposed, 16.0 years.
Interventions	Assisted reproductive technology (ART)
Outcomes	Endometrial cancer. Cases were ascertained by record linkage to the Cancer Registry of Norway (CRN). Incident cases in cohort, 636; in exposed cohort, 5.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Reigstad 2015 *(Continued)*

Selection bias (comparability)	High risk	Quote: "After removal of subjects who delivered after emigrating from Norway, and those with a cancer prior to the start of follow-up". Comment: Outcome not likely to be present at start. Quote: "Women who had no registered ART pregnancies were classified as non-ART". Comment: Non-exposed drawn from the same population as the exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "To adjust for the age difference between ART women and non-ART women, we used the age of study subjects as the time-scale. Confounder adjustment was made for age at start of follow-up, calendar period, region of residence in Norway and parity as a time-varying covariate, as previously described". Comment: Analyses inadequately controlling for potential confounding factors.
Performance bias	High risk	Quote: "All deliveries (from Week 22) in Norway have been recorded in the MBRN since its establishment in 1967. The reporting of data on ART pregnancies started in 1984 (the year the first baby was born after IVF in Norway). For each child born, the following data were extracted from the MBRN: date of birth of mother and child, parity, present region of residence, exposure to ART, the specific method of ART". Comment: Exposure to ovary-stimulation drugs was ascertained by a secure source, namely, medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "All women with at least one diagnosis of invasive cancer during the period 1 January 1953 through 31 December 2010 were identified through linkage of the MBRN data to the Cancer Registry of Norway (CRN) using each woman's unique personal identification number". Comment: Outcome was ascertained by record linkage.
Attrition bias	Low risk	Quote: "The completeness of the CRN enabled accurate ascertainment of cancer, with negligible losses to follow-up". Comment: Follow-up was expected to be rather complete.
Selective reporting (reporting bias)	High risk	Results of stratified analyses were not presented.
Other bias	High risk	Quote from Table 1: "Follow-up time, person years (median): 15.9". Comment: Length of follow-up was considered adequate (> 10 years). Comment: Non-RCT study.

Venn 1999

Methods	Retrospective cohort.

Venn 1999 *(Continued)*

Participants	The cohort consisted of 29,700 women who registered with at least one of 10 participating Australian IVF clinics before Jan 1, 1994. Women whose usual residence was outside Australia (n = 623), or whose date of birth or age was unknown (n = 520) were excluded. Exposed were 20,656 women who had at least one IVF treatment cycle with ovarian stimulation to induce multiple folliculogenesis, including stimulated cycles that were cancelled before oocyte collection. Unexposed were considered 9044 women who registered for IVF but did not receive treatment or had 'natural' cycle treatment without ovarian stimulation. Four women with cancer diagnosis before start of IVF treatment were excluded. Follow-up was from the time each woman entered the cohort until the first of: date of cancer diagnosis, death, or Dec 31 of the year of complete cancer data for her state of residence. Median follow-up of the exposed cohort, 7 years; of the unexposed cohort, 10 years.
Interventions	At least one IVF treatment cycle with ovarian stimulation to induce multiple folliculogenesis. Drugs used were clomiphene citrate, human menopausal gonadotropin, both clomiphene citrate and human menopausal gonadotropin, human menopausal gonadotropin and gonadotropin-releasing hormone agonist. Data on number of fertility treatment cycles were available.
Outcomes	Endometrial cancer ascertained by record linkage to population-based cancer registries held by the state or by the National Cancer Statistics Clearing House and to the National Death Index. Incident cases in cohort, 12; in exposed cohort, 5.
Notes	Subfertility investigations routinely used by IVF clinics and referring gynaecologists included hormone assays, ultrasonography, diagnostic laparoscopy, and semen analysis. The cause of subfertility was classified as tubal, male factor, endometriosis, ovarian disorders (including ovulation disorders, polycystic ovary syndrome, premature menopause, and oophorectomy), other factors (including cervical factors, other uterine abnormalities, donor egg recipients for genetic disease, altruistic egg donors), or unexplained.

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias (comparability)	High risk	Quote: "Any diagnosis of cancer immediately before a woman's registration with an IVF programme was checked to confirm that cancer preceded referral for IVF. Four women with cancer were referred for IVF with the aim of producing embryos for freezing before cancer therapy started; they were excluded from the analysis". Comment: Outcome not likely to be present at start. Quote: "Women classified as unexposed were those who registered for IVF but did not receive treatment (95%) or who had 'natural' cycle treatment without ovarian stimulation (5%)". Comment: Non-exposed drawn from the same population as the exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "For the SIR, the age-specific rates for the three cancers were compared across three calendar periods (1981–85, 1986–90, and 1991–95) and across the states of Australia". Comment: Analyses adjusted only for age.
Performance bias	High risk	Quote: "Data collected from clinics were woman's name and date of birth, partner's name, address, date of registration with the clinic, and cause of subfertility. Information about IVF treatment consisted of dates of treatment cycles, type of treatment (e.g. stimulated cycle or frozen embryo transfer), fer-

Venn 1999 *(Continued)*

		tility drugs used for ovarian stimulation, number of oocytes collected, and whether the cycle was cancelled before oocyte collection". Comment: Exposure to ovary-stimulation drugs was ascertained by a secure source, namely, medical records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "Ascertainment of cancer cases was by record linkage to population-based cancer registries held by the state or by the National Cancer Statistics Clearing House and to the National Death Index". Comment: Ascertainment of outcome by record linkage.
Attrition bias	Low risk	Quote: "Although the registries covered all states and territories in Australia, and loss to follow-up outside the country is likely to have been negligible, we may have missed women with cancer who had changed their names since participating in an IVF programme. We have estimated that more than 25% of breast cancers would have had to be missed for the SIR to be greater than 1·0 in this IVF cohort—an unlikely occurrence". Comment: Follow-up was expected to be rather complete.
Selective reporting (reporting bias)	Low risk	Comment: "All of the study's prespecified (primary and secondary) outcomes that were of interest in the review have been reported in the prespecified way".
Other bias	High risk	Quote from Table 1: "Median duration of follow-up in exposed women: 7 years". Comment: Inadequate length of follow-up (< 10 years). Comment: Non-RCT study.

Yli-Kuha 2012

Methods	Retrospective cohort.
Participants	Exposed were 9175 women who received IVF including intracytoplasmic sperm injection and frozen embryo transfer treatments in Finland between 1996 and 1998, identified from the reimbursements for drugs or drug combinations that were specific to these subfertility treatments. Controls consisted of 9175 women randomly picked from the Population Register maintained by the Social Insurance Institution and matched to IVF women by age and municipality. Mean follow-up, 7.8 years.
Interventions	IVF treatment.
Outcomes	Endometrial cancer cases identified through linkage of IVF women and their controls to the nationwide Finnish Cancer Registry between 1996 and 2004. Cancers diagnosed before IVF treatments were excluded for the controls, the age at which the matched IVF woman began IVF treatment was used. Incident cases in total cohort, 5; in exposed cohort, 4.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Yli-Kuha 2012 *(Continued)*

Selection bias (comparability)	High risk	Quote: "The cancer incidences were calculated first starting from the last IVF treatment (covering the whole follow-up time) and secondly starting from 12 months after the last recorded IVF treatment". Comment: Outcome not likely to be present at start. Quote: "The control women were randomly picked from the Population Register maintained by the Social Insurance Institution and matched to IVF women by age and municipality". Comment: Non-exposed drawn from the same population as the exposed cohort. Comment: No comparability on cause of subfertility, diabetes mellitus, polycystic ovary syndrome (PCOS), and obesity was ensured.
Selection bias (confounding)	High risk	Quote: "IVF women and their controls were matched for age and residence, conditional logistic regression analysis after adjustment for socio-economic position and marital status". Comment: Analyses inadequately controlled for potential confounders.
Performance bias	High risk	Quote: "The women were identified from the reimbursements for time for a cancer after infertility treatments among IVF women and drugs or drug combinations that are specific to these infertility treatments. Each woman having received one of these treatments was recorded once in the cohort regardless of the number of drug purchases from 1996 to 1998". Comment: Exposure to ovary-stimulation drugs was ascertained by official records. Blindness regarding the allocated interventions not guaranteed.
Detection bias	Low risk	Quote: "In order to identify cancer cases, IVF women and their controls were linked to the Finnish Cancer Registry". Comment: Outcome was ascertained by record linkage.
Attrition bias	Low risk	Quote: "The coverage of the registry is considered very good: according to an earlier study, it records 99% of solid tumours". Comment: Follow-up was expected to be rather complete.
Selective reporting (reporting bias)	Unclear risk	Comment: It is unclear whether analyses by specific ovulation induction drug could be performed.
Other bias	High risk	Quote: "The follow-up time was until 31 December 2004, on average 7 years and 9 months". Comment: Follow-up was considered to be inadequate. Comment: Non-RCT study.

- amenorrhoea: the absence of a menstrual period in a woman of reproductive age
- anovulation: non-release of an oocyte during a menstrual cycle
- ART: assisted reproductive technology
- biphasic: having two phases
- CC: clomiphene citrate
- endometriosis: a condition characterized by painful menses and abnormal growth of endometrial tissue outside the uterus
- folliculogenesis: maturation of the ovarian follicle
- hMG: human menopausal gonadotropin

- hyperprolactinaemia: increased blood levels of the hormone prolactin
- hysterosalpingography: radiological imaging of the uterus and the fallopian tubes (salpinges)
- ICD: international classification codes
- Intracytoplasmic: within the cytoplasm of a cell
- IVF: in vitro fertilization
- laparoscopy: operation through small incisions with the aid of a camera
- luteal phase: the second phase of the menstrual cycle after relase of the oocyte
- non-neoplastic: conditions not related to a tumor
- oligomenorrhoea: infrequent or very light menstruation
- oocyte: female egg cell
- PCOS: polycystic ovarian syndrome; a common endocrine system disorder among women of reproductive age frequently associated high free androgen levels and the presence of many growing follicles in the ovaries
- pregnanediol: a protein produced from the metabolism of the hormone progesterone
- SIR: standardized incidence rate
- SMR: standardized mortality rate

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

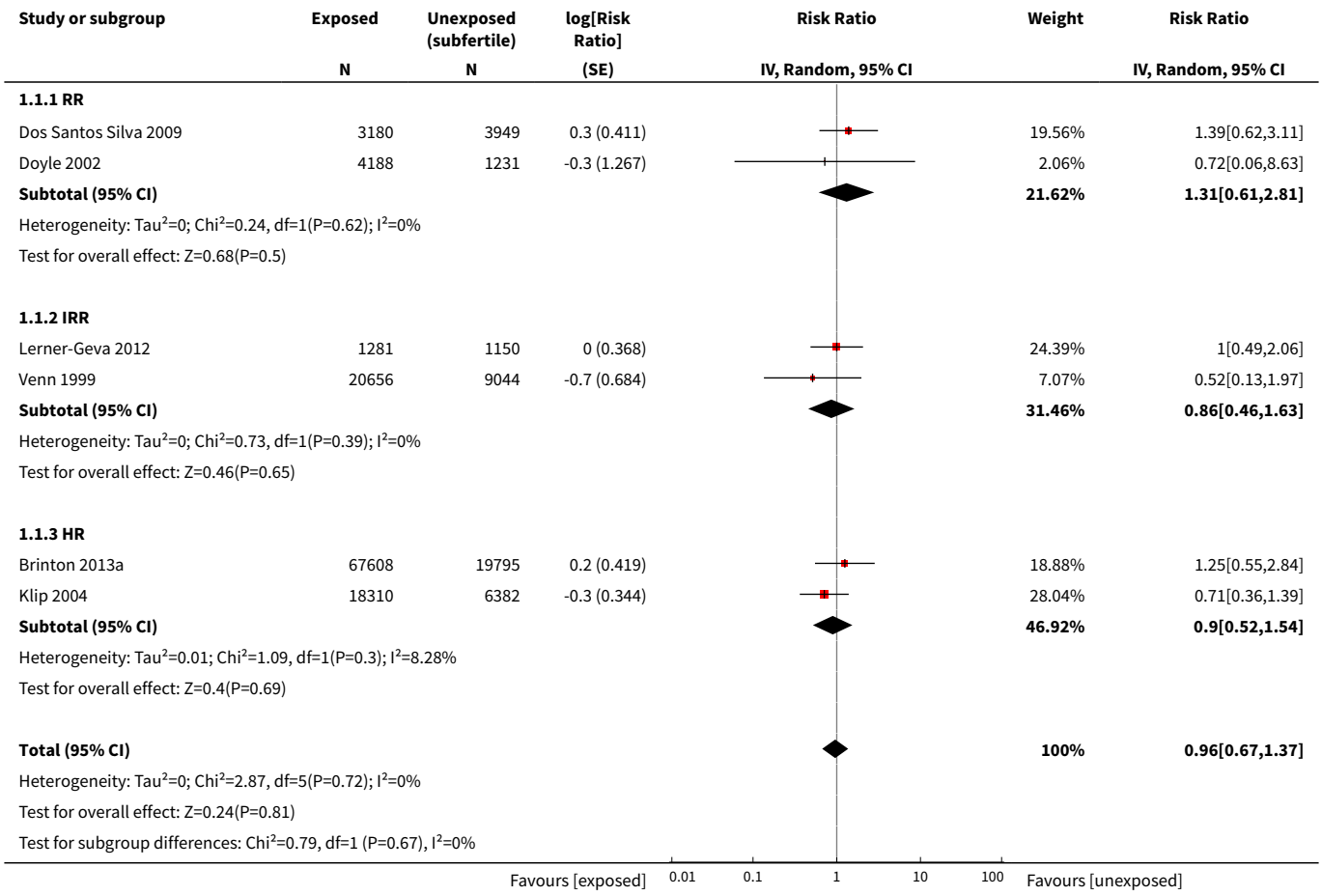
Study	Reason for exclusion
Brinton 1989	Data on ovarian stimulation not stated.
DeMichele 2008	Data on ovarian stimulation not stated.
Holody-Zareba 2014	Tamoxifen use of breast cancer treatment.
Klemetti 2005	Data on endometrial cancer not stated.
Wild 2000	Clomiphene citrate used only for treatment of polycystic ovary syndrome.
Yang 2015	Data on fertility treatments not presented.

