Human Reproduction Update, Vol.19, No.2 pp. 105–123, 2013
Advanced Access publication on December 18, 2012 doi:10.1093/humupd/dms051

human reproduction update

Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer—a systematic review and meta-analysis

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Submitted on July 25, 2012; resubmitted on October 4, 2012; accepted on October 23, 2012

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BACKGROUND: In response to the ongoing debate on the long-term effects of assisted reproduction technologies, such as IVF, we systematically reviewed and meta-analyzed available evidence on the association between controlled ovarian hyperstimulation for IVF and risk of ovarian, endometrial and cervical cancer.

METHODS: Eligible studies were identified and pooled effect estimates for relative risk (RR) were calculated by cancer type among two reference groups (general population or infertile women), through fixed- or random-effects models as appropriate.

RESULTS: Nine cohort studies were synthesized, corresponding to a total size of 109 969 women exposed to IVF, among whom 76 incident cases of ovarian, 18 of endometrial and 207 cases of cervical cancer were studied. The synthesis of studies with general population as the reference group pointed to a statistically significant positive association between IVF and increased risk for ovarian (RR = 1.50, 95%

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confidence interval (CI): 1.17–1.92) and endometrial (RR = 2.04, 95% CI: 1.22–3.43), but not cervical (RR = 0.86, 95% CI: 0.49–1.49) cancers. On the contrary, when infertile women were used as the reference group, no significant associations with ovarian, endometrial or cervical cancer types were noted (RR = 1.26, 95% CI: 0.62–2.55 RR = 0.45, 95% CI: 0.18–1.14 and RR = 5.70, 95% CI: 0.28–117.20, respectively).

CONCLUSIONS: IVF does not seem to be associated with elevated cervical cancer risk, nor with ovarian or endometrial cancer when the confounding effect of infertility was neutralized in studies allowing such comparisons. Of note, only one study provided follow-up longer than 10 years for the group exposed to IVF. Future cohort studies should preferably use infertile women as the reference group, rely on IVF-registered valid exposure data, adjust for a variety of meaningful confounders and adopt relatively longer follow-up periods before sound conclusions are drawn.

Key words: ovarian cancer / endometrial cancer / cervical cancer / infertility / IVF

Introduction

Prevention and treatment of subfertility is an emerging public health priority in developed countries (Wright *et al.*, 2005; CDC, 2010). In the USA alone a dismal figure of up to 7.7 million women of fertile age (15–44 years) are estimated to seek medical advice for fertility problems by the year 2025 (Stephen and Chandra, 1998). Postponement of the first pregnancy to a later age on account of the need to pursue career opportunities, along with the growing awareness of treatment options, are linked with advanced maternal age, whereas ovarian ageing and infertility seem counterbalanced by the success of assisted reproduction technologies (ARTs) (Connolly *et al.*, 2009; Kimberly *et al.*, 2012). As a result, an upward trend in the number of women receiving subfertility treatment has been noted; nowadays, a large proportion of these women are undergoing ovarian stimulation and IVF.

Reports on a tentative association between fertility medication received for ovarian stimulation and several types of gynaecological cancer, notably ovarian, endometrial and cervical types, have emerged since the mid-1960s, but sound scientific evidence is still limited. The earlier published positive findings (Whittemore *et al.*, 1992; Rossing *et al.*, 1994; Akhmedkhanov *et al.*, 2001b; Brinton *et al.*, 2005; Brinton, 2007) were subject to several limitations, including small sample size, bias, imprecise information on drug exposure, namely type and duration of treatment and indications; furthermore, a lack of control for important confounding factors, such as causes of subfertility, parity or family history of cancer is noted. In addition, most studies tended to suffer from insufficient follow-up periods thereby preventing the accurate calculation of long-term treatment effect estimates (Land and Evers, 2003; Kashyap *et al.*, 2004; Brinton *et al.*, 2005; Mahdavi *et al.*, 2006; Choi *et al.*, 2007; Cetin *et al.*, 2008; Jensen *et al.*, 2008, 2009a, b; Källén, 2008; Zreik *et al.*, 2008; Vlahos *et al.*, 2010a; Impicciatore and Tiboni, 2011). Actually, the evidence regarding a tentative direct tumorigenic effect of fertility medication for ovarian stimulation is weak and controversial and relies mainly on *in vitro* studies (Huhtaniemi, 2010).

Specific types of gynecological cancers have been traditionally associated with early age of menarche and late age of menopause (Vo and Carney, 2007), low parity, infertility (Stadel, 1975; Ron *et al.*, 1987; Dahlgren *et al.*, 1991; Brinton *et al.*, 1992, 2004; Adami *et al.*, 1994; Venn *et al.*, 1995; Bristow and Karlan, 1996; Meirow and Schenker, 1996; Klip *et al.*, 2000; Ness *et al.*, 2002; Brinton, 2007; Cetin *et al.*, 2008; Jensen *et al.*, 2008, 2009a, b; Källén, 2008; Salehi *et al.*, 2008; Zreik *et al.*, 2008; Sueblinvong and Carney, 2009), tubal factor and unexplained infertility (Venn *et al.*, 1999; Ness *et al.*, 2002; Cetin *et al.*, 2008), as well as ovulatory disorders, such as polycystic ovary syndrome (PCOS) (Escobedo *et al.*, 1991; Rossing *et al.*, 1994; Homburg, 1996; Schildkraut *et al.*, 1996; Gregory *et al.*, 2002), endometriosis (Brinton *et al.*, 2004; Ness and Modugno, 2006; Vlahos *et al.*, 2010b) and germline mutations in *BRCA* genes associated with occult primary ovarian insufficiency (Whittemore *et al.*, 1992; Goshen *et al.*, 1998; Brinton *et al.*, 2004; Cetin *et al.*, 2008; Källén, 2008; Zreik *et al.*, 2008; Oktay *et al.*, 2010; Impicciatore and Tiboni, 2011; Källén *et al.*, 2011). The use of gonadotrophins along with other medications is considered a necessary step for controlled ovarian hyperstimulation (COH) in IVF, so as to maximize the chances of a positive outcome; their popularity as the preferred prescription has been steadily increasing over the last 30 years (Wysowski, 1993). Gonadotrophins are known to induce a variety of biological effects in the epithelium; changes in cell proliferation, apoptosis, cell adhesion and chemosensitivity have been frequently reported (Risch, 1998; Konishi *et al.*, 1999; Konishi, 2006) along with up to a five-fold increase in normal blood concentrations of estradiol (MacLachlan *et al.*, 1989). In order to inhibit a premature rise in LH and prevent ovulation, GnRH agonists and antagonists are the most frequently used components of the regimens; small continuous doses of agonists exert a reversible biochemical castration by removing the overlay of gonadal steroids (Conn and Crowley, 1994), while antagonists directly prevent a premature rise of LH (Olivennes, 2006).

Epithelial ovarian cancer is the sixth most common cancer among females (Permuth-Wey and Sellers, 2009), accounting for 4% of all cases (Meirow and Schenker, 1996), and the most life-threatening gynecological cancer with a 5-year survival of only 30–35% (Ahmed *et al.*, 1996). Several theories have been developed for ovarian tumorigenesis, including 'Fathalla's incessant ovulation' (Fathalla, 1971; Casagrande *et al.*, 1979), puncture trauma during oocyte retrieval (Merviel *et al.*, 2009), depletion of ovarian follicles (Smith and Xu, 2008), inflammation (Ness and Cottreau, 1999), stromal entrapment of the surface epithelium (Cramer and Welch, 1983) and endometriosis (Paulson, 1997; Ness and Modugno, 2006). Others pertain to the role of androgen/progesterone (Risch, 1998; Cottreau *et al.*, 2003), and gonadotrophins combined with the presence of estrogens and growth factor receptors (Stadel, 1975; Cramer and Welch, 1983; Wimalasena *et al.*, 1992; Bast *et al.*, 1993; Lukanova and Kaaks, 2005; Konishi, 2006; Choi *et al.*, 2007; Huhtaniemi, 2010). The underlying pathophysiological mechanisms implicate increased serum gonadotrophins (Mohle *et al.*, 1985; Shoham, 1994) and steroid levels (Fishel and Jackson, 1989; Clinton and Hua,