DATA AND ANALYSES

Comparison 1. Exposure to any drug; comparison group: subfertile; any

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	6	156774	Risk Ratio (Random, 95% CI)	0.96 [0.67, 1.37]
1.1 RR	2	12548	Risk Ratio (Random, 95% CI)	1.31 [0.61, 2.81]
1.2 IRR	2	32131	Risk Ratio (Random, 95% CI)	0.86 [0.46, 1.63]
1.3 HR	2	112095	Risk Ratio (Random, 95% CI)	0.90 [0.52, 1.54]

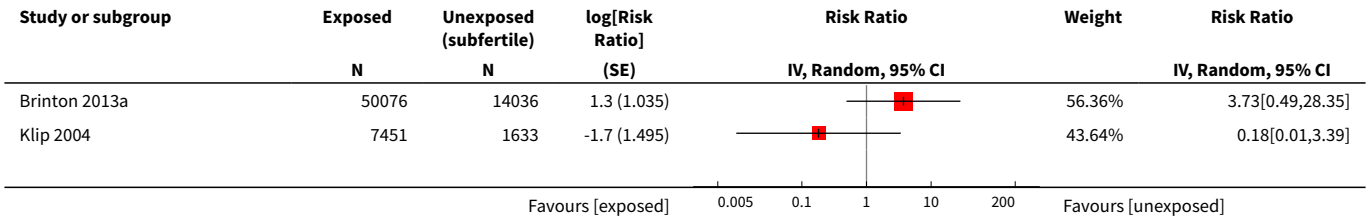
Analysis 1.1. Comparison 1 Exposure to any drug; comparison group: subfertile; any, Outcome 1 Endometrial cancer; subgroup by effect estimate.

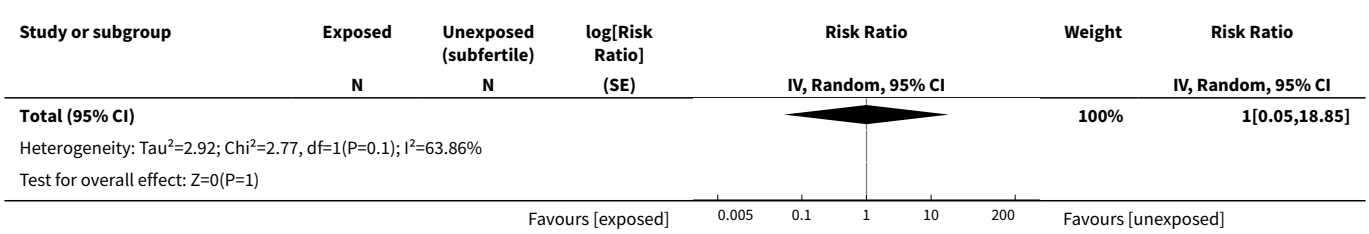


Comparison 2. Exposure to any drug; comparison group: subfertile; parous women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	2		Risk Ratio (Random, 95% CI)	1.00 [0.05, 18.85]

Analysis 2.1. Comparison 2 Exposure to any drug; comparison group: subfertile; parous women, Outcome 1 Endometrial cancer; subgroup by effect estimate.

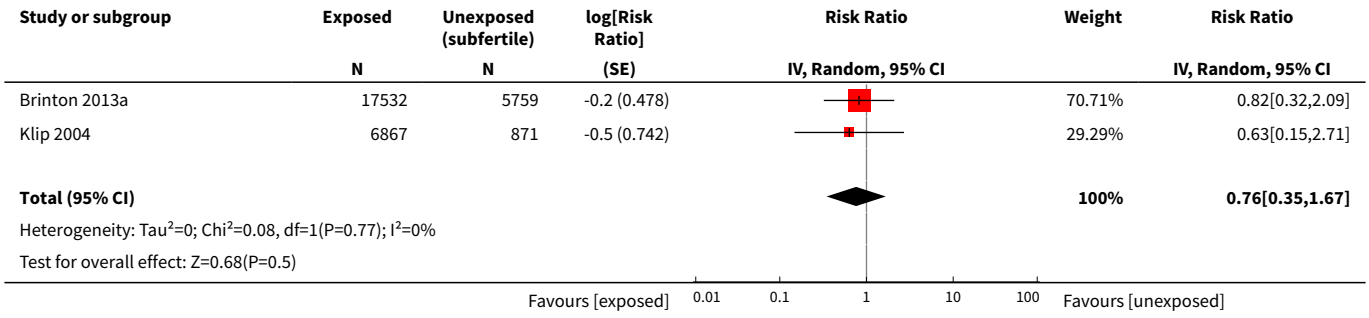




Comparison 3. Exposure to any drug; comparison group: subfertile; nulliparous women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	0.76 [0.35, 1.67]

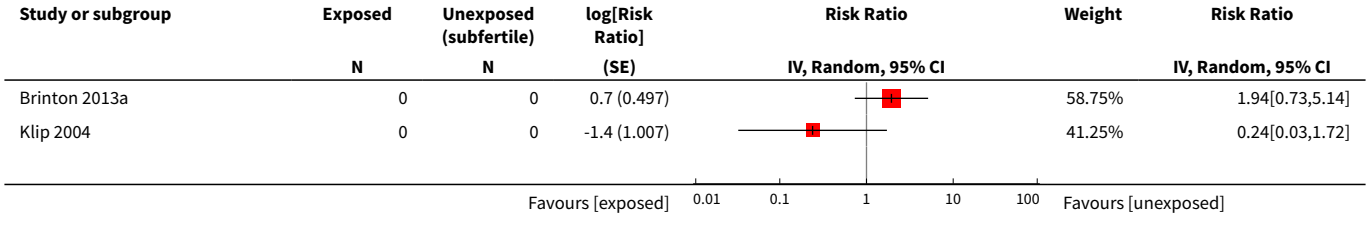
Analysis 3.1. Comparison 3 Exposure to any drug; comparison group: subfertile; nulliparous women, Outcome 1 Endometrial cancer.

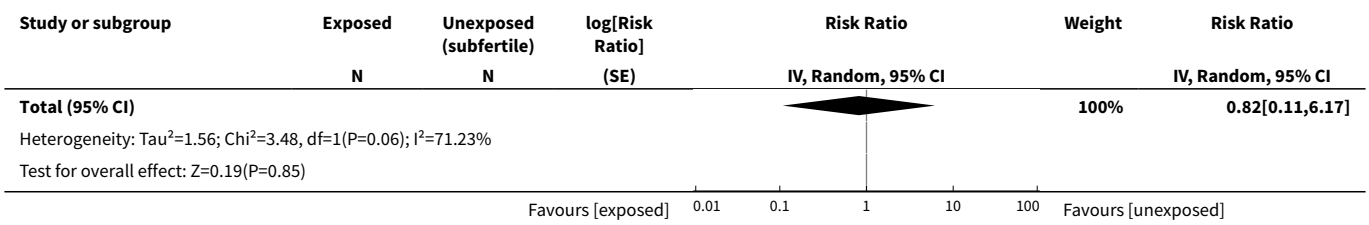


Comparison 4. Exposure to any drug; comparison group: subfertile; low number of cycles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	0.82 [0.11, 6.17]

Analysis 4.1. Comparison 4 Exposure to any drug; comparison group: subfertile; low number of cycles, Outcome 1 Endometrial cancer.

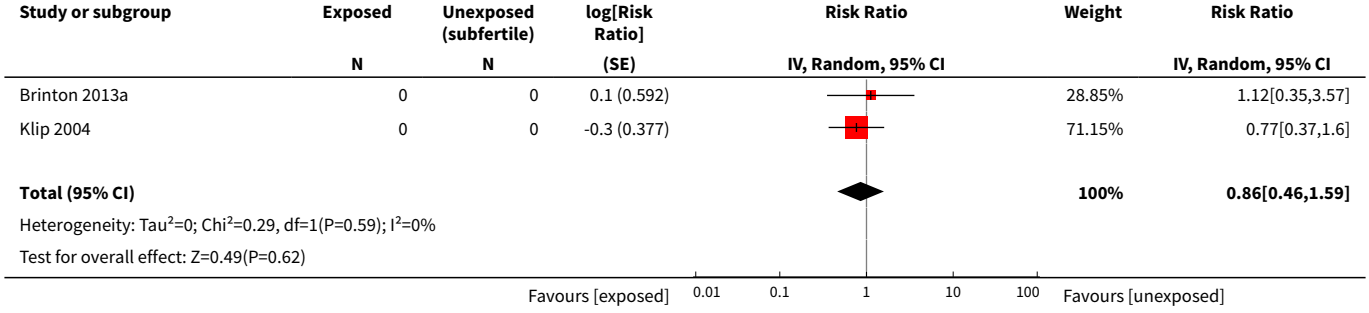




Comparison 5. Exposure to any drug; comparison group: subfertile; medium number of cycles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	0.86 [0.46, 1.59]

Analysis 5.1. Comparison 5 Exposure to any drug; comparison group: subfertile; medium number of cycles, Outcome 1 Endometrial cancer.

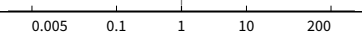


Comparison 6. Exposure to any drug; comparison group: general population; any

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	15	1.762829E6	Risk Ratio (Random, 95% CI)	1.75 [1.18, 2.61]
1.1 SIR	7	165366	Risk Ratio (Random, 95% CI)	1.61 [0.92, 2.82]
1.2 OR	4	22450	Risk Ratio (Random, 95% CI)	1.87 [0.96, 3.64]
1.3 IRR	1	647704	Risk Ratio (Random, 95% CI)	1.71 [0.11, 25.85]
1.4 HR	2	821278	Risk Ratio (Random, 95% CI)	1.51 [0.32, 7.19]
1.5 RR	1	106031	Risk Ratio (Random, 95% CI)	3.52 [1.67, 7.41]

Analysis 6.1. Comparison 6 Exposure to any drug; comparison group: general population; any, Outcome 1 Endometrial cancer; subgroup by effect estimate.

Study or subgroup	Exposed	Unexposed (General)	log[Risk Ratio]	Risk Ratio	Weight	Risk Ratio
	N	N	(SE)	IV, Random, 95% CI		IV, Random, 95% CI
6.1.1 SIR						
Dor 2002	5026	0	0.8 (0.707)		5%	2.25[0.56,8.99]
Dos Santos Silva 2009	3180	0	0.8 (0.236)		10.74%	2.31[1.45,3.66]
Doyle 2002	4188	0	0.2 (0.577)		6.25%	1.2[0.39,3.72]
Klip 2004	18310	0	1.1 (0.408)		8.34%	3[1.35,6.68]
Luke 2015	113226	0	-0.3 (0.164)		11.59%	0.74[0.54,1.02]
Potashnik 1999	780	0	1.1 (0.707)		5%	2.99[0.75,11.94]
Venn 1999	20656	0	0.1 (0.447)		7.82%	1.09[0.45,2.61]
Subtotal (95% CI)					**54.73%**	**1.61[0.92,2.82]**
Heterogeneity: Tau^2=0.37; Chi^2=23.81, df=6(P=0); I^2=74.81%						
Test for overall effect: Z=1.68(P=0.09)						
6.1.2 OR						
Benshushan 2001	17	366	0.3 (0.559)		6.45%	1.4[0.47,4.18]
Parazzini 2001	10	2345	-0.2 (0.783)		4.4%	0.8[0.17,3.71]
Parazzini 2010	18	1344	1.2 (0.569)		6.34%	3.26[1.07,9.94]
Yli-Kuha 2012	9175	9175	1.4 (1.118)		2.63%	4[0.45,35.79]
Subtotal (95% CI)					**19.82%**	**1.87[0.96,3.64]**
Heterogeneity: Tau^2=0; Chi^2=2.86, df=3(P=0.41); I^2=0%						
Test for overall effect: Z=1.85(P=0.06)						
6.1.3 IRR						
Kristiansson 2007	8716	638988	0.5 (1.387)		1.84%	1.71[0.11,25.85]
Subtotal (95% CI)					**1.84%**	**1.71[0.11,25.85]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.39(P=0.7)						
6.1.4 HR						
Calderon-Margalit 2009	567	14463	1.2 (0.497)		7.19%	3.39[1.28,8.97]
Reigstad 2015	16525	789723	-0.4 (0.457)		7.69%	0.69[0.28,1.69]
Subtotal (95% CI)					**14.87%**	**1.51[0.32,7.19]**
Heterogeneity: Tau^2=1.04; Chi^2=5.56, df=1(P=0.02); I^2=82.02%						
Test for overall effect: Z=0.52(P=0.6)						
6.1.5 RR						
Kessous 2016	4363	101668	1.3 (0.38)		8.74%	3.52[1.67,7.41]
Subtotal (95% CI)					**8.74%**	**3.52[1.67,7.41]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.32(P=0)						
Total (95% CI)					**100%**	**1.75[1.18,2.61]**
Heterogeneity: Tau^2=0.33; Chi^2=40.08, df=14(P=0); I^2=65.07%						
Test for overall effect: Z=2.76(P=0.01)						
Test for subgroup differences: Chi^2=2.96, df=1 (P=0.56), I^2=0%						



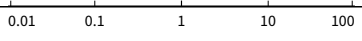
Favours [exposed] Favours [unexposed]

Comparison 7. Exposure to any drug; comparison group: general population; low number of cycles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	2.33 [0.93, 5.87]

Analysis 7.1. Comparison 7 Exposure to any drug; comparison group: general population; low number of cycles, Outcome 1 Endometrial cancer.

Study or subgroup	Exposed N	Unexposed (general) N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Klip 2004	9107	0	0.7 (0.707)		34.35%	2[0.5,8]
Venn 1999	6346	0	-0.3 (1)		19.38%	0.71[0.1,5.07]
Venn 1999	3712	0	1.5 (0.577)		46.27%	4.29[1.38,13.29]
Total (95% CI)					**100%**	**2.33[0.93,5.87]**
Heterogeneity: Tau²=0.15; Chi²=2.54, df=2(P=0.28); I²=21.24%						
Test for overall effect: Z=1.79(P=0.07)						



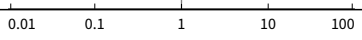
Favours [exposed] Favours [unexposed]

Comparison 8. Exposure to any drug; comparison group: general population; medium number of cycles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	3.39 [0.77, 14.87]

Analysis 8.1. Comparison 8 Exposure to any drug; comparison group: general population; medium number of cycles, Outcome 1 Endometrial cancer.

Study or subgroup	Exposed N	Unexposed (general) N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Klip 2004	4261	0	1.8 (0.577)		63.55%	6[1.94,18.6]
Venn 1999	5157	0	0.2 (1)		36.45%	1.25[0.18,8.87]
Total (95% CI)					**100%**	**3.39[0.77,14.87]**
Heterogeneity: Tau²=0.56; Chi²=1.85, df=1(P=0.17); I²=45.81%						
Test for overall effect: Z=1.62(P=0.11)						

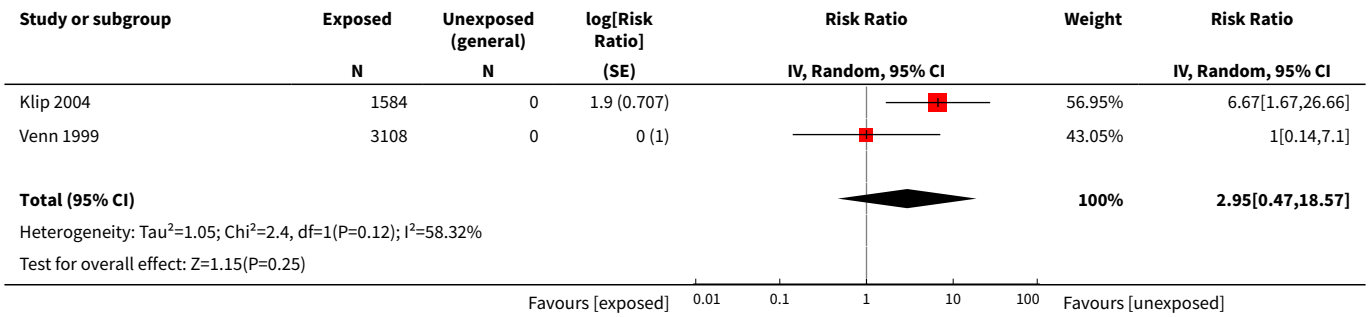


Favours [exposed] Favours [unexposed]

Comparison 9. Exposure to any drug; comparison group: general population; 0-3 number of oocytes retrieved

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	2.95 [0.47, 18.57]

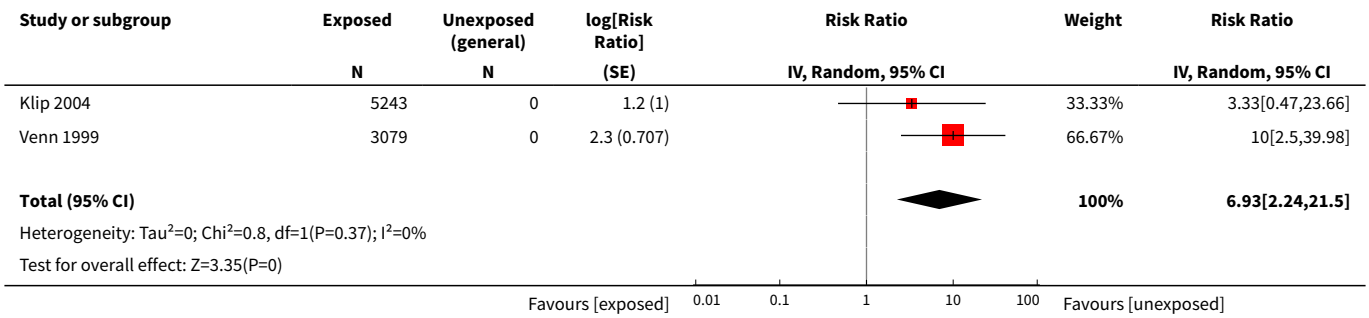
Analysis 9.1. Comparison 9 Exposure to any drug; comparison group: general population; 0-3 number of oocytes retrieved, Outcome 1 Endometrial cancer.



Comparison 10. Exposure to any drug; comparison group: general population; >10 number of oocytes retrieved

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	6.93 [2.24, 21.50]

Analysis 10.1. Comparison 10 Exposure to any drug; comparison group: general population; >10 number of oocytes retrieved, Outcome 1 Endometrial cancer.

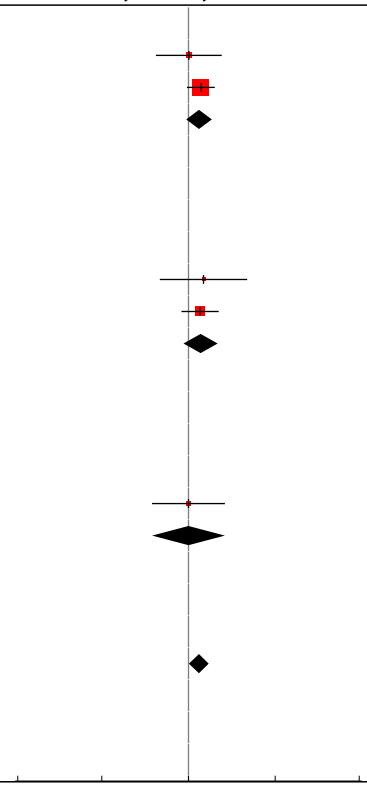


Comparison 11. Exposure to clomiphene; comparison group: subfertile: any

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	5	92849	Risk Ratio (Random, 95% CI)	1.32 [1.01, 1.71]
1.1 HR	2	82318	Risk Ratio (Random, 95% CI)	1.32 [0.94, 1.86]
1.2 RR	2	8259	Risk Ratio (Random, 95% CI)	1.38 [0.88, 2.17]
1.3 IRR	1	2272	Risk Ratio (Random, 95% CI)	1.0 [0.38, 2.63]

Analysis 11.1. Comparison 11 Exposure to clomiphene; comparison group: subfertile: any, Outcome 1 Endometrial cancer; subgroup by effect estimate.

Study or subgroup	Exposed N	Unexposed (subfertile) N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
11.1.1 HR						
Brinton 2013a	52691	19795	0 (0.447)		8.97%	1.01[0.42,2.42]
Brinton 2013b	3756	6076	0.3 (0.189)		50.39%	1.39[0.96,2.01]
Subtotal (95% CI)					**59.36%**	**1.32[0.94,1.86]**
Heterogeneity: Tau^2=0; Chi^2=0.43, df=1(P=0.51); I^2=0%						
Test for overall effect: Z=1.62(P=0.11)						
11.1.2 RR						
Dos Santos Silva 2009	2984	3949	0.4 (0.592)		5.12%	1.49[0.47,4.75]
Jensen 2009	446	880	0.3 (0.252)		28.17%	1.36[0.83,2.23]
Subtotal (95% CI)					**33.29%**	**1.38[0.88,2.17]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%						
Test for overall effect: Z=1.39(P=0.17)						
11.1.3 IRR						
Lerner-Geva 2012	1122	1150	0 (0.494)		7.35%	1[0.38,2.63]
Subtotal (95% CI)					**7.35%**	**1[0.38,2.63]**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)					**100%**	**1.32[1.01,1.71]**
Heterogeneity: Tau^2=0; Chi^2=0.81, df=4(P=0.94); I^2=0%						
Test for overall effect: Z=2.05(P=0.04)						
Test for subgroup differences: Chi^2=0.35, df=1 (P=0.84), I^2=0%						

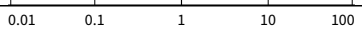


Comparison 12. Exposure to clomiphene; comparison group: subfertile; low dosage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	1.30 [0.78, 2.17]

Analysis 12.1. Comparison 12 Exposure to clomiphene; comparison group: subfertile; low dosage, Outcome 1 Endometrial cancer.

Study or subgroup	Exposed N	Unexposed (subfertile) N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Brinton 2013a	1274	6076	0.3 (0.27)		92.68%	1.39[0.82,2.36]
Dos Santos Silva 2009	0	0	-0.5 (0.959)		7.32%	0.58[0.09,3.8]
Total (95% CI)					**100%**	**1.3[0.78,2.17]**
Heterogeneity: Tau^2=0; Chi^2=0.77, df=1(P=0.38); I^2=0%						
Test for overall effect: Z=1.02(P=0.31)						



Favours [exposed] Favours [unexposed]

Comparison 13. Exposure to clomiphene; comparison group: subfertile; medium dosage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	1.27 [0.76, 2.13]

Analysis 13.1. Comparison 13 Exposure to clomiphene; comparison group: subfertile; medium dosage, Outcome 1 Endometrial cancer.

Study or subgroup	Exposed N	Unexposed (subfertile) N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Brinton 2013a	1216	6076	0.2 (0.287)		84.19%	1.26[0.72,2.21]
Dos Santos Silva 2009	0	0	0.3 (0.663)		15.81%	1.33[0.36,4.88]
Total (95% CI)					**100%**	**1.27[0.76,2.13]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.94); I^2=0%						
Test for overall effect: Z=0.91(P=0.36)						

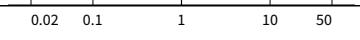
Favours [exposed] Favours [unexposed]

Comparison 14. Exposure to clomiphene; comparison group: subfertile; high dosage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	1.69 [1.07, 2.68]

Analysis 14.1. Comparison 14 Exposure to clomiphene; comparison group: subfertile; high dosage, Outcome 1 Endometrial cancer.

Study or subgroup	Exposed N	Unexposed (subfertile) N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Brinton 2013a	1266	6076	0.4 (0.266)		78.38%	1.5[0.89,2.52]
Dos Santos Silva 2009	0	0	1 (0.506)		21.62%	2.62[0.97,7.06]
Total (95% CI)					**100%**	**1.69[1.07,2.68]**
Heterogeneity: Tau^2=0; Chi^2=0.95, df=1(P=0.33); I^2=0%						
Test for overall effect: Z=2.24(P=0.03)						



Favours [exposed] Favours [unexposed]

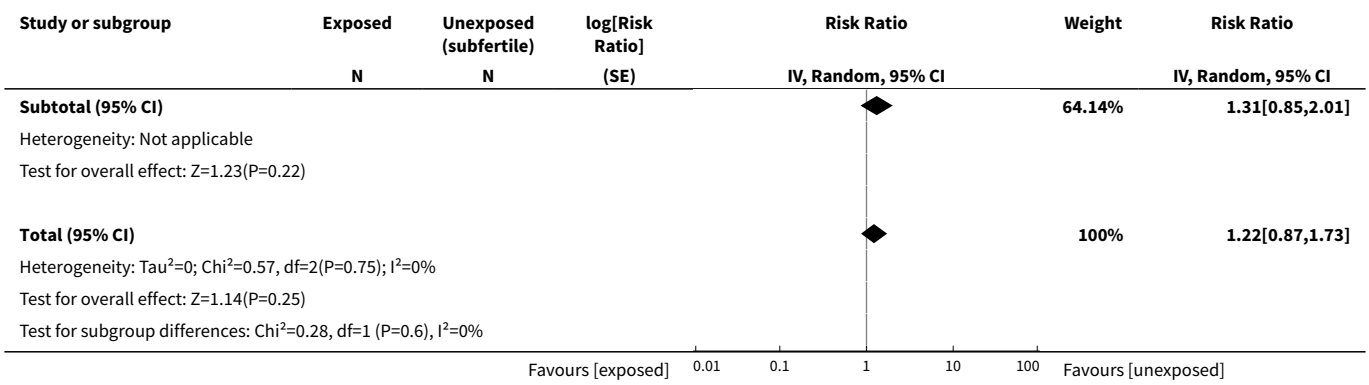
Comparison 15. Exposure to clomiphene; comparison group: subfertile; medium number of cycles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	3		Risk Ratio (Random, 95% CI)	1.22 [0.87, 1.73]
1.1 RR	2		Risk Ratio (Random, 95% CI)	1.08 [0.61, 1.92]
1.2 HR	1		Risk Ratio (Random, 95% CI)	1.31 [0.85, 2.01]

Analysis 15.1. Comparison 15 Exposure to clomiphene; comparison group: subfertile; medium number of cycles, Outcome 1 Endometrial cancer; subgroup by effect estimate.