1997; Bai *et al.*, 2000; Kraemer *et al.*, 2001). The inflammatory environment (Ness and Cottreau, 1999), the increased cell proliferation and transformation of surface cells (Bai *et al.*, 2000; Parrott *et al.*, 2001; Choi *et al.*, 2002) and/or the compromised DNA synthesis and subsequent errors (Murdoch, 2003; Tonguç *et al.*, 2011) may constitute further mechanisms. Finally, an altered paracrine activity (Wang *et al.*, 2002; Hu *et al.*, 2003; Choi *et al.*, 2005), the expression of molecular activators and genes (Chien *et al.*, 1994; Doraiswamy *et al.*, 2000; Gregory *et al.*, 2002; Rimon *et al.*, 2004; Choi *et al.*, 2005) and induction of immune tolerance (Bukovsky, 2006; Labidi-Galy *et al.*, 2011) together with the protein kinase C pathway (Ohtani *et al.*, 2001; Sheng *et al.*, 2003) may contribute to the pathogenesis. Moreover, surprisingly, recent findings implicated the Fallopian tube fimbria as a possible site of origin of ovarian carcinomas (Karst and Drapkin, 2010). Direct attribution remains, however, controversial (Balen, 1995; Glud *et al.*, 1998; Roger *et al.*, 1998; Zheng *et al.*, 2000; Akhmedkhanov *et al.*, 2001a; Basille *et al.*, 2006; Choi *et al.*, 2007; Huhtaniemi, 2010).

Endometrial cancer, the most common malignancy of the lower female genital tract, accounting for 8% of all cases (Boring *et al.*, 1994; Bamberger *et al.*, 1998; Akhmedkhanov *et al.*, 2001a), is a hormone-dependent malignancy in the majority of cases. Actually, a hyper-estrogenic milieu and changes in endometrial secretory profiles through higher concentrations of various molecules caused by supra-physiological gonadotrophin levels during COH (Fishel and Jackson, 1989; Boomsma *et al.*, 2010) represent risk factors. Of note, PCOS (through anovulation) and unexplained infertility have also been linked directly to endometrial cancer (Escobedo *et al.*, 1991; Homburg, 1996; Venn *et al.*, 1999; Gregory *et al.*, 2002; Navaratnarajah *et al.*, 2008).

Cervical cancer has been linked to factors causing infertility, such as pelvic adhesions or tubal stenosis on account of previous pelvic infections (Dor *et al.*, 2002; Lerner-Geva *et al.*, 2003), whereas nowadays human papilloma virus is considered the main risk factor for the disease. Similarly, higher rates of human papilloma virus (Spandorfer *et al.*, 2006) and/or abnormal cervical smears (van Hamont *et al.*, 2006) have been associated with higher numbers of cervical procedures, hence an increased need for multiple IVF attempts (Jakobsson *et al.*, 2008); yet, these claims have been disputed by others (Strehler *et al.*, 1999; Källén *et al.*, 2011).

The aim of this study is to systematically review and meta-analyze the published studies on the association between COH for IVF and risk of ovarian, endometrial and cervical cancers. Furthermore, we attempted to disentangle the confounding effect of infertility through subanalyses on studies using infertile women as the reference group, as contrasted to those using general population reference groups, after adjustment for meaningful available confounding factors. RCTs on this topic have not been performed for ethical reasons; hence, the review is by necessity restrained solely to non-randomized study designs.

Methods

This systematic review was conducted in accordance with the PRISMA guidelines (Liberati *et al.*, 2009) and in line with the *a priori* protocol agreed by all authors.

Search strategy for the identification of studies

A broad range search strategy was developed for Ovid Medline (Supplementary data, Fig. S1), with no language or study design restrictions and a search period running from 1966 to May 2012. Reference lists of relevant articles were hand searched for potentially eligible studies ('snowball' procedure). The National Institute of Clinical Excellence (NICE) fertility assessment and treatment guidelines (NICE, 2004) were also hand searched. Relevant 'Letters to the Editor' on previously published or unpublished series were examined for potentially useable data and/or information.

Study authors were contacted, in most cases successfully, for methodological clarifications—especially regarding duplicate cohorts—and retrieval of missing data.

Study Eligibility

Studies comparing the risk of ovarian, endometrial or cervical cancers among women undergoing all regimens and COH protocols for IVF using the general population or infertile women as reference populations were considered in this systematic review.

We excluded case series and case reports, *in vitro* and animal studies, and studies exclusively assessing the treatment of cancer or fertility preservation after cancer treatment. Whole studies or subpopulations of studies reporting on benign or borderline tumors were not included; indeed, published results regarding borderline tumors of the ovary in association with ART exposure may well differ from those presented herein. Additionally, studies of ovarian stimulation for ovulation induction for sexual intercourse or intrauterine insemination and not for IVF were also excluded, as the protocol of treatment in these cases is different from that used in IVF (lack of GnRH agonist or antagonist use and usually lower doses of gonadotrophins).

Data extraction

Three authors (P.K., T.N.S. and M.T.) designed and pilot-tested an *ad hoc* developed excel sheet for data extraction, which was eventually approved by the authors' team.

Collected data included general information (title, author, year, journal, geographical and clinical setting), study characteristics (design, follow-up, inclusions/exclusions), participants' characteristics [age, ascertainment of exposure and outcome, dose and protocol of IVF, histology, type of infertility, stimulation drugs before IVF, matching factors (if applicable)] and results, i.e. number of participants, reference population, odds ratio (OR), hazard ratio (HR), standardized incidence ratio (SIR), incidence rate ratio (IRR) as reported, and associated raw data for re-calculation (data checking) or *de novo* estimation of missing measures by our team, and any multivariate analyses adjustment factors (if applicable).

Eight authors (C.S., T.N.S., P.K., M.T., M.S., I.M., T.P. and A.S.), in pairs, performed the primary evaluation of titles and abstracts identified through the search and provided the list of potentially eligible studies; two authors (C.S. and P.K.) performed the final selection of the potential eligible studies of this review. Each author extracted the data independently from their pair author, using the agreed data extraction excel form. If multiple publications using the same cohort were identified, the most recent or more complete publication was used for data extraction but information from all relevant publications was used if required. Disagreements were resolved by team consensus.

Assessment of quality of included studies

Based on the extracted data, the quality of the included studies was evaluated using the nine-item Newcastle-Ottawa Quality scale, a widely used tool for the quality assessment of observational/non-randomized studies

(Wells et al., 2011). With respect to whether the follow-up was enough for outcomes to occur, the minimum follow-up of the exposed group was set at 10 years, given that ovarian and endometrial cancers reach their peak incidence after 55 years of age (Adami et al., 2008) and IVF exposure occurs, as a rule, during the later part of the reproductive years. Concerning completeness of the follow-up, a cut-off level of women lost during the follow-up was set at 10%. Regarding the item 'demonstration that outcome of interest was not present at start of study', studies excluding cancer cases occurring during the first year of follow-up were considered to fulfil this baseline assumption.

Assessment of risk of bias across studies

The intention was to assess publication bias across studies separately by cancer type (ovarian and endometrial cervical) using Egger's formal statistical test (Egger et al., 1997) at the 90% level. However, the number of included studies per cancer type (<10 in all analyses) was small; additionally this test is known to have low power even when there is an adequate number of studies in the meta-analysis. Hence, in the absence of a robust formal test, no testing for publication bias was carried out.

Data synthesis

The effect estimates that were extracted, if available, or *de novo* calculated from available data, were SIRs, IRRs, HRs and ORs. SIRs were estimated as the ratio of the observed over expected number of cases for exposed women. The 95% confidence interval (CI) for log(SIR) was constructed via the term $\pm$ 1.96/[square root (*O*)], where *O* was the observed number of events (Alder et al., 2006). IRRs and their 95% CIs were estimated from the number of incident cases and person-years for exposed and unexposed women, using the epitab STATA commands (StataCorp, 2009). Maximally adjusted effect estimates (ORs and HRs) were additionally extracted on the total of the sample, wherever possible. All analyses were carried out and reported separately for each type of cancer (ovarian, endometrial and cervical).

Since the absolute risk of endometrial, ovarian or cervical cancer is low, the four measures of association are expected to yield similar estimates of relative risk (RR). Consequently, we presented all RR estimates pooled together, as appropriate, so that comprehensiveness of the analysis and maximization of the statistical power are ensured (Larsson et al., 2007; Adami et al., 2008). Results are always shown as subgroup analyses by reference population (general or infertile population), the latter allowing control for the confounding effect of infertility *per se*. In addition, subanalyses are presented by type of effect measure (SIRs and ORs) within the subgroup of studies treating the general population as the reference. On the contrary, regarding studies treating infertile women as the reference group, no further subanalyses (on HRs and IRRs) are presented, as subgroups contained only one study, in all cases.