Study or subgroup	Exposed N	Unexposed (subfertile) N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
15.1.1 RR						
Dos Santos Silva 2009	0	0	0.5 (0.762)		5.32%	1.58[0.35,7.04]
Jensen 2009	269	880	0 (0.318)		30.53%	1.01[0.54,1.88]
Subtotal (95% CI)					**35.86%**	**1.08[0.61,1.92]**
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%						
Test for overall effect: Z=0.26(P=0.79)						
15.1.2 HR						
Brinton 2013a	2455	6076	0.3 (0.22)		64.14%	1.31[0.85,2.01]

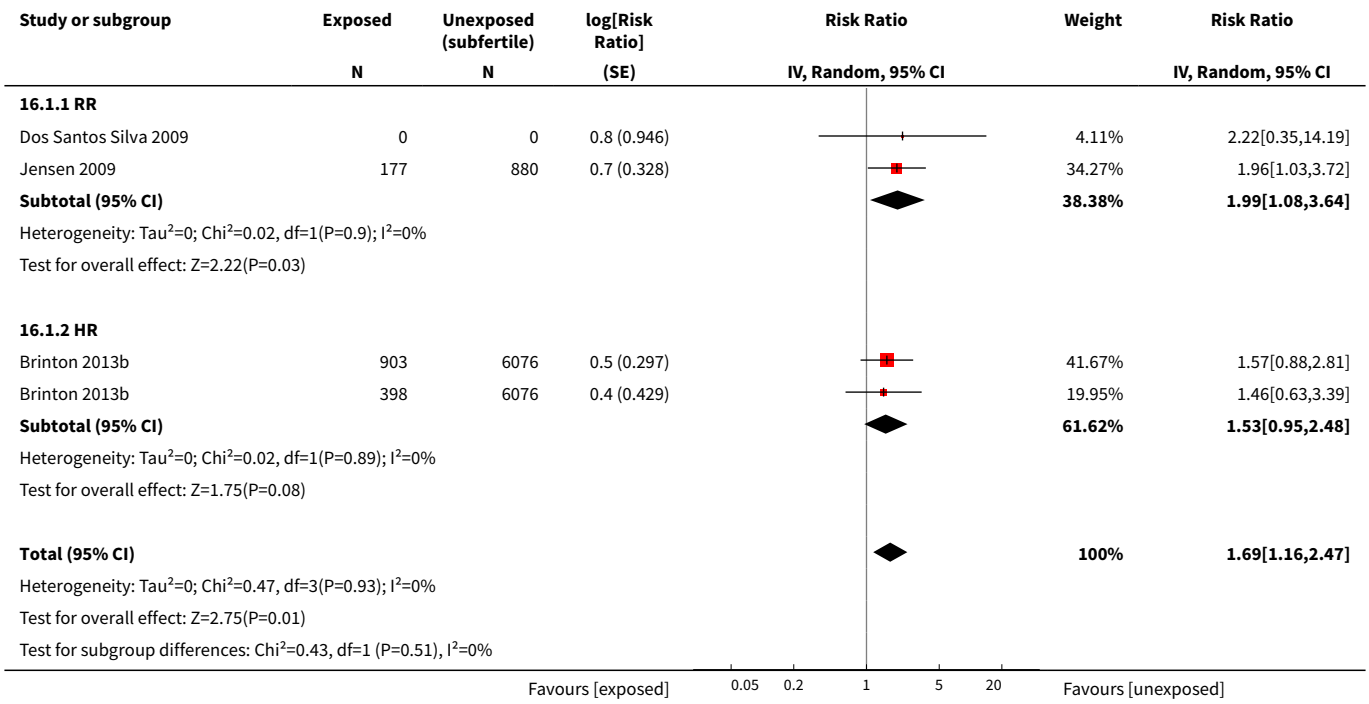
Favours [exposed] Favours [unexposed]



Comparison 16. Exposure to clomiphene; comparison group: subfertile; high number of cycles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	3		Risk Ratio (Random, 95% CI)	1.69 [1.16, 2.47]
1.1 RR	2		Risk Ratio (Random, 95% CI)	1.99 [1.08, 3.64]
1.2 HR	1		Risk Ratio (Random, 95% CI)	1.53 [0.95, 2.48]

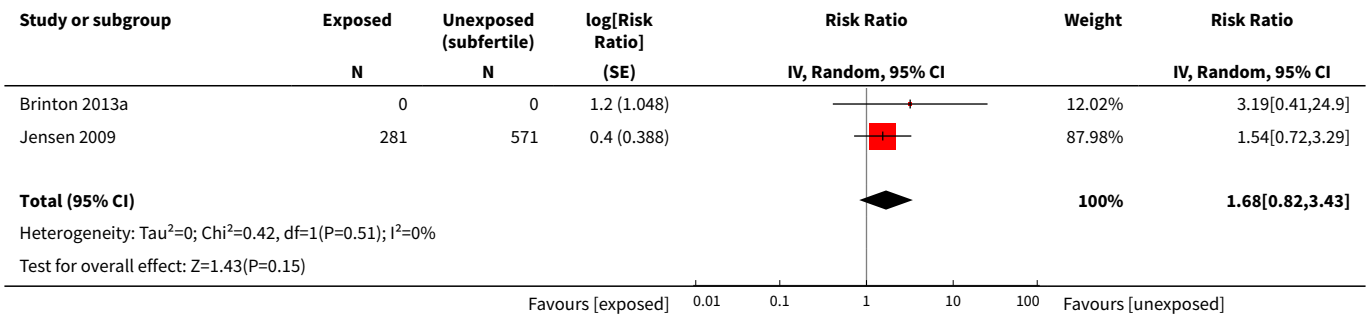
Analysis 16.1. Comparison 16 Exposure to clomiphene; comparison group: subfertile; high number of cycles, Outcome 1 Endometrial cancer; subgroup by effect estimate.



Comparison 17. Exposure to clomiphene; comparison group: subfertile: parous women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	2		Risk Ratio (Random, 95% CI)	1.68 [0.82, 3.43]

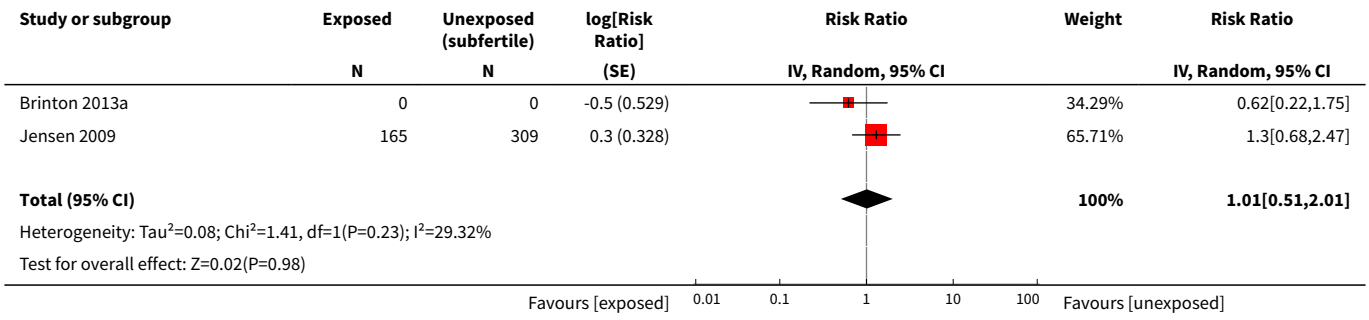
Analysis 17.1. Comparison 17 Exposure to clomiphene; comparison group: subfertile: parous women, Outcome 1 Endometrial cancer; subgroup by effect estimate.



Comparison 18. Exposure to clomiphene; comparison group: subfertile; nulliparous women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	1.01 [0.51, 2.01]

Analysis 18.1. Comparison 18 Exposure to clomiphene; comparison group: subfertile; nulliparous women, Outcome 1 Endometrial cancer.

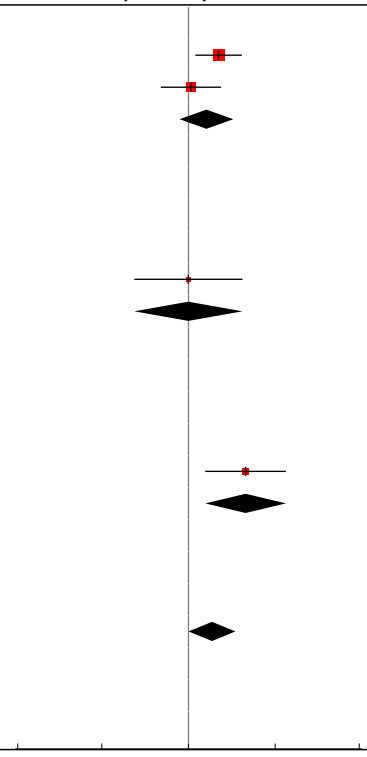


Comparison 19. Exposure to clomiphene; comparison group: general population; any

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	4	19614	Risk Ratio (Random, 95% CI)	1.87 [1.00, 3.48]
1.1 SIR	2	4106	Risk Ratio (Random, 95% CI)	1.61 [0.79, 3.29]
1.2 OR	1	683	Risk Ratio (Random, 95% CI)	1.00 [0.24, 4.19]
1.3 HR	1	14825	Risk Ratio (Random, 95% CI)	4.56 [1.56, 13.33]

Analysis 19.1. Comparison 19 Exposure to clomiphene; comparison group: general population; any, Outcome 1 Endometrial cancer; subgroup by effect estimate.

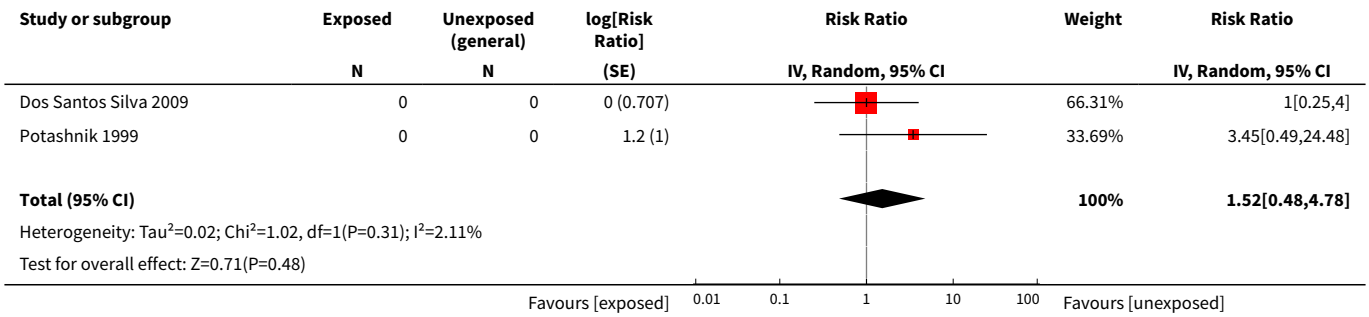
Study or subgroup	Exposed N	Unexposed (General) N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
19.1.1 SIR						
Dos Santos Silva 2009	2984	0	0.8 (0.316)		35.87%	2.22[1.2,4.13]
Lerner-Geva 2012	1122	0	0.1 (0.408)		29.02%	1.07[0.48,2.38]
Subtotal (95% CI)					**64.9%**	**1.61[0.79,3.29]**
Heterogeneity: Tau^2=0.14; Chi^2=2.02, df=1(P=0.16); I^2=50.38%						
Test for overall effect: Z=1.31(P=0.19)						
19.1.2 OR						
Benshushan 2001	12	671	-0 (0.733)		14.09%	1[0.24,4.19]
Subtotal (95% CI)					**14.09%**	**1[0.24,4.19]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.01(P=1)						
19.1.3 HR						
Calderon-Margalit 2009	362	14463	1.5 (0.547)		21.01%	4.56[1.56,13.33]
Subtotal (95% CI)					**21.01%**	**4.56[1.56,13.33]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.77(P=0.01)						
Total (95% CI)					**100%**	**1.87[1,3.48]**
Heterogeneity: Tau^2=0.18; Chi^2=5.57, df=3(P=0.13); I^2=46.16%						
Test for overall effect: Z=1.96(P=0.05)						
Test for subgroup differences: Chi^2=3.52, df=1 (P=0.17), I^2=43.2%						



Comparison 20. Exposure to clomiphene; comparison group: general population; low dosage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	1.52 [0.48, 4.78]

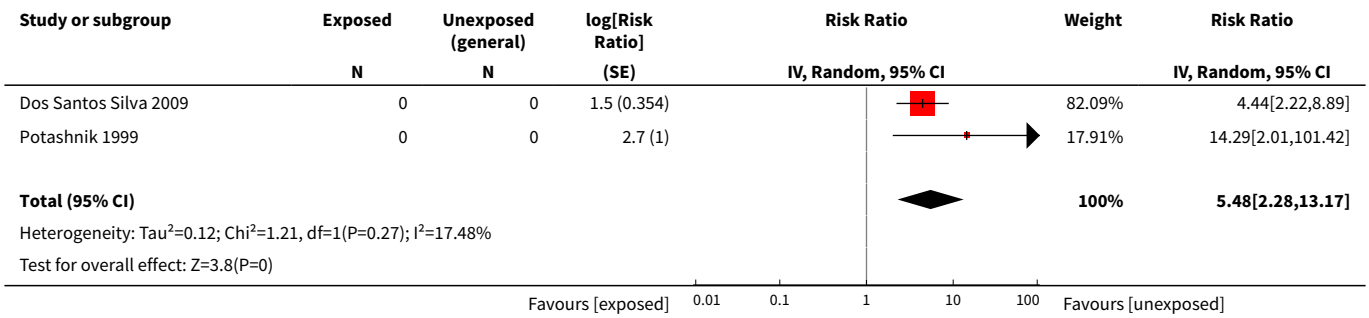
Analysis 20.1. Comparison 20 Exposure to clomiphene; comparison group: general population; low dosage, Outcome 1 Endometrial cancer.



Comparison 21. Exposure to clomiphene; comparison group: general population; high dosage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	5.48 [2.28, 13.17]

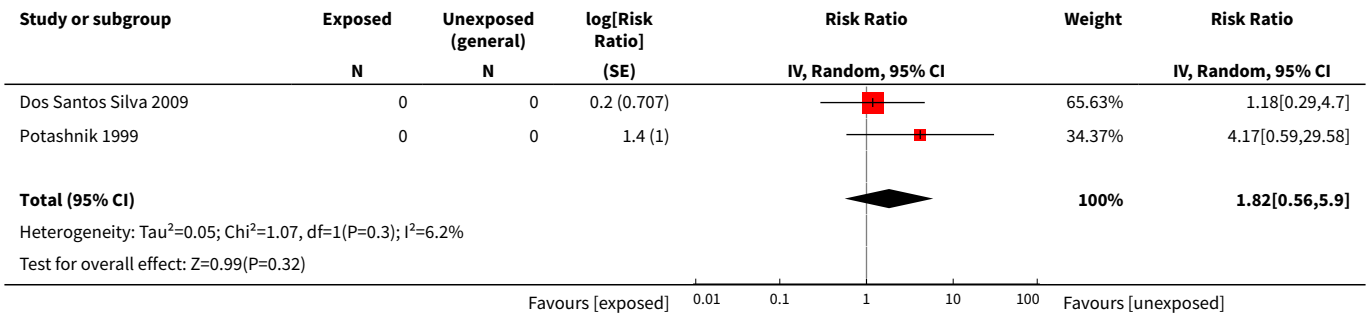
Analysis 21.1. Comparison 21 Exposure to clomiphene; comparison group: general population; high dosage, Outcome 1 Endometrial cancer.



Comparison 22. Exposure to clomiphene; comparison group: general population; low number of cycles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	1.82 [0.56, 5.90]

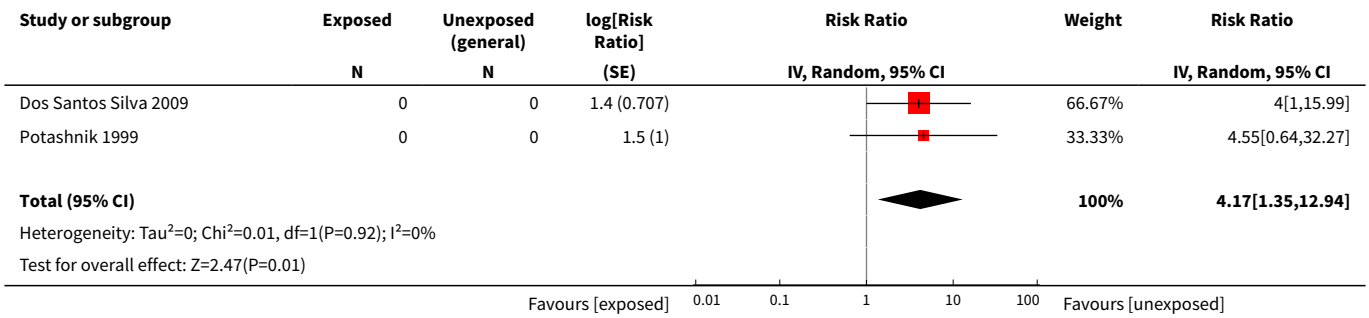
Analysis 22.1. Comparison 22 Exposure to clomiphene; comparison group: general population; low number of cycles, Outcome 1 Endometrial cancer.



Comparison 23. Exposure to clomiphene; comparison group: general population; high number of cycles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	4.17 [1.35, 12.94]

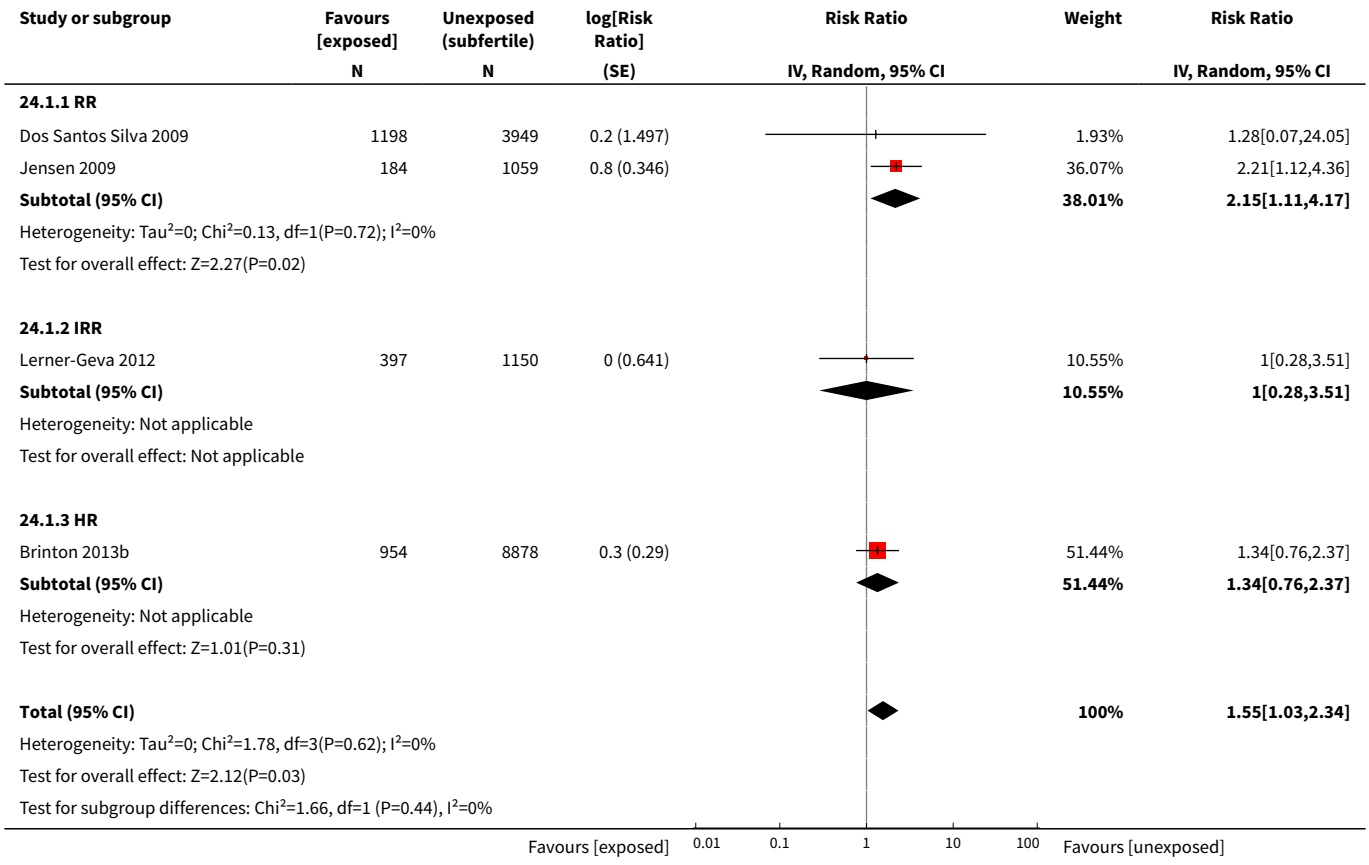
Analysis 23.1. Comparison 23 Exposure to clomiphene; comparison group: general population; high number of cycles, Outcome 1 Endometrial cancer.



Comparison 24. Exposure to gonadotropins; comparison group: subfertile; any

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	4	17769	Risk Ratio (Random, 95% CI)	1.55 [1.03, 2.34]
1.1 RR	2	6390	Risk Ratio (Random, 95% CI)	2.15 [1.11, 4.17]
1.2 IRR	1	1547	Risk Ratio (Random, 95% CI)	1.0 [0.28, 3.51]
1.3 HR	1	9832	Risk Ratio (Random, 95% CI)	1.34 [0.76, 2.37]

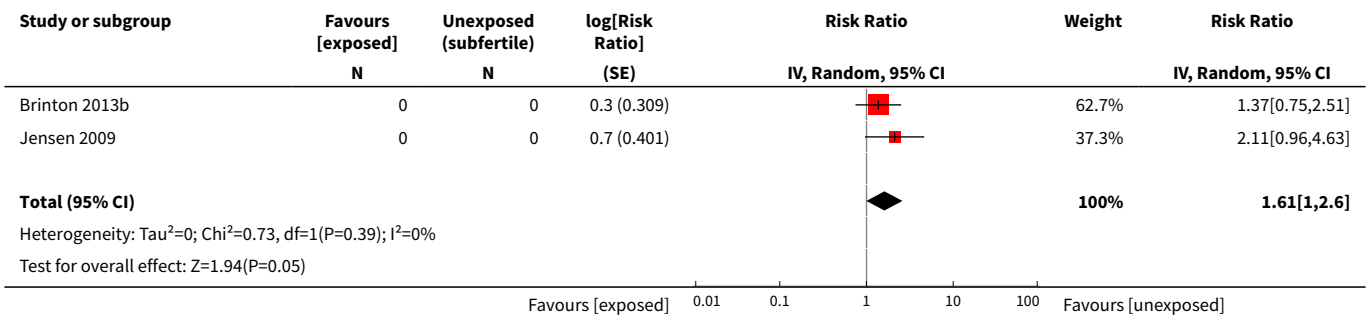
Analysis 24.1. Comparison 24 Exposure to gonadotropins; comparison group: subfertile; any, Outcome 1 Endometrial cancer; subgroup by effect estimate.



Comparison 25. Exposure to gonadotropins; comparison group: subfertile; medium number of cycles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	1.61 [1.00, 2.60]

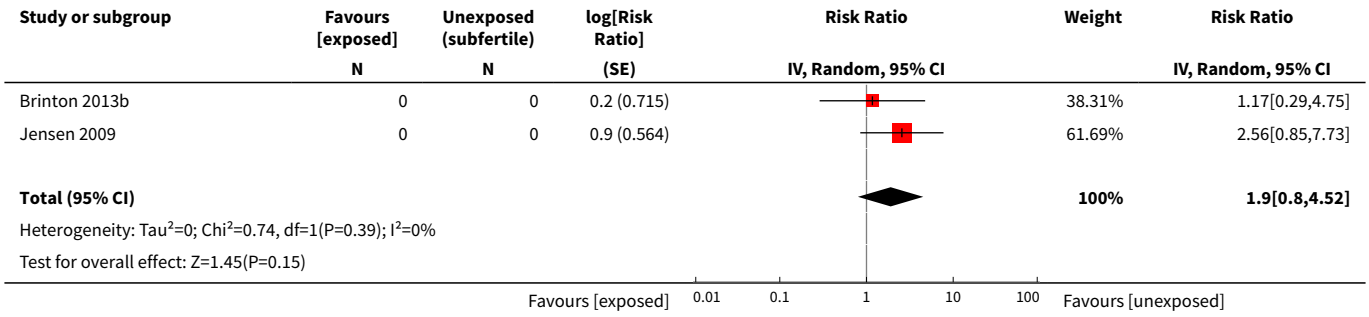
Analysis 25.1. Comparison 25 Exposure to gonadotropins; comparison group: subfertile; medium number of cycles, Outcome 1 Endometrial cancer.



Comparison 26. Exposure to gonadotropins; comparison group: subfertile; high number of cycles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	1.90 [0.80, 4.52]

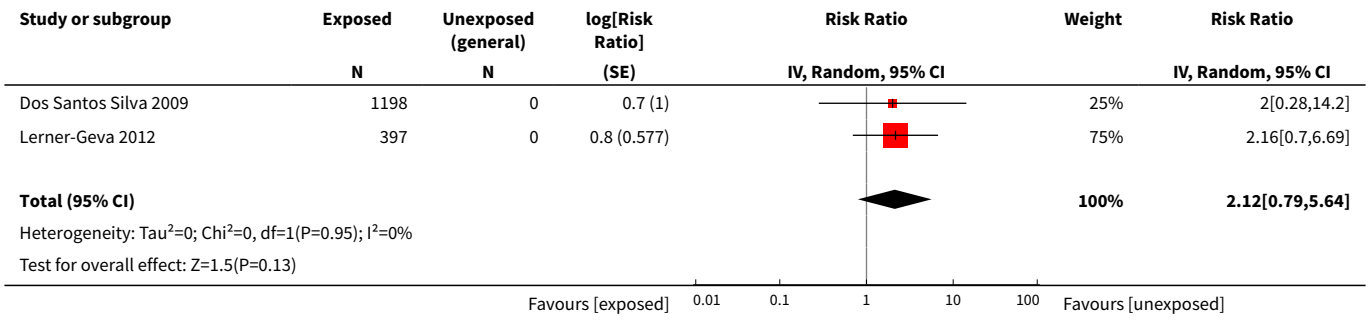
Analysis 26.1. Comparison 26 Exposure to gonadotropins; comparison group: subfertile; high number of cycles, Outcome 1 Endometrial cancer.