Meta-analysis was carried out using the STATA *metan* command. Fixed (Mantel-Haenszel) or random effects (DerSimonian-Laird) models were used to calculate pooled effect estimates. Between-study heterogeneity was assessed by using Cochran Q statistic (significance level at $P < 0.1$) and by estimating I^2. In case of significant heterogeneity, irrespective of the I^2 estimation, random effects models were employed to allow for it (Higgins and Green, 2011).

Some of the included studies reported separately data including or excluding incident cases diagnosed during the first year of follow-up. When available, both sets of data were utilized to perform analyses of effect estimates so as to make the distinction between causal effects and tumor-promoting effects, the latter reflected mainly upon incident cases presenting during the first year of follow-up.

Our initial purpose was to carry out subgroup analyses according to the number of cycles of IVF, histological type of cancer, age group, pregnancy occurrence, type of subfertility, agent and protocol used for COH, as well as across strata of confounders. Respective data were either insufficient or unavailable in the included studies hence the planned subgroup analyses could not be carried out.

The statistical analysis was independently performed by two groups (TNS/PK in Athens and MT in Oxford), using STATA Software (STATA Corporation, College Station, TX, USA). Disagreements were again resolved by team consensus.

Results

Results of the search strategy

The search algorithm yielded 7785 records; of them, 7722 were excluded as irrelevant on the basis of title and abstract. The full text article of the remaining 63 studies was obtained and assessed according to the eligibility criteria. Fifty studies were excluded with reasons (Althuis et al., 2005a, b; Benshushan et al., 2001; Chene et al., 2009; Croughan et al., 2001; Cusidó et al., 2007; Doyle et al., 2002; Franceschi et al., 1994; Gocze et al., 2000; Goodman et al., 2001; Harlow et al., 1988; Joly et al., 1974; Kelsey et al., 1982; La Vecchia et al., 1985; Lopes et al., 1993; Modan et al., 1998; Mosgaard et al., 1997, 1998; Nieto et al., 2001; Parazzini et al., 1997, 2001a, b, 2010; Potashnik et al., 1999; Purdie et al., 1995; Risch et al., 1996; Rodriguez et al., 1998; Rossing et al., 1996, 2004; Sanner et al., 2009; Senö et al., 1996; Shapiro, 1995; Shu et al., 1989; Shushan et al., 1996; Silva Idos et al., 2009; Unkila-Kallio et al., 1997, 1998, 2000; Vlahos, 1998; Willemsen et al., 1993), as shown in Supplementary data, Table SI. Another four (Venn et al., 2001a, b; Källén et al., 2005; Finnström et al., 2011) were excluded because of overlapping data with already included studies, leaving a total of nine studies for this meta-analysis (Venn et al., 1995, 1999; Dor et al., 2002; Klip et al., 2002; Lerner-Geva et al., 2003; Kristiansson et al., 2007; Källén et al., 2011; van Leeuwen et al., 2011; Yli-Kuha et al., 2012). Details of the study selection process, including a PRISMA flow chart, are presented in Fig. 1.

Several of the included studies comprised data for more than one type of cancer; data on ovarian cancer were available in six studies (Venn et al., 1999; Dor et al., 2002; Lerner-Geva et al., 2003; Källén et al., 2011; van Leeuwen et al., 2011; Yli-Kuha et al., 2012) five on endometrial (Venn et al., 1999; Dor et al., 2002; Klip et al., 2002; Kristiansson et al., 2007; Yli-Kuha et al., 2012) and another five on cervical cancer (Venn et al., 1995; Dor et al., 2002; Lerner-Geva et al., 2003; Källén et al., 2011; Yli-Kuha et al., 2012).

The selected nine studies (Table I) included a total cohort size of 109 969 women exposed to IVF, two of which were performed in Australia (Venn et al., 1995, 1999), two in Israel (Dor et al., 2002; Lerner-Geva et al., 2003), two in the Netherlands (Klip et al., 2002; van Leeuwen et al., 2011), two in Sweden (Kristiansson et al., 2007; Källén et al., 2011) and one in Finland (Yli-Kuha et al., 2012), yielding 76 incident cases of ovarian, 18 of endometrial and 207 of cervical cancer.

All studies reported comparisons versus the general population, whereas comparisons versus infertile women were directly or indirectly presented in four studies (Venn et al., 1995, 1999; Klip et al., 2002; van Leeuwen et al., 2011). The distinction between the two follow-up intervals (total follow-up or excluding first year after IVF) was made in

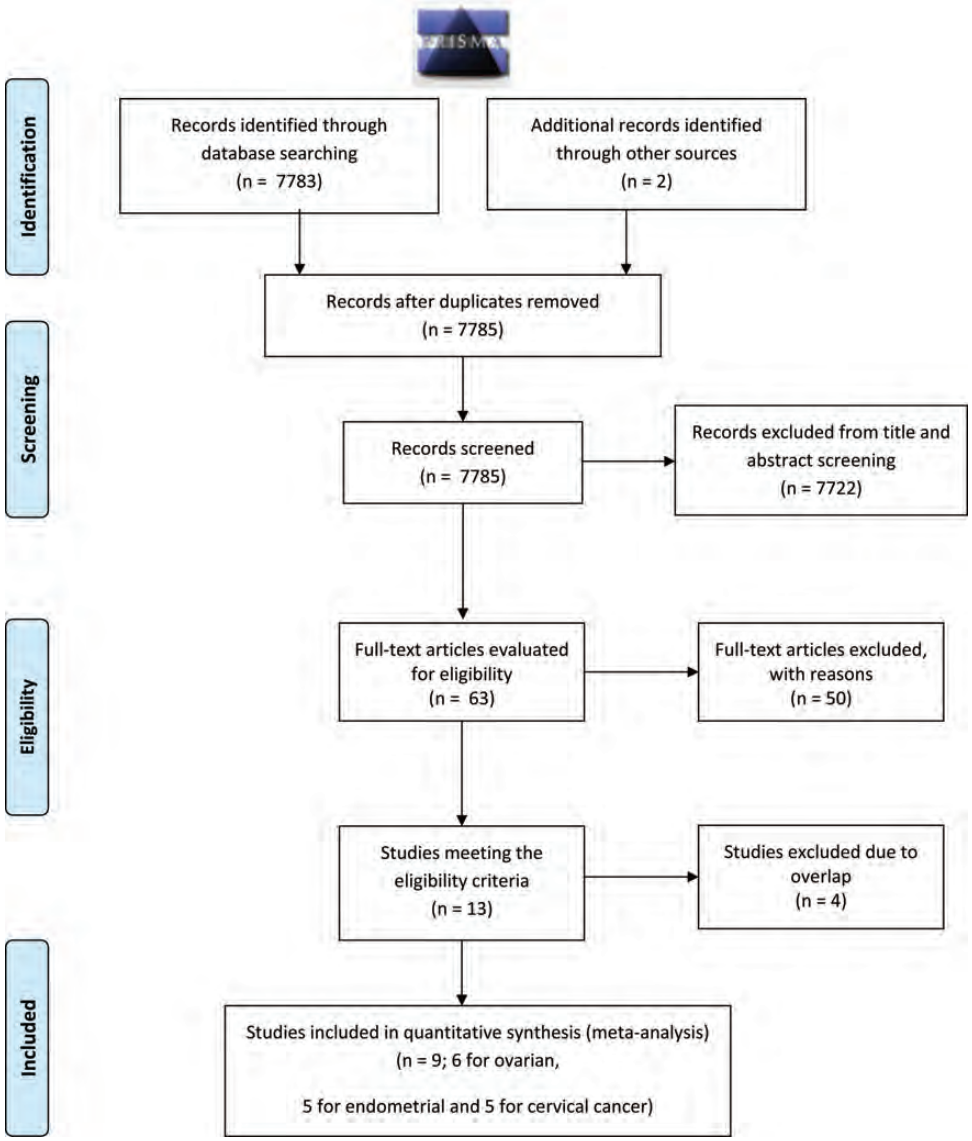

Figure 1 Prisma flowchart.

three studies (Lerner-Geva *et al.*, 2003; van Leeuwen *et al.*, 2011; Yli-Kuha *et al.*, 2012).