Comparison 27. Exposure to gonadotropins; comparison group: general population; any

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2	1595	Risk Ratio (Random, 95% CI)	2.12 [0.79, 5.64]

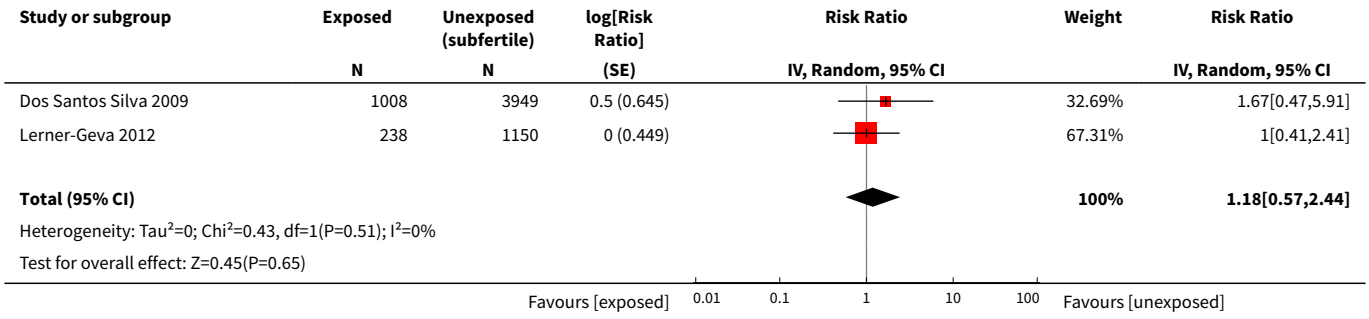
Analysis 27.1. Comparison 27 Exposure to gonadotropins; comparison group: general population; any, Outcome 1 Endometrial cancer.



Comparison 28. Exposure to clomiphene + gonadotropins; comparison group: subfertile; any

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2	6345	Risk Ratio (Random, 95% CI)	1.18 [0.57, 2.44]

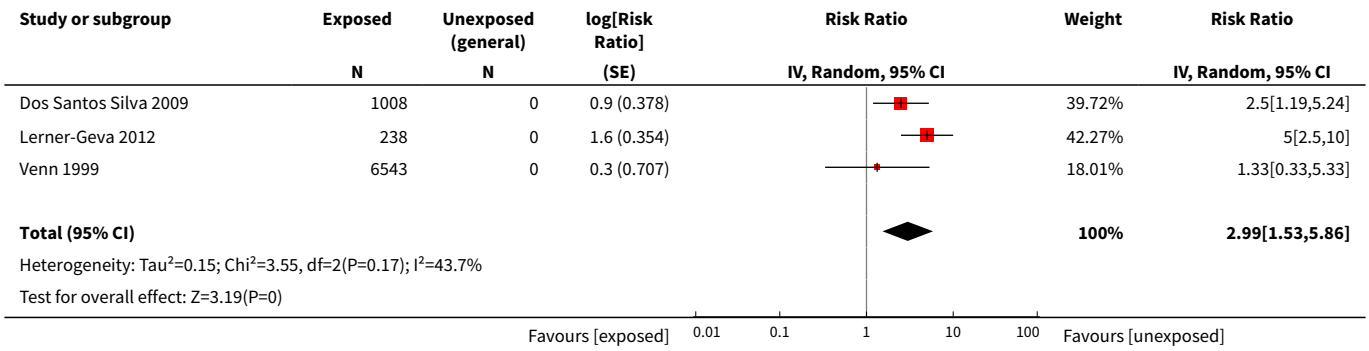
Analysis 28.1. Comparison 28 Exposure to clomiphene + gonadotropins; comparison group: subfertile; any, Outcome 1 Endometrial cancer.



Comparison 29. Exposure to clomiphene + gonadotropins; comparison group: general population; any

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	3	7789	Risk Ratio (Random, 95% CI)	2.99 [1.53, 5.86]

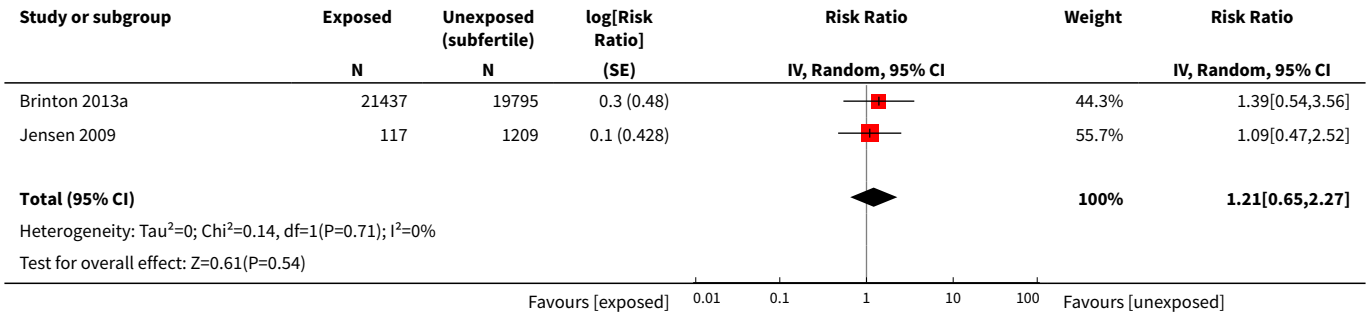
Analysis 29.1. Comparison 29 Exposure to clomiphene + gonadotropins; comparison group: general population; any, Outcome 1 Endometrial cancer.



Comparison 30. Exposure to GnRH; comparison group: subfertile; any

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2	42558	Risk Ratio (Random, 95% CI)	1.21 [0.65, 2.27]

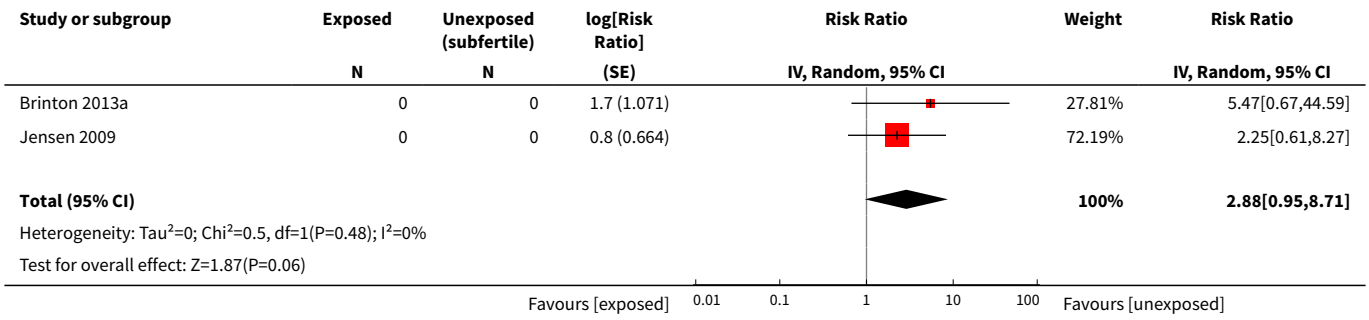
Analysis 30.1. Comparison 30 Exposure to GnRH; comparison group: subfertile; any, Outcome 1 Endometrial cancer.



Comparison 31. Exposure to GnRH; comparison group: subfertile; parous women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	2.88 [0.95, 8.71]

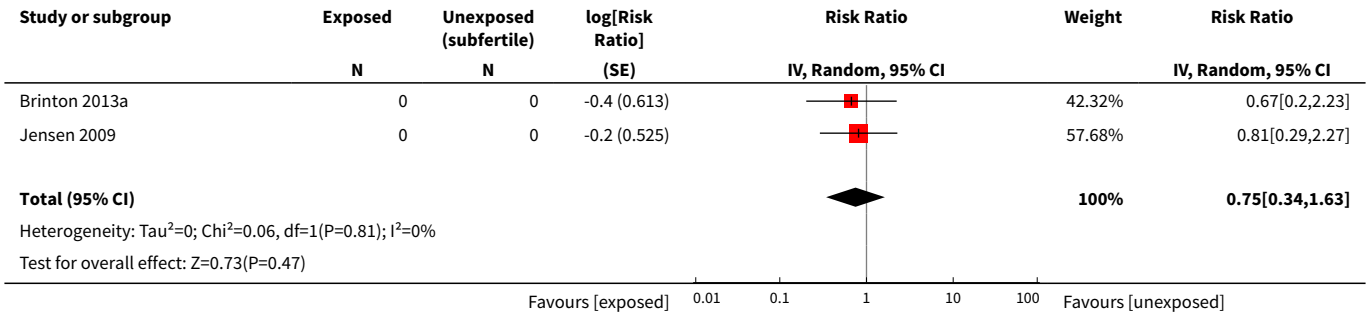
Analysis 31.1. Comparison 31 Exposure to GnRH; comparison group: subfertile; parous women, Outcome 1 Endometrial cancer.



Comparison 32. Exposure to GnRH; comparison group: subfertile; nulliparous women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2		Risk Ratio (Random, 95% CI)	0.75 [0.34, 1.63]

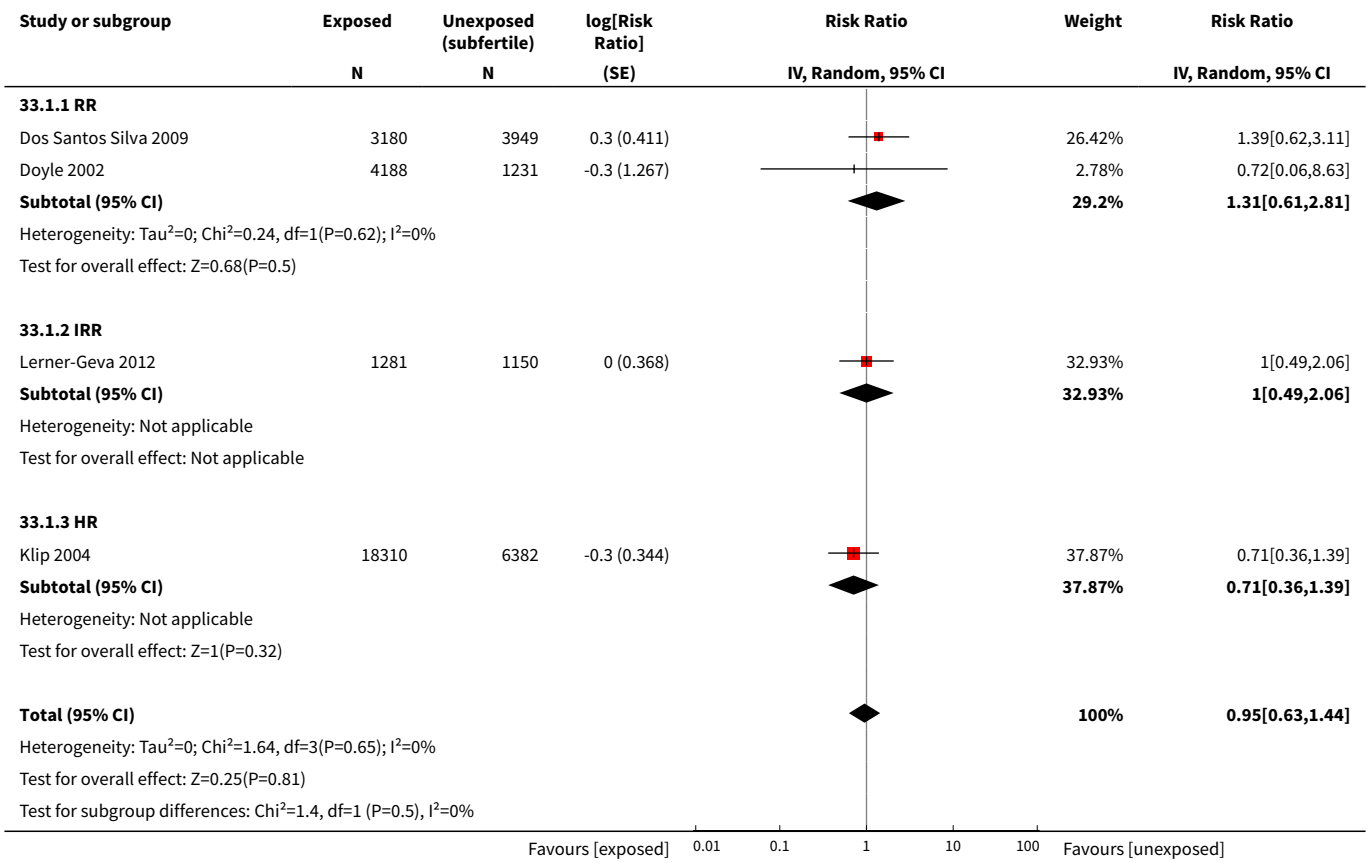
Analysis 32.1. Comparison 32 Exposure to GnRH; comparison group: subfertile; nulliparous women, Outcome 1 Endometrial cancer.



Comparison 33. Exposure to any drug; comparison group: subfertile; any; follow-up >10 years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	4	39671	Risk Ratio (Random, 95% CI)	0.95 [0.63, 1.44]
1.1 RR	2	12548	Risk Ratio (Random, 95% CI)	1.31 [0.61, 2.81]
1.2 IRR	1	2431	Risk Ratio (Random, 95% CI)	1.0 [0.49, 2.06]
1.3 HR	1	24692	Risk Ratio (Random, 95% CI)	0.71 [0.36, 1.39]

Analysis 33.1. Comparison 33 Exposure to any drug; comparison group: subfertile; any; follow-up >10 years, Outcome 1 Endometrial cancer; subgroup by effect estimate.

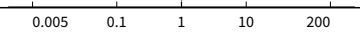


Comparison 34. Exposure to any drug; comparison group: general population; any; follow-up>10 years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	5	129209	Risk Ratio (Random, 95% CI)	2.52 [1.80, 3.53]
1.1 SIR	3	8148	Risk Ratio (Random, 95% CI)	2.17 [1.44, 3.26]
1.2 HR	1	15030	Risk Ratio (Random, 95% CI)	3.39 [1.28, 8.97]
1.3 RR	1	106031	Risk Ratio (Random, 95% CI)	3.52 [1.67, 7.41]

Analysis 34.1. Comparison 34 Exposure to any drug; comparison group: general population; any; follow-up>10 years, Outcome 1 Endometrial cancer; subgroup by effect estimate.

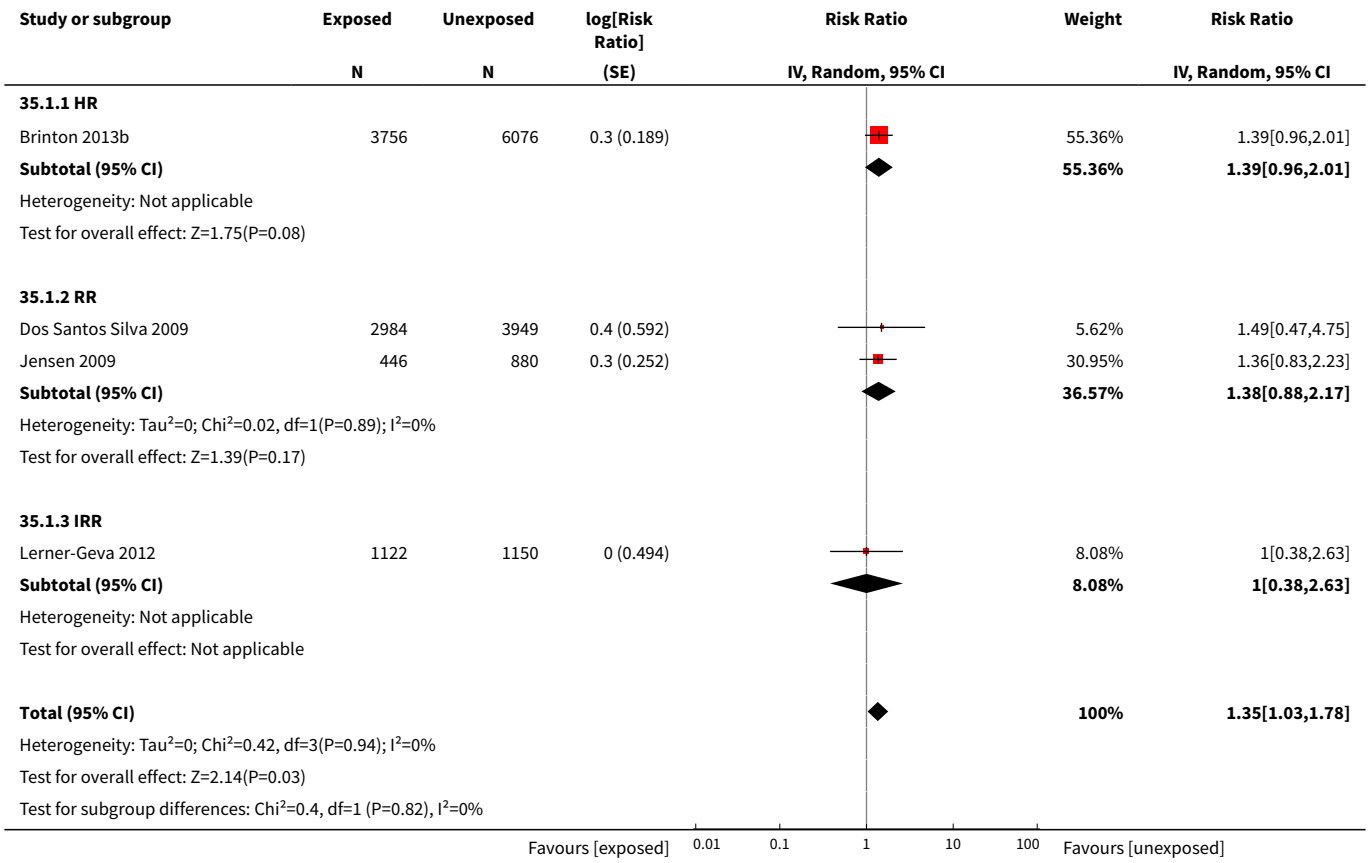
Study or subgroup	Exposed N	Unexposed (general) N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
34.1.1 SIR						
Dos Santos Silva 2009	3180	0	0.8 (0.236)		52.95%	2.31[1.45,3.66]
Doyle 2002	4188	0	0.2 (0.577)		8.83%	1.2[0.39,3.72]
Potashnik 1999	780	0	1.1 (0.707)		5.88%	2.99[0.75,11.94]
Subtotal (95% CI)					**67.66%**	**2.17[1.44,3.26]**
Heterogeneity: Tau^2=0; Chi^2=1.32, df=2(P=0.52); I^2=0%						
Test for overall effect: Z=3.71(P=0)						
34.1.2 HR						
Calderon-Margalit 2009	567	14463	1.2 (0.497)		11.92%	3.39[1.28,8.97]
Subtotal (95% CI)					**11.92%**	**3.39[1.28,8.97]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.46(P=0.01)						
34.1.3 RR						
Kessous 2016	4363	101668	1.3 (0.38)		20.41%	3.52[1.67,7.41]
Subtotal (95% CI)					**20.41%**	**3.52[1.67,7.41]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.32(P=0)						
Total (95% CI)					**100%**	**2.52[1.8,3.53]**
Heterogeneity: Tau^2=0; Chi^2=2.98, df=4(P=0.56); I^2=0%						
Test for overall effect: Z=5.4(P<0.0001)						
Test for subgroup differences: Chi^2=1.66, df=1 (P=0.44), I^2=0%						



Comparison 35. Exposure to clomiphene; comparison group: subfertile; any; follow-up>10 years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	4	20363	Risk Ratio (Random, 95% CI)	1.35 [1.03, 1.78]
1.1 HR	1	9832	Risk Ratio (Random, 95% CI)	1.39 [0.96, 2.01]
1.2 RR	2	8259	Risk Ratio (Random, 95% CI)	1.38 [0.88, 2.17]
1.3 IRR	1	2272	Risk Ratio (Random, 95% CI)	1.0 [0.38, 2.63]

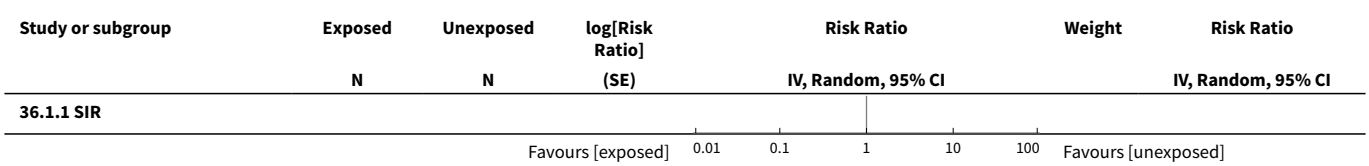
Analysis 35.1. Comparison 35 Exposure to clomiphene; comparison group: subfertile; any; follow-up>10 years, Outcome 1 Endometrial cancer; subgroup by effect estimate.

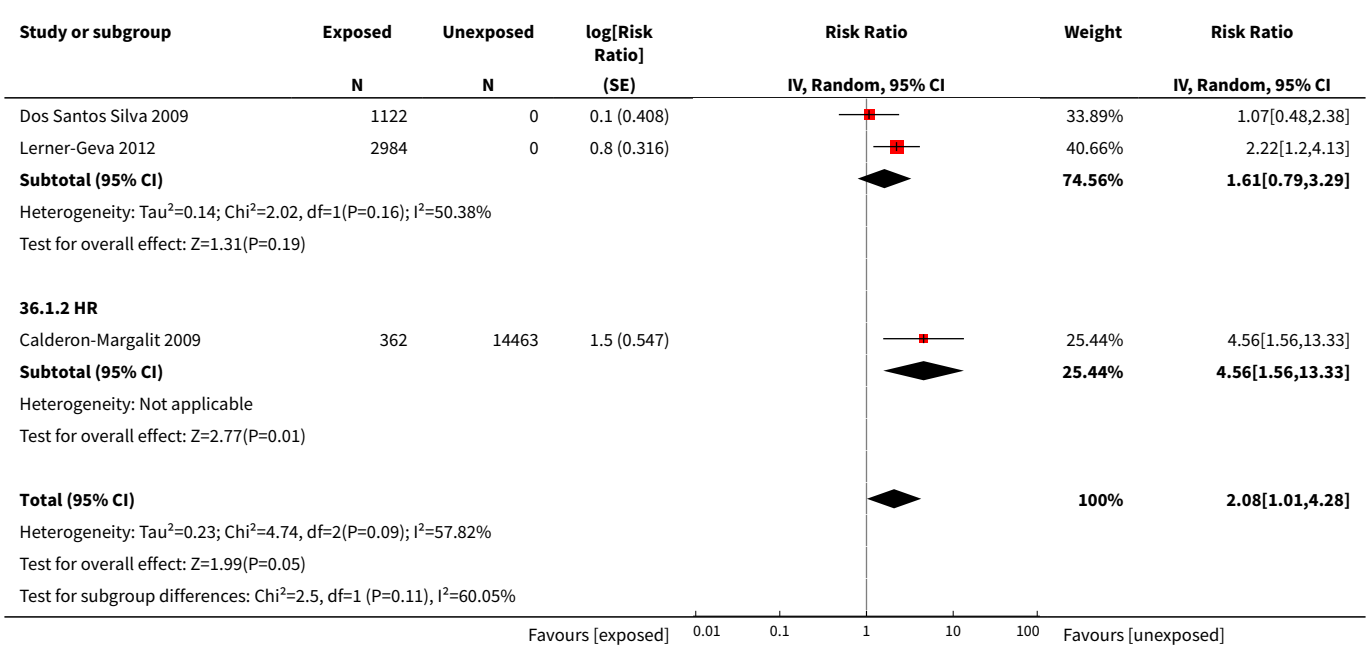


Comparison 36. Exposure to clomiphene; comparison group: general population; any; follow-up>10 years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	3	18931	Risk Ratio (Random, 95% CI)	2.08 [1.01, 4.28]
1.1 SIR	2	4106	Risk Ratio (Random, 95% CI)	1.61 [0.79, 3.29]
1.2 HR	1	14825	Risk Ratio (Random, 95% CI)	4.56 [1.56, 13.33]

Analysis 36.1. Comparison 36 Exposure to clomiphene; comparison group: general population; any; follow-up>10 years, Outcome 1 Endometrial cancer; subgroup by effect estimate.

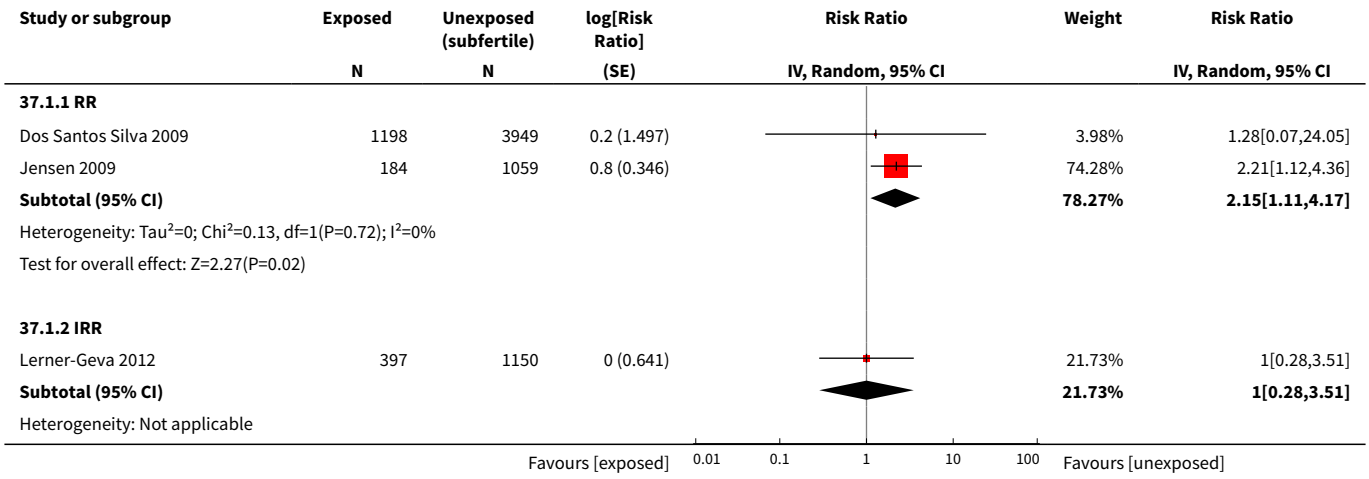


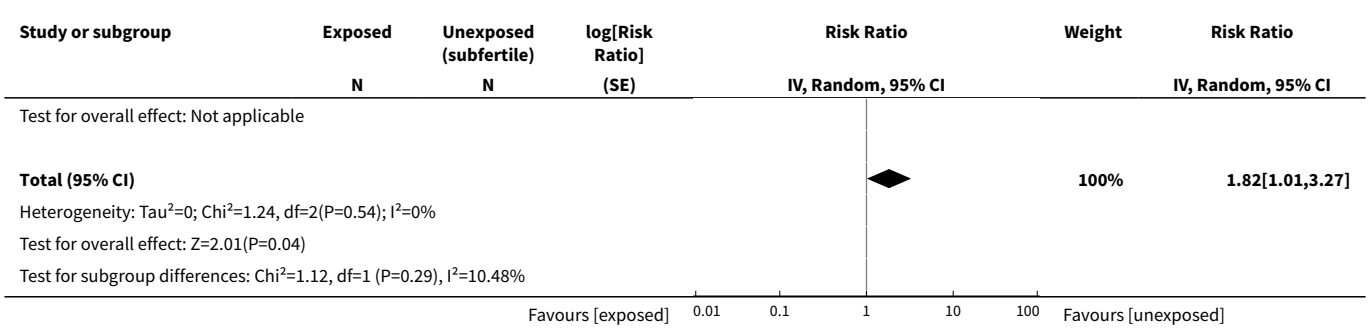


Comparison 37. Exposure to gonadotropins; comparison group: subfertile; any; follow-up>10 years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer; subgroup by effect estimate	3	7937	Risk Ratio (Random, 95% CI)	1.82 [1.01, 3.27]
1.1 RR	2	6390	Risk Ratio (Random, 95% CI)	2.15 [1.11, 4.17]
1.2 IRR	1	1547	Risk Ratio (Random, 95% CI)	1.0 [0.28, 3.51]

Analysis 37.1. Comparison 37 Exposure to gonadotropins; comparison group: subfertile; any; follow-up>10 years, Outcome 1 Endometrial cancer; subgroup by effect estimate.