Quality of included studies

Rating of the quality of studies according to the Newcastle–Ottawa score is presented in the Supplementary data, Table SII, while the PRISMA Checklist in the Supplementary data, Table SIII. Quality scores ranged between 5 and 9. For all included studies bar one (van Leeuwen *et al.*, 2011) the follow-up time for exposed women was not long enough (<10 years). While nearly all studies ensured the comparability by adjusting/matching on age, only three of them (Källén *et al.*, 2011; van Leeuwen *et al.*, 2011; Yli-Kuha *et al.*, 2012) ensured the comparability for additional factors, i.e. also adjusting for year of delivery and smoking (Källén *et al.*, 2011), frequency matching on subfertility diagnoses and adjusting for endometriosis (van Leeuwen *et al.*, 2011), matching on residence as well as adjusting for marital status and socioeconomic position (Yli-Kuha *et al.*, 2012). Lastly, frequency matching was used to control for subfertility diagnoses and adjustment for endometriosis.

Analyses by cancer type

The results of all analyses performed to address the question of a putative increased risk for specific cancer types after COH for IVF, as well as those of *a priori* defined subgroup analyses, are presented below and in Table II, by cancer type.

Ovarian cancer

The synthesis of studies preferring effect estimates which excluded the first year of follow-up after IVF is presented in Table II. Studies with the general population as the reference group pointed to a statistically significant association between IVF and increased ovarian cancer risk (pooled effect estimate = 1.50, 95% CI: 1.17–1.92, fixed effects,

Table I Characteristics of included studies of the impact of controlled ovarian hyperstimulation for IVF on ovarian, endometrial and cervical cancer.

Study publication	Country, region	Study period (including follow-up)	Cancer site[a]	Cohort size	Total number of exposed women	Number of incident cases combined [ovarian; endometrial; cervical]	Number of exposed cases (ovarian; endometrial; cervical)	Mean follow-up in total cohort (years)	Mean follow-up in exposed women (years)	Study protocol for IVF	Effect estimates	Reference group	Adjusting factors	Excludes first year of follow-up
Dor *et al.* (2002)	Israel (Tel Hashomer, Tel Aviv)	1981–1996	Ovary Endometrium Cervix	5026	5026	1; 2; 1	1; 2; 1	3.6	3.6	1. CC/hMG, FSH, LH 2. hMG 3. GnRH-agonist/ hMG	SIR	General population	None	Yes
Källén *et al.* (2011)	Sweden (All IVF clinics)	1982–2006	Ovary Endometrium[a] Cervix	1 388 371	23 192	1779; NA; 33 538[b]	26; NA; 164[b]	NR	8.3	NR	OR	General population	year of delivery, maternal age at delivery and smoking	No
Klip *et al.* (2002)	Netherlands (12 clinics)	1980–1997	Ovary[a] Endometrium	23 592	17 485	NA; 6; NA	NA; 6; NA	5.7	5.4	NR	SIR[c], HR[d]	Both	HR: age at end of follow up	No
Kristiansson *et al.* (2007)	Sweden	1981–2001	Ovary[a] Endometrium Cervix[a]	6 47 704	8716	NA; 79; NA	NA; 1; NA	11.5	6.4	Classic IVF/ICSI cycles Ovum transfer in a natural cycle or frozen–thawed embryo transfer were excluded	IRR (calc)	General population	None	No
Lerner-Geva *et al.* (2003)	Israel (Tel Aviv)	1984–1996	Ovary Cervix	1082	1082	3; NA; 3 (3; NA; 1)	3; NA; 3 (3; NA; 1)	6.5	6.5	NR	SIR	General population	None	Both
van Leeuwen *et al.* (2011)	Netherlands (12 clinics)	1983–2007	Ovary	25 152	19 146	42; NA; NA (37; NA; NA)	30; NA; NA (28; NA; NA)	14.8	14.3	Until 1989: CC/hMG FSH/hMG After 1990: GnRH-a/FSH	SIR[c], HR[d]	Both	HR: age at end of follow-up, endometriosis	Both
Venn *et al.* (1999)	Australia (10 IVF clinics)	1978–1996	Ovary Endometrium Cervix[a]	29 700	20 583	13; 12; NA	7; 5; NA	8.5	7.0	CC CC/HMG HMG HMG/ GnRH-agonist	SIR[c], IRR[d] (calc)	Both	None	No
Venn *et al.* (1995)	Australia (Melbourne)	1978–1993	Ovary[a] Endometrium[a] Cervix	10 358	5564	NA; NA; 6	NA; NA; 5	6.3	5.2	Until 1987: CC + hMC + hCG 1987–1990: GnRH-a instead of CC 1990–1992: GnRH + hMG/ FSH + hCG	SIR[c], IRR[d] (calc)	Both	None	No
Yli-Kuha *et al.* (2012)	Finland	1996–2004	Ovary Endometrium Cervix	18 350	9175	12; 6; 101 (11; 5; 91)	9; 4; 34 (8; 4; 32)	7.8	7.8	NR	OR	General population	Socio-economic position and marital status	Both

Study publication	Mean age in total cohort (years)	Mean age in exposed women (years)	Cohort characteristics	Study Protocol for IVF	Ascertainment of exposure	Ascertainment of cancer	Histology	Type of infertility	Subanalyses provided
Dor *et al.* (2002)	34.0 at first treatment 37.5 at end of follow-up	34.0 at first treatment 37.5 at end of follow-up	Exposed: treated for subfertility and had at least 1 cycle of IVF	1. CC/ hMG,FSH,LH 2. hMG 3. GnRH-agonist/ hMG	Medical records	Israel National Cancer Registry	NR	Data only for the firsst Department (1254 women overall): 48.7% mechanical, 8.6% ovulatory, 19.4% male factor, 23.3% unexplained	None
Källén *et al.* (2011)	NR	32.0 at first delivery 40.3 at end of follow-up	Exposed: women who delivered an infant following IVF treatment	NR	National Board of Health and Welfare	Swedish Cancer Registry	Ovary: 23% serous, 4% mucinous, 15% endometrioid, 8% clear cell, 8% granulosa cell, 31% cystadenomas, 4% thecom, 7% unspecified Cervical: 78% *in situ*	NR	None
Klip *et al.* (2002)	32.7 at first treatment 39.7 at end of follow-up	33.1 at first treatment 38.6 at end of follow-up	Exposed: diagnosed with subfertility problems and had at least one cycle of IVF Nonexposed: over 18 years old, unable to achieve conception after one or more years of frequent unprotected intercourse	NR	Medical records for 53%; responded questionnaires for 66.9%	Netherlands Cancer Registry	50% adenocarcinoma; 16.7% adenocarcinoma with squamous metaplasia; 8.3% leiomyosarcoma; 16.7% complex mixed and stromal neoplasms; 8.3% choriocarcinoma	Endometrial exposed: endometriosis 25%, male factor 38%, hormonal factor 13%, unexplained 13%, missing 13%, (male factor only 13%)	Year of birth, Age at first visit/ treatment, Time since first visit/ treatment Years of follow-up (<5, ≥5), Type of subfertility, No of cycles, No of oocytes, Total HMG/ FSH ampoules, Ever OHSS, Parity, Previous FD use
Kristiansson *et al.* (2007)	26.8 at first conception leading to delivery	32.8 at first conception leading to delivery	Exposed: live birth following pregnancy achieved by IVF Nonexposed: live birth without such treatment	Classic IVF/ICSI cycles Ovum transfer in a natural cycle or frozen–thawed embryo transfer were excluded	Swedish register from all IVF clinics (1986 onwards)	Swedish National Cancer Registry	NR	NR	None
Lerner-Geva *et al.* (2003)	32.7 at first treatment 38.7 at end of follow-up	32.7 at first treatment 38.7 at end of follow-up	Exposed: diagnosed with subfertility problems and had at least one cycle of IVF	NR	Medical records	Israel National Cancer Registry	NR	42.14% mechanical, 24.2% hormonal, 30.1% male, 3.5% unexplained	None