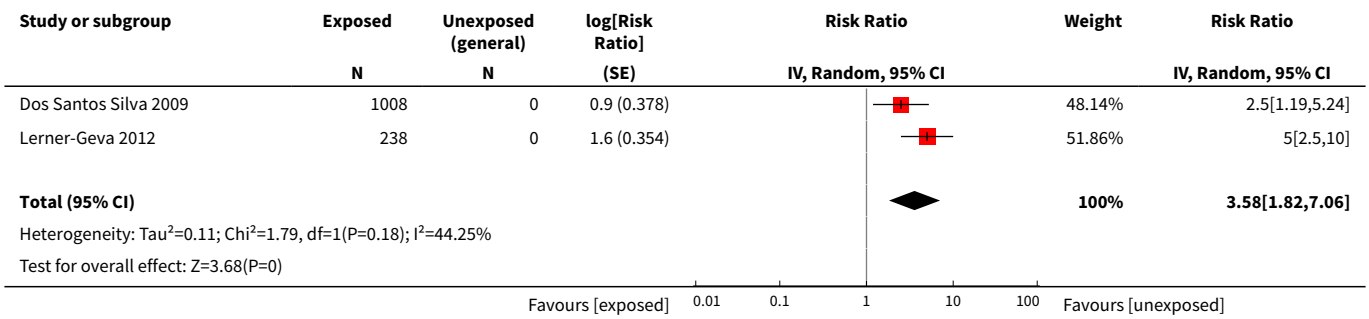




Comparison 38. Exposure to clomiphene + gonadotropins; comparison group: general population; any; follow-up>10 years

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial cancer	2	1246	Risk Ratio (Random, 95% CI)	3.58 [1.82, 7.06]

Analysis 38.1. Comparison 38 Exposure to clomiphene + gonadotropins; comparison group: general population; any; follow-up>10 years, Outcome 1 Endometrial cancer.



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Ovulation Induction] explode all trees
#2 (ovar* near/5 (stimulat* or hyperstimulat* or hyper-stimulat* or enhanced follicular recruitment)
#3 MeSH descriptor: [Fertility Agents] explode all trees
#4 ((fertil* or infertil* or subfertil*) near/5 (drug* or agent*)
#5 MeSH descriptor: [Reproductive Techniques, Assisted] explode all trees
#6 ((assist* near/5 reproduct*) or ART or (in vitro near/5 fertili*) or IVF or ICSI or intracytoplasmic sperminject ion)
#7 MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees
#8 (selective next (estrogen or oestrogen) next receptor next modulator*)
#9 (SERM* or tamoxifen or clomiphene or clomifen*)
#10 MeSH descriptor: [Gonadotropins] explode all trees
#11 MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees
#12 (gonadotropin* or luteinizing hormone* or follicle stimulating hormone* or LH or FSH or hMG or hCG or GnRH*)
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

#14 MeSH descriptor: [Uterine Neoplasms] explode all trees
#15 MeSH descriptor: [Endometrial Hyperplasia] explode all trees
#16 (endometr* or uter* or womb) near/5 (cancer* or carcinoma* or malignan* or neoplas* or tumor* or tumour* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or hyperplasia*)
#17 #14 or #15 or #16
#18 #13 and #17

Appendix 2. MEDLINE search strategy

1 exp Ovulation Induction/
2 (ovar* adj5 (stimulat* or hyperstimulat* or hyper-stimulat* or enhanced follicular recruitment).mp.
3 exp Fertility Agents/
4 ((fertil* or infertil* or subfertil*) adj5 (drug* or agent*).mp.
5 exp Reproductive Techniques, Assisted/
6 ((assist* adj5 reproduct*) or ART or (in vitro adj5 fertili*) or IVF or ICSI or intracytoplasmic sperm injection).mp.
7 exp Selective Estrogen Receptor Modulators/
8 (selective adj (estrogen or oestrogen) adj receptor adj modulator*).mp.
9 (SERM* or tamoxifen or clomiphene or clomifen*).mp.
10 exp Gonadotropins/
11 exp Gonadotropin-Releasing Hormone/
12 (gonadotropin* or luteinizing hormone* or follicle stimulating hormone* or LH or FSH or hMG or hCG or GnRH*).mp.
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 exp Uterine Neoplasms/
15 Endometrial Hyperplasia/
16 ((endometr* or uter* or womb) adj5 (cancer* or carcinoma* or malignan* or neoplas* or tumor* or tumour* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or hyperplasia*).mp.
17 14 or 15 or 16
18 13 and 17
19 randomized controlled trial.pt.
20 controlled clinical trial.pt.
21 randomized.ab.
22 placebo.ab.
23 drug therapy.fs.
24 randomly.ab.
25 trial.ab.
26 groups.ab.
27 exp Cohort Studies/
28 (cohort* or propsective* or retrospective*).mp.
29 exp case-control studies/
30 (case* and control*).mp.
31 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 18 and 31
33 exp animals/ not humans.sh.
34 32 not 33

key:
mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier
fs=floating subheading
ab=abstract

Appendix 3. Embase search strategy

1 ovulation induction/
2 (ovar* adj5 (stimulat* or hyperstimulat* or hyper-stimulat* or enhanced follicular recruitment).mp.
3 exp fertility promoting agent/
4 ((fertil* or infertil* or subfertil*) adj5 (drug* or agent*).mp.
5 exp infertility therapy/
6 ((assist* adj5 reproduct*) or ART or (in vitro adj5 fertili*) or IVF or ICSI or intracytoplasmic sperm injection).mp.
7 selective estrogen receptor modulator/
8 (selective adj (estrogen or oestrogen) adj receptor adj modulator*).mp.
9 (SERM* or tamoxifen or clomiphene or clomifen*).mp.
10 gonadotropin/

11 gonadorelin/
12 (gonadotropin* or luteinizing hormone* or follicle stimulating hormone* or LH or FSH or hMG or hCG or GnRH*).mp.
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 exp uterus tumor/
15 endometrium hyperplasia/
16 ((endometr* or uter* or womb) adj5 (cancer* or carcinoma* or malignan* or neoplas* or tumor* or tumour* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or hyperplasia*).mp.
17 14 or 15 or 16
18 13 and 17
19 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 cohort analysis/
34 (cohort* or prospective* or retrospective*).mp.
35 exp case control study/
36 (case* and control*).mp.
37 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
38 13 and 18 and 37
39 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
40 38 not 39

key:
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

Appendix 4. Data extraction form

General information
Title
Author
Year
Journal
Geographical setting (country, region)
Clinical setting
Study characteristics
Study period
Study design

(Continued)

Cohort size (for cohort studies only)
Cohort characteristics (for cohort studies only)
Number of incident cases in the cohort (for cohort studies only)
Number of cases (for case-control studies only)
Number of controls (for case-control studies only)
Reference group (general population or subfertile women)
Characteristics of participants
Inclusion and exclusion criteria
Mean age of total cohort (for cohort studies only)
Mean age of exposed women (for cohort studies only)
Mean age of cases (for case-control studies only)
Mean age of controls (for case-control studies only)
Race
Gynaecological and reproductive history
Gravidity
Parity
Definition of infertility
Type of infertility
Histology
Interventions
Type and agent of fertility treatment
Dosage of fertility treatment
Number of fertility treatment cycles
Age at time of first fertility treatment
Years since time since first fertility treatment
Results
Effect estimate type
Exclusion of first year of follow-up

(Continued)

Subanalyses provided
Effect estimate (maximally adjusted)
Lower confidence limit
Upper confidence limit
Data for recalculation or de novo estimation of measures
Observed number of exposed cases (for cohort studies only)
Observed number of unexposed cases (for cohort studies only)
Expected number of exposed cases (for cohort studies only)
Expected number of unexposed cases (for cohort studies only)
Total number of person-years among exposed cases (for cohort studies only)
Total number of person-years among unexposed cases (for cohort studies only)
Number of exposed cases (for case-control studies only)
Number of exposed controls (for case-control studies only)
Assessment of risk of bias
Consecutive series of cases (for case-control studies)
Population-based or hospital-based controls (for case-control studies)
Controls derived from the same population as cases (for case-control studies)
Non-exposed women drawn from the same population as the exposed cohort (for cohort studies)
Matching factors
Adjusting factors
Ascertainment of exposure
Ascertainment of cancer
Mean follow-up in total cohort (for cohort studies only)
Mean follow-up in exposed women (for cohort studies only)
At least 80% of women in all groups included in the final analysis

CONTRIBUTIONS OF AUTHORS

- Skalkidou A: conceived the idea of the review, contributed to study design, critical evaluation of the studies, extraction of data and interpretation of the findings, provided clinical gynaecological expertise, and prepared the draft.

- Sergentanis TN: conceived of the idea of the review, contributed to study design, critical evaluation of the studies, extraction of data and interpretation of the findings, performed statistical analysis, and prepared the draft.
- Gialamas SP: contributed to study design, critical evaluation of the studies, extraction of data and interpretation of the findings, and prepared the draft.
- Georgakis MK: contributed to study design, critical evaluation of the studies, extraction of data and interpretation of the findings, performed statistical analysis, and prepared the draft.
- Psaltopoulou T: contributed to study design, critical evaluation of the studies, extraction of data and interpretation of the findings, provided endocrinological clinical expertise, and prepared the draft.
- Trivella M: contributed to study design, critical evaluation of the studies, extraction of data and interpretation of the findings, provided statistical and methodological expertise, and prepared the draft.
- Siristatidis CS: contributed to study design, critical evaluation of the studies, extraction of data and interpretation of the findings, provided clinical gynaecological expertise, and prepared the draft.
- Evangelou E: contributed to study design, critical evaluation of the studies, extraction of data and interpretation of the findings, performed statistical analysis, provided statistical and methodological expertise, and prepared the draft.
- Petridou ET: conceived of the idea, contributed to study design, critical evaluation of the studies, extraction of data and interpretation of the findings, performed statistical analysis, selected coauthors, provided training, convened meetings, prepared the draft, provided final approval, and acted as a guarantor of the study protocol.

All review authors reviewed and approved the final version of the review.

DECLARATIONS OF INTEREST

- Skalkidou A: None known
- Sergentanis TN: None known
- Gialamas SP: None known
- Psaltopoulou T: None known
- Georgakis MK: None known
- Trivella M: None known
- Siristatidis CS: None known
- Evangelou E: Coinvestigator and site co-PI for grants from EFSA and FP7
- Petridou ET: My previous position as training co-ordinator and as a statistical editor/referee for Cochrane groups (Anaesthesia, Wounds, Breast Cancer, and Sexually Transmitted Infections), are independent of my involvement in this review. I declare that my involvement here as an author has no related financial relationships.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A broader search strategy was used for the purposes of this review, compared to the algorithm stated in the protocol. All algorithms were developed and run by Jane Hayes and Jo Platt, the Information Specialists for the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.

Regarding the 'risk of bias' assessment, slight modifications were implemented after team consensus. In particular, comparability on the cause of subfertility were added to comparability of groups, PCOS was added to confounding/adjustment factors, and blinding of participants and personnel regarding the allocated interventions was evaluated with regards to performance bias. It was initially also planned to create a separate table with confounding and adjustment factors that were controlled by each study; however, all relevant data pertaining to the adjustment factors are now available in the 'Risk of bias' tables (subsection 'Selection bias (confounding)') and we considered that the construction of a separate table would be redundant.

Furthermore, although we aimed to use the Robins tool for assessment of risk of bias, as this was not yet available at the start of the review process, a customized version of the Newcastle-Ottawa scale was used instead, in accordance with a previous Cochrane review (Rizzuto 2013).

Lastly, we did not transform effect estimates, if they were reported differently within studies, as stated in the protocol, but we rather pooled the effect estimates, presenting also subgroup analyses by type of effect estimate, to ensure the objective presentation of our data to the scientific audience. As endometrial cancer is a rather rare outcome, we believe that this approach is the most appropriate. We came to this decision following discussions with our methodology expert, Dr. Trivella and team consensus. This approach was also in accordance with our previously published meta-analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Case-Control Studies; Chorionic Gonadotropin [administration & dosage] [adverse effects]; Clomiphene [administration & dosage] [*adverse effects]; Drug Therapy, Combination [adverse effects]; Endometrial Neoplasms [*chemically induced] [epidemiology]; Fertility Agents, Female [administration & dosage] [*adverse effects]; Gonadotropin-Releasing Hormone [administration & dosage] [adverse effects]; Gonadotropins [*adverse effects]; Infertility, Female [complications] [*drug therapy]; Ovulation Induction; Retrospective Studies; Risk

MeSH check words

Female; Humans