Continued

Table I *Continued*

Study publication	Country, region	Study period (including follow-up)	Cancer site[a]	Cohort size	Total number of exposed women	Number of incident cases combined [ovarian; endometrial; cervical]	Number of exposed cases (ovarian; endometrial; cervical)	Mean follow-up in total cohort (years)	Mean follow-up in exposed women (years)	Study protocol for IVF	Effect estimates	Reference group	Adjusting factors	Excludes first year of follow-up
van Leeuwen *et al.* (2011)	48.0 at end of follow-up	47.5 at end of follow-up	Exposed: diagnosed with subfertility problems and had at least one cycle of IVF Nonexposed: diagnosed subfetile before IVF became a routine procedure and underwent tubal surgery and/or hormonal treatments (frequency matched to distribution of subfertility diagnoses)	Until 1989: CC/hMG FSH/hMG After 1990: GnRH-a/FSH	IVF clinics registry (obligatory)	Netherlands Cancer Registry	NR	31.5% tubal, 10.3% endometriosis, 28.7% male factor, 6.7% male factor, 17.8% unexplained, 4.8% other factors, 17.3% missing	Follow-up, No. of cycles, Subfertility diagnosis, Previous FD use, Parity, Total hMG/FSH ampules, No of oocytes (total, mean, maximum)					
Venn *et al.* (1999)	30.7 at entry 39.9 at end of follow-up	31.0 at entry 39.0 at end of follow-up	Exposed: evaluated for subfertility and had at least one IVF treatment cycle with ovarian stimulation (including stimulated cycles that were cancelled) Unexposed: referred for IVF but untreated or had 'natural cycle' treatment without ovarian stimulation	CC CC/HMG HMG HMG/GnRH-agonist	Medical records, computerized data for four clinics	State population-based Cancer Registies, National Cancer Statistics Clearing House and National Death Index	66.6% endometrial adenocarcinomas, 16.6% stromal sarcomas, 16.6% leiomyosarcomas	33.1% tubal, 23.6% male factor, 13.5% endometriosis, 4.0% ovarian defect, 3.2% other, 10.9% Unexplained, 11.4% missing	No of stimulated cycles Fertility drugs Mean number of oocytes per stimulated cycle					
Venn *et al.* (1995)	31.5 at entry 38 at end of follow-up	32.0 at entry 38.0 at end of follow-up	Exposed: evaluated for subfertility and exposed to IVF Unexposed: referred for IVF but untreated or had 'natural cycle' treatment without ovarian stimulation	Until 1987: CC + hMC + hCG 1987–1990: GnRH-a instead of CC 1990–1992: GnRH+hMG/FSH + hCG	1978–1990 Medical records, 1990–1992 computerized records kept by Monash IVF programme	Victorian Cancer Registry (VCR), National Cancer Statistics Clearing House (NCSCH)	NR	43.4% Tubal, 23.2% male factor, 13.2% endometriosis, 6.2% ovarian disorders, 18.7% unexplained, 3.5% other causes, 8.4% missing	None					

Yli-Kuha *et al.* (2012)	33.5 at first treatment	33.5 at first treatment	Exposed: received IVF (including ICSI and FET); Unexposed: population register (matched by age, municipality)	NR	Identified by reimbursment for drugs or drug combinations specific to these treatments	Finnish Cancer Registry	NR	NR	None

OR, odds ratio; HR, hazard ratio; SIR, standardized incidence ratio; IRR, incidence rate ratio; NA, not applicable; NR, not reported. One study reported ovarian cancer only (van Leeuwen *et al.*, 2011), one ovarian and endometrial (Klip *et al.*, 2002), one ovarian and cervical (Lerner-Geva *et al.*, 2003) and the rest six all three types of cancer.
[a]The cancer sites and the studies with an asterisk are not used in the analysis, either due to overlap or due to insufficient data provided.
[b]Includes *in situ*.
[c]Versus general population.
[d]Versus infertile population.

Fig. 2a), whereas in contrast, the RR estimate from the analysis treating infertile women as the reference group was far from being statistically significant (pooled effect estimate = 1.26, 95% CI: 0.62–2.55, fixed effects, Fig. 2b). Subanalyses on SIRs and ORs among studies which adopted comparison versus the general population pointed to positive associations (Supplementary data, Figs S2 and S3), although the subanalysis on SIRs did not reach formal significance (pooled effect estimate = 1.19, 95% CI: 0.86–1.64, fixed effects). The alternative approach synthesizing effect estimates derived from the total follow-up (Table II, Supplementary data, Figs S4–S7) yielded similar results as the aforementioned analyses.

Endometrial cancer

Despite the limited number endometrial cancer cases included in the review and similarly to ovarian cancer, pooling of studies versus general population indicated a statistically significant and sizeable association between IVF and increased endometrial cancer risk (pooled effect estimate = 2.04, 95% CI: 1.22–3.43, fixed effects, Fig. 3a). In contrast, the analysis treating infertile women as the reference group clearly showed no increased risk for the disease following IVF experience (pooled effect estimate = 0.45, 95% CI: 0.18–1.14, fixed effects, Fig. 3b). For studies treating the general population as the reference category, the subanalyses on SIRs (pooled effect estimate = 1.97, CI: 1.15–3.40, fixed effects) and ORs (pooled effect estimate = 2.86, 95% CI: 0.52–15.75, fixed effects) pointed to positive associations (Supplementary data, Figs S8 and S9), although the subanalysis on ORs, based only on two studies, did not reach formal significance. The alternative approach preferring effect estimates derived from the total follow-up yielded a similar pattern of results (Table II, Supplementary data, Figs S10–S13).

Cancer of the cervix

IVF was not associated with increased risk for cervical cancer either at the synthesis of studies versus general population (pooled effect estimate = 0.86, 95% CI: 0.49–1.49, random effects, Fig. 4a) or at the sole study treating infertile women as the reference group. Regarding the studies which adopted comparison versus the general population (Fig. 4b and Supplementary data, Fig. S14), the subanalysis on ORs pointed to an intriguing inverse association between IVF and risk of cervical cancer (pooled effect estimate = 0.60, 95% CI: 0.52–0.70, fixed effects). The alternative approach preferring effect estimates derived from the total follow-up reproduced the aforementioned set of findings (Table II, Supplementary data, Figs S15–S17).

Discussion

The *lege artis* synthesis of all nine so far published studies on cancer risk among women undergoing COH for IVF highlight the methodologically and conceptually challenging nature of IVF as an exposure and potential risk factor in cancer epidemiology. As expected, COH for IVF does not seem to increase the risk for the non-hormone-dependent cervical cancer, whereas inconclusive results are drawn for ovarian and endometrial cancers. The notion of 'reference category' in the construction of models and comparisons leaves the statistical background and comes to the interpretational foreground, as studies adopting different reference populations, notably general population as contrasted to infertile women, yield discrepant results. Specifically, the significant and sizeable

Table II Results of the meta-analyses examining the association between IVF and endometrial, ovarian and cervical cancer.

	Ovarian cancer				Endometrial cancer				Cervical cancer			
	n[a]	Effect estimate (95% CI)	*P*	Heterogeneity I^2, P[b]	*n*[a]	Effect estimate (95% CI)	*P*	Heterogeneity I^2, P[b]	*n*[a]	Effect estimate (95% CI)	*P*	Heterogeneity I^2, P[b]
Approach preferring[c] estimates which excluded the first year of follow-up after IVF												
Analysis versus general population	6	**1.50 (1.17–1.92)**	0.001	22.5%, 0.265	5	**2.04 (1.22–3.43)**	0.007	0.0%, 0.491	5	0.86 (0.49–1.49)[R]	0.585	70.2%, 0.009
Subanalysis on SIRs	4	1.19 (0.86–1.64)	0.293	0.0%, 0.679	3	**1.97 (1.15–3.40)**	0.014	33.8%, 0.221	3	1.54 (0.47–5.09)[R]	0.480	64.0%, 0.062
Subanalysis on ORs	2	**2.10 (1.43–3.10)**	<0.001	0.0%, 0.918	2	2.86 (0.52–15.75)	0.227	0.0%, 0.632	2	**0.60 (0.52–0.70)**	<0.001	0.0%, 0.661
Analysis versus infertile women[d]	2	1.26 (0.62–2.55)	0.521	0.0%, 0.451	2	0.45 (0.18–1.14)	0.093	0.0%, 0.789	1	5.70 (0.28–117.20)	0.259	NC, NC[e]
Approach preferring[c] estimates derived from total follow-up												
Analysis versus general population	6	**1.65 (1.07–2.55)[R]**	0.022	52.1%, 0.064	5	**1.97 (1.18–3.27)**	0.009	0.0%, 0.553	5	0.85 (0.49–1.48)[R]	0.556	70.8%, 0.008
Subanalysis on SIRs	4	1.42 (0.74–2.76)[R]	0.294	58.1%, 0.067	3	**1.97 (1.15–3.40)**	0.014	33.8%, 0.221	3	1.54 (0.47–5.08)[R]	0.480	63.9%, 0.063
Subanalysis on ORs	2	**2.13 (1.45–3.13)**	<0.001	0.0%, 0.769	2	1.91 (0.46–8.04)	0.376	0.0%, 0.923	2	**0.60 (0.52–0.70)**	<0.001	0.0%, 0.518
Analysis versus infertile women[d]	2	1.05 (0.55–2.01)	0.874	0.0%, 0.685	2	0.45 (0.18–1.14)	0.093	0.0%, 0.789	1	5.70 (0.28–117.20)	0.259	NC, NC[e]

Bold cells denote statistically significant associations. All pooled effect estimates were derived from fixed-effects analyses, except for cells marked with [R](random-effects).
CI, confidence interval. NC, not calculable.
[a]Number of studies.
[b]*P*-value derived from Cochran Q statistic.
[c]The distinction between the two follow-up intervals (excluding first year after IVF and total) was made only in three studies (Lerner-Geva *et al.*, 2003; van Leeuwen *et al.*, 2011; Yli-Kuha *et al.*, 2012).
[d]All analyses were based on IRRs.

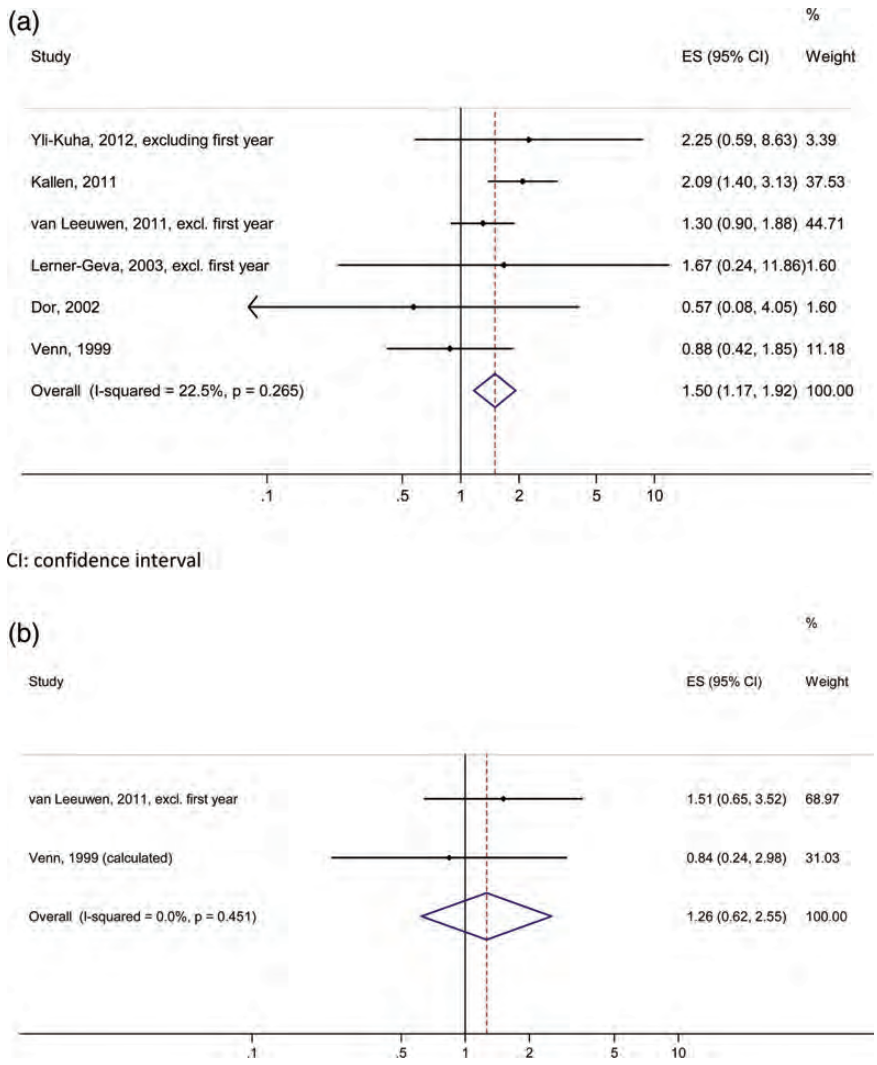

Figure 2 (**a**) Forest plot presenting combined effect estimates [standardized incidence ratio (SIRs), odds ratios (ORs)] for ovarian cancer in women exposed to IVF, preferring estimates excluding the first year of follow-up after IVF. ES, effect size (relative risk). (**b**) Forest plot presenting incidence rate ratios (IRRs) for ovarian cancer in women exposed to IVF versus infertile women, preferring estimates excluding the first year of follow-up after IVF.

associations with ovarian and endometrial cancers were not maintained when infertile population was used as the reference, essentially confirming the role of infertility as a confounding factor in the risk of developing gynaecological cancers. Overall, the associations examined in this meta-analysis should be interpreted with caution owing to the small number of available studies in the literature, imperfections of exposure data, lack of adjustment for meaningful confounders in the included studies and relatively short follow-up periods.

The importance of infertility as a risk factor for gynecological cancer (Cetin *et al.*, 2008) clearly emerged in this meta-analysis. Indeed, the pooled effect estimates derived from the analyses treating infertile women as the reference group seems to yield a clearer picture of the role mediated by IVF, as they are supposedly free from any superimposed confounding effects of infertility. However, there seems to be further room for methodological improvement in the individual studies, as adjusted effect estimates were provided only in one out of the two included studies (van Leeuwen *et al.*, 2011); the IRRs derived from the other one (Venn *et al.*, 1999) were crude (unadjusted), not allowing the examination of the contribution of other potential risk factors.

In order to gain insight into possible tumor-promoting effects, as well as into the possibility of diagnostic access bias, we have followed an alternative approach excluding cancer cases emerging in the first year after IVF treatment. Indeed, several reports have endorsed an increased incidence within this time window of exposure to IVF drugs, whereas the hormonal changes enhanced by respective medication and the close medical surveillance of women before, during and after each cycle have been considered to contribute to the early detection of gynecological cancers (Venn *et al.*, 1995, 2001a, b; Dor *et al.*, 2002; Lerner-Geva *et al.*, 2003). Of note, our alternative approach yielded essentially the same pattern of results as the analysis based on the total follow-up period, findings that designated a slender role of events recorded within the first year. Nevertheless, it should be stressed that only three (Lerner-Geva *et al.*, 2003; van

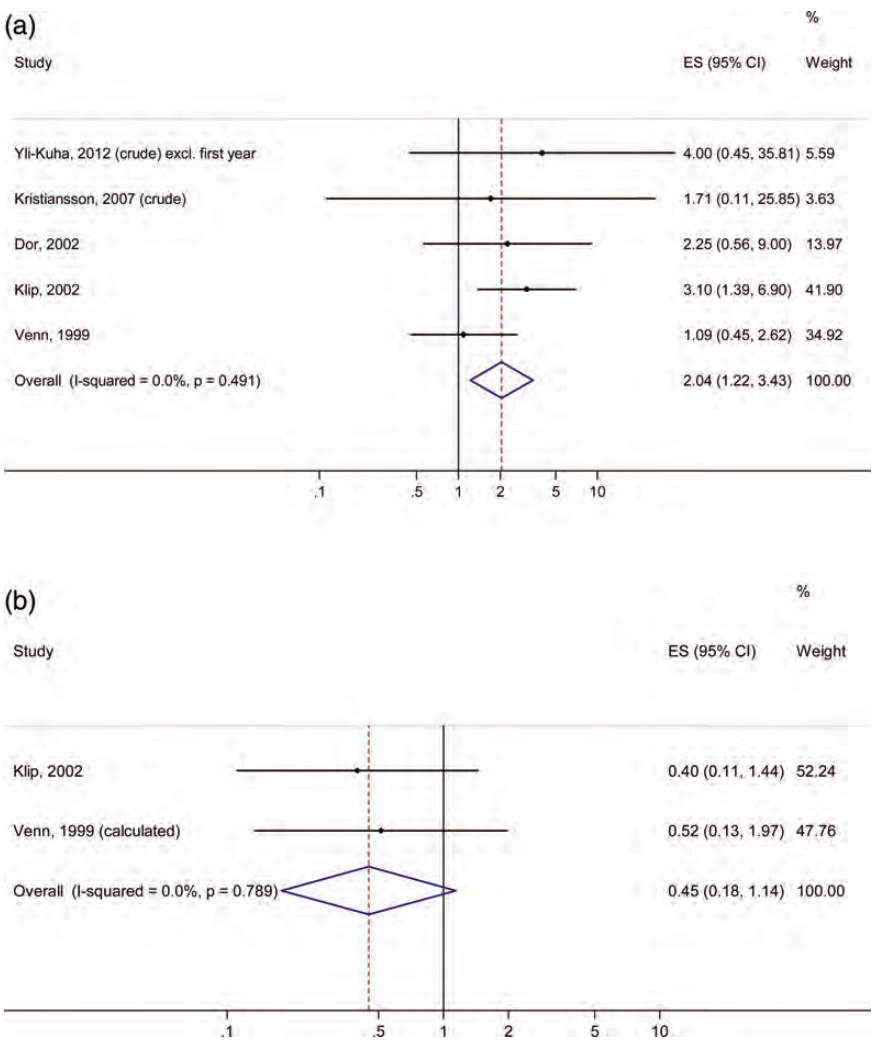

Figure 3 (**a**) Forest plot presenting combined effect estimates (SIRs, ORs) for endometrial cancer in women exposed to IVF, preferring estimates excluding the first year of follow-up after IVF. (**b**) Forest plot presenting IRRs for endometrial cancer in women exposed to IVF versus infertile women, preferring estimates excluding the first year of follow-up after IVF.

Leeuwen *et al.*, 2011; Yli-Kuha *et al.*, 2012) of the nine included studies made the distinction, while the total number of observed cancer cases (especially endometrial cancer cases) was small; consequently, the observed differentiation of results may have been blunted, to a certain extent.

Pooling of SIRs and ORs was undertaken in the analysis of studies treating the general population as the reference group, given their asymptotic convergence to RR assuming the rarity of the outcome variable (Larsson *et al.*, 2007). The significant results noted for the ovarian and endometrial cancers SIRs (four and three studies, respectively) and ORs (two studies for each cancer type) subgroup analyses should be interpreted with caution owing to the small number of studies in the analysis. Regarding cervical cancer, the subanalysis on ORs pointed to a rather inverse association, namely a protective role of IVF. As a rule, women who seek IVF are considered to have stable sexual relations and hence could be at a low risk for this type of cancer; surprisingly, however, a recent study (van Hamont *et al.*, 2006) reported that women undergoing IVF are diagnosed with a high-grade cervical lesion almost twice as frequently compared with women in the general population. It should thus be kept in mind that the inverse association between IVF and cervical cancer may well be prone to confounding and diagnostic access bias, as IVF women may be treated for cervical lesions prior to the development of cervical cancer. Regarding confounding, parity (International Collaboration of Epidemiological Studies of Cervical Cancer, 2006) and socioeconomic status (SES) (Parikh *et al.*, 2003) are interwoven and thus have been associated with decreased cervical cancer risk; women undergoing IVF may well be privileged in terms of both factors. Noticeably, neither of the two studies in this subanalysis adjusted for both factors; Yli-Kuha *et al.* (2012) adjusted for SES, whereas Källén *et al.* (2011) restricted their analysis to women who gave birth without adjustment for SES.

The use of ovarian stimulation drugs prior to IVF might also be a confounding factor but data provided in the studies under analysis

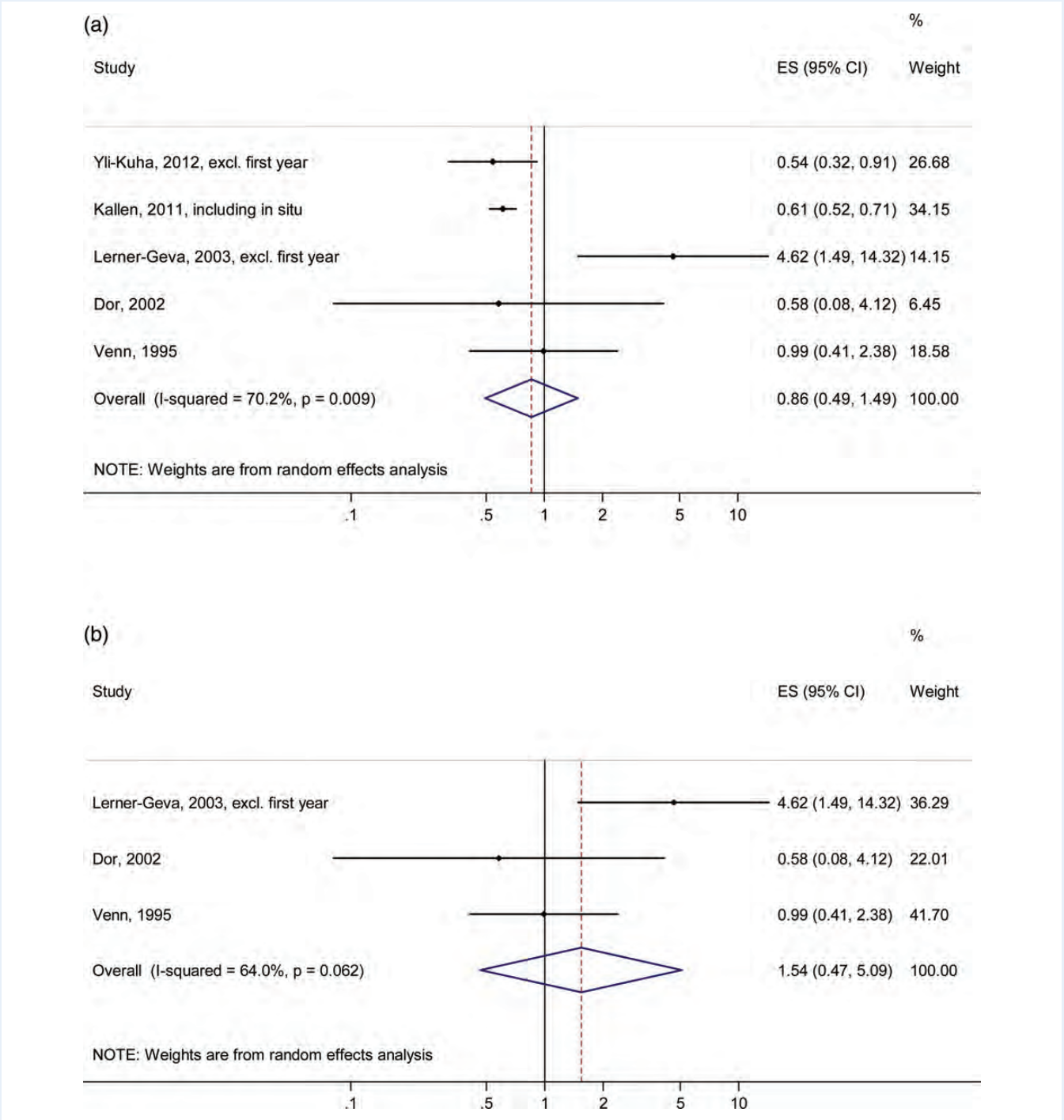

Figure 4 (**a**) Forest plot presenting combined effect estimates (SIRs, ORs) for cervical cancer in women exposed to IVF, preferring estimates excluding the first year of follow-up after IVF. (**b**) Forest plot presenting SIRs for cervical cancer in women exposed to IVF versus general population, preferring estimates excluding the first year of follow-up after IVF.

were rather scarce and incomplete to allow proper examination of their impact. The results of the current meta analysis are, however, in line with the evidence coming from previous reviews on ovarian stimulation drugs; most found no relationship between medication and ovarian (Ness *et al.*, 2002; Venn *et al.*, 2003; Kashyap *et al.*, 2004; Brinton *et al.*, 2005; Kanakas and Mantzavinos, 2006; Mahdavi *et al.*, 2006; Brinton, 2007; Källén, 2008; Devesa *et al.*, 2010; Lerner-Geva *et al.*, 2010; Vlahos *et al.*, 2010a, b; Impicciatore and Tiboni, 2011) or endometrial cancer (Kanakas and Mantzavinos, 2006; Brinton, 2007; Källén, 2008; Vlahos *et al.*, 2010a), whereas in other studies the results were inconclusive (Meirow and Schenker, 1996; Glud *et al.*, 1998; Ayhan *et al.*, 2004; Zreik *et al.*, 2008; Lerner-Geva *et al.*, 2010; Impicciatore and Tiboni, 2011). In two studies a direct relationship was attributed (Whittemore *et al.*, 1992; Bukovic *et al.*,

2011), triggering the prevailing uncertainty. Lastly, a meta-analysis of seven case–control and three cohort studies, showed a trend towards an ovarian cancer risk-lowering benefit of ovulation-induction drugs, showing that infertile women themselves may gain even more from ART than the expected reproductive benefits (Kashyap *et al.*, 2004).

Numerous published reports point out the weaknesses of individual findings and consequently recommend the development of studies capturing larger populations and longer follow-ups, relying on more precise data with better adjustments for confounding factors (Del Priore *et al.*, 1995; Burmeister and Healy, 1998; Klip *et al.*, 2000; Gadducci *et al.*, 2004; Cetin *et al.*, 2008; Jensen *et al.*, 2008; Dauplat *et al.*, 2009; Webb, 2009). Others suggest the inclusion as the control group of subfertile women who have indication to use respective drugs but were eventually not treated (Venn *et al.*, 1995; Klip *et al.*, 2000; Kashyap *et al.*, 2004; Jensen *et al.*, 2008; Calderon-Margalit *et al.*, 2009), or comparisons between IVF or non-IVF treated women who have given birth (Källén, 2008); alternatively, there are suggestions for investigation of the possible carcinogenic effects of these drugs in certain subgroups, e.g. infertile women who do not subsequently get pregnant, or to focus on certain histological subtypes—as there may exist different risk factors (Glud *et al.*, 1998; Kashyap *et al.*, 2004; Mahdavi *et al.*, 2006; Soegaard *et al.*, 2007); or those with genetic predisposition, PCOS and endometriosis (Meirow and Schenker, 1996; Zreik *et al.*, 2008). Lastly, short courses of ovarian stimulation (Crosbie and Menon, 2005; Zreik *et al.*, 2008) are proposed in order to monitor for cancer development (during the initial infertility work-up (Zreik *et al.*, 2008). The ultimate goal of these suggestions is to come up with sound estimates enabling proper consultation by specialists of subfertile couples seeking IVF, as the latter seem to increasingly turn for advice to both the Internet and health providers.

The inherent limitations of the included studies are reflected in the current meta-analysis. A major, unavoidable shortcoming pertained to the short follow-up periods, reflected in the quality ratings of included studies. Indeed, only one study (van Leeuwen *et al.*, 2011) has provided follow-up longer than 10 years for the exposed group; longer follow-up periods seem indispensable, as both ovarian and endometrial cancers reach their peak incidence after the age of 55 years (Adami *et al.*, 2008), whereas IVF exposure occurs mostly during the late reproductive years.

A plethora of records (over 7000) were retrieved in our initial search, which resulted, however, in a paucity of the studies ($n = 9$) eligible for inclusion in the meta-analysis. By necessity, studies examining ovulation stimulation and/or ART in general were excluded; this could be considered an advantage, however, as ovulation stimulation or induction may have a different impact on cancer incidence, compared with IVF alone. Repeated attempts to communicate with the authors of respective papers, in the case of questionable IVF reporting or other data and details on the eligibility for inclusion, were not always successful and as a result valuable data from large studies were excluded. This was the case, for example, with a cohort (Jensen *et al.*, 2009a,b) on >50 000 infertile women suffering endometrial or ovarian cancer following the use of infertility drugs; the authors did not specifically assess COH for IVF but concluded that use of gonadotrophins and more than six cycles of clomiphene citrate (and not GnRH analogs) increased the uterine cancer risk, observed after 10 years of follow-up, findings that were not changed when results were stratified by parity status or adjusted for infertility or use of oral contraceptives. In a similar context, another fundamental reporting problem was that missing information limited our ability to explore a relationship between COH medications and cancer with regard to type, protocol, dose used and number of cycles of IVF, type of subfertility, histological type of cancer, age group and pregnancy occurrence, despite our initial intention; for instance, age-related differential effects of IVF which have been supported in the context of breast cancer (Stewart *et al.*, 2012) could not be examined in our meta-analysis. Lastly, IRRs among infertile women were based on crude estimates, whereas several studies used SIRs, which compare the number of observed cancers in the study cohort of interest to the number expected based on rates met in the general population. SIRs inherently correspond to RR estimates adjusted only for age and calendar time (Jensen *et al.*, 2008), usually leading to overestimation of cancer risk (Klip *et al.*, 2000; Mahdavi *et al.*, 2006; Jensen *et al.*, 2008). More elaborate approaches, for example exploring the cancer risk among IVF women as contrasted to that among other women *who had already given birth* in order to control for the effect of pregnancy itself on cancer risk (Källén *et al.*, 2005) were relatively rare.

Notwithstanding these limitations, this systematic review with clear definitions of exposures (COH for IVF) and outcomes, no language restriction and adherence to procedures that maximize the potential to avoid extraction, recording, conformity and retrieval bias and control for the impact of infertility, provides a valuable summary of the results of scientific publications so far. Moreover, the review identifies pivotal study design and reporting elements that should be considered in future studies, so that further light can be shed on the thus far inconclusive scientific evidence. In particular, whereas population-based cohort studies provide estimates of the combined burden due to infertility, COH and IVF, special caution should be devoted in the design of studies aiming to disentangle the tentative increase in risk on account of IVF alone, by specific type of infertility. To this end, linkage studies with accurate and detailed IVF registered exposure data and cancer outcomes particularly among infertile women, controlling for known confounding factors, such as parity and SES, seem warranted.

Issues for clarification also include the possibility that pregnancy itself, even after IVF, may outweigh a possible risk on account of the medication used and eventually exert, via the subsequent pregnancy, a higher protective effect against cancer of the ovary and endometrium. On the other hand, the level of risk for women who continue to remain infertile despite the larger doses and/or longer durations of drugs they have received during this treatment remains to be assessed in future studies.

In summing up the results of published studies, IVF is not associated with elevated cervical cancer risk; nor seems to be associated with ovarian or endometrial cancer when the confounding effect of infertility is taken into account. Future cohort studies, however, properly designed to disentangle the sole effect of IVF should preferably use infertile women as the reference group, rely on IVF-registered valid exposure data, adjust for a variety of meaningful confounders and adopt relatively longer follow-up periods before sound conclusions are drawn. Thus, it may take some time before new epidemiological studies and consequent systematic reviews and meta-analyses can

amass the follow-up times required to fully address long-term effects of IVF on gynecological cancer risk.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/.

Acknowledgements

We would like to thank Dr Asher Shushan, Dr Carlo La Vecchia, Dr Louise Brinton, and Dr Michelle Althuis for their feedback regarding the lack of data availability in their databases; Dr Liat Lerner-Geva for her reply regarding potential overlap between studies; and Dr Allan Jensen for his kind explanation concerning his denial to provide data. This work was partially supported by the National and Kapodistrian University of Athens.

Authors' roles

S.C. contributed to study design, critical evaluation of the studies, extraction of data and interpretation of the findings, drafted the article, gave final approval of the version to be published and secured the invited review. S.T.N. contributed to study design, critical evaluation of the studies, extraction and interpretation of data, performed statistical analysis, drafted the article and gave final approval of the version to be published. K.P. contributed to study design, critical evaluation of the studies, extraction and interpretation of data, performed statistical analysis, drafted the article and gave final approval of the version to be published. T.M. contributed to study design, critical evaluation of the studies, extraction and interpretation of data, performed statistical analysis, drafted the article and gave final approval of the version to be published. S.M. contributed to the critical evaluation of the studies, extraction and interpretation of data, revised the article critically for important intellectual content and gave final approval of the version to be published. M.I. contributed to the critical evaluation of the studies, extraction and interpretation of data, revised the article critically for important intellectual content and gave final approval of the version to be published. P.T. contributed to study design, critical evaluation of the studies, extraction and interpretation of data, drafted the article and gave final approval of the version to be published. S.A. contributed to study design, critical evaluation of the studies, extraction and interpretation of data, drafted the article and gave final approval of the version to be published. P.E.T. conceived the idea of the study, contributed to study design, critical evaluation of the studies, extraction and interpretation of data, performed statistical analysis, drafted the article, gave final approval of the version to be published and will act as a guarantor of the study.

Funding

No external funding was either sought or obtained for this study.

Conflict of interest

None declared.

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