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

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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%
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., 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 (Meirov 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 estrogen 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, 1991).
Association between IVF and gynaecological cancers

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 usable 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.
occurring, 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; Benschusun 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; Senô 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 S1. 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,
three studies (Lerner-Geva et al., 2003; van Leeuwen et al., 2011; Yli-Kuha et al., 2012).

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.

<table>
<thead>
<tr>
<th>Study publication</th>
<th>Country, region</th>
<th>Study period (including follow-up)</th>
<th>Cancer site*</th>
<th>Cohort size</th>
<th>Total number of exposed women</th>
<th>Number of incident cases combined [ovarian; endometrial; cervical]</th>
<th>Number of exposed cases (ovarian; endometrial; cervical)</th>
<th>Mean follow-up in total cohort (years)</th>
<th>Mean follow-up in exposed women (years)</th>
<th>Study protocol for IVF</th>
<th>Effect estimates</th>
<th>Reference group</th>
<th>Adjusting factors</th>
<th>Excludes first year of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dor et al. (2002)</td>
<td>Israel (Tel Hashomer, Tel Aviv)</td>
<td>1981–1996</td>
<td>Ovary Endometrium Cervix</td>
<td>5026</td>
<td>5026</td>
<td>1; 2; 1</td>
<td>1; 2; 1</td>
<td>3.6</td>
<td>3.6</td>
<td>1. CC/hMG, FSH, LH 2. hMG 3. GnRH-agonist/ hMG</td>
<td>SIR</td>
<td>General population</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Källén et al. (2011)</td>
<td>Sweden (All IVF clinics)</td>
<td>1982–2006</td>
<td>Ovary Endometrium* Cervix</td>
<td>1 388 371</td>
<td>23 192</td>
<td>1779; NA, 33 5389</td>
<td>26; NA, 1649</td>
<td>NR</td>
<td>8.3</td>
<td>NR</td>
<td>OR</td>
<td>General population</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Klip et al. (2002)</td>
<td>Netherlands (12 clinics)</td>
<td>1980–1997</td>
<td>Ovary* Endometrium</td>
<td>23 592</td>
<td>17 485</td>
<td>NA; 6; NA</td>
<td>NA; 6; NA</td>
<td>5.7</td>
<td>5.4</td>
<td>NR</td>
<td>SIR*, HR9</td>
<td>Both</td>
<td>HR: age at end of follow up</td>
<td>No</td>
</tr>
<tr>
<td>Kristiansen et al. (2007)</td>
<td>Sweden</td>
<td>1981–2001</td>
<td>Ovary* Endometrium Cervix*</td>
<td>6 47 704</td>
<td>8716</td>
<td>NA; 79; NA</td>
<td>NA; 1; NA</td>
<td>11.5</td>
<td>6.4</td>
<td>Classic IVF/ICSI cycles Ovum transfer in a natural cycle or frozen-thawed embryo transfer were excluded</td>
<td>SIR</td>
<td>General population</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Lerner-Geva et al. (2003)</td>
<td>Israel (Tel Aviv)</td>
<td>1984–1996</td>
<td>Ovary Cervix</td>
<td>1082</td>
<td>1082</td>
<td>3; NA; 3</td>
<td>3; NA; 3</td>
<td>6.5</td>
<td>6.5</td>
<td>NR</td>
<td>SIR</td>
<td>General population</td>
<td>None</td>
<td>Both</td>
</tr>
<tr>
<td>Venn et al. (1999)</td>
<td>Australia (10 IVF clinics)</td>
<td>1978–1996</td>
<td>Ovary Endometrium Cervix*</td>
<td>29 700</td>
<td>20 583</td>
<td>13; 12; NA</td>
<td>7; 5; NA</td>
<td>8.5</td>
<td>7.0</td>
<td>CC</td>
<td>SIR*, IRR9 (calc)</td>
<td>Both</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Yli-Kuha et al. (2012)</td>
<td>Finland</td>
<td>1996–2004</td>
<td>Ovary Endometrium Cervix</td>
<td>18 350</td>
<td>9175</td>
<td>12; 6; 101 (11; 5; 91)</td>
<td>9; 4; 34 (8; 4; 32)</td>
<td>7.8</td>
<td>7.8</td>
<td>NR</td>
<td>OR</td>
<td>General population</td>
<td>Socio-economic position and marital status</td>
<td>Both</td>
</tr>
<tr>
<td>Study publication</td>
<td>Mean age in total cohort (years)</td>
<td>Mean age in exposed women (years)</td>
<td>Cohort characteristics</td>
<td>Study Protocol for IVF</td>
<td>Ascertainment of exposure</td>
<td>Ascertainment of cancer</td>
<td>Histology</td>
<td>Type of infertility</td>
<td>Subanalyses provided</td>
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<tr>
<td>Dor et al. (2002)</td>
<td>34.0 at first treatment 37.5 at end of follow-up</td>
<td>34.0 at first treatment 37.5 at end of follow-up</td>
<td>Exposed treated for subfertility and had at least 1 cycle of IVF</td>
<td>i. CC/ hMG/FSH/LH 2. hMG 3. GnRH-agonist/ hMG</td>
<td>Medical records</td>
<td>Israel National Cancer Registry</td>
<td>NR</td>
<td>Data only for the first Department (1254 women overall): 48.7% mechanical, 8.6% ovulatory, 19.4% male factor, 23.3% unexplained</td>
<td>None</td>
<td></td>
<td></td>
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<tr>
<td>Källén et al. (2011)</td>
<td>NR</td>
<td>32.0 at first delivery 40.3 at end of follow-up</td>
<td>Exposed women who delivered an infant following IVF treatment</td>
<td>NR</td>
<td>National Board of Health and Welfare</td>
<td>Swedish Cancer Registry</td>
<td>Ovary: 23% serous, 4% mucinous, 13% endometrioid, 8% clear cell, 8% granulosa cell, 31% cystadenomas, 4% thecom, 7% unspecified Cancer: 78% in situ</td>
<td>None</td>
<td></td>
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<tr>
<td>Klip et al. (2002)</td>
<td>32.7 at first treatment 39.7 at end of follow-up</td>
<td>33.1 at first treatment 38.6 at end of follow-up</td>
<td>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</td>
<td>NR</td>
<td>Medical records for 53%, responded questionnaires for 66.9%</td>
<td>Netherlands Cancer Registry</td>
<td>Endometrial exposed endometriosis 25%, male factor 38%, hormonal factor 13%, unexplained 13%, missing 13% (male factor only 13%)</td>
<td>Year of birth, Age at first visit/treatment, Time since first visit/treatment Years of follow-up (&lt;5, ≥5), Type of subfertility, No of cycles, No of oocytes Total HMG/FSH ampoules, Ever OHSS, Parity, Previous PD use</td>
<td>None</td>
<td></td>
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<tr>
<td>Kristiansson et al. (2007)</td>
<td>26.8 at first conception leading to delivery</td>
<td>32.8 at first conception leading to delivery</td>
<td>Exposed live birth following pregnancy achieved by IVF Nonexposed live birth without such treatment</td>
<td>Classic IVF/ICSI cycles Orum transfer in a natural cycle or frozen-thawed embryos transfer were excluded</td>
<td>Swedish register from all IVF clinics (1986 onwards)</td>
<td>Swedish National Cancer Registry</td>
<td>NR</td>
<td>NR</td>
<td>None</td>
<td></td>
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<tr>
<td>Lerner-Geva et al. (2003)</td>
<td>32.7 at first treatment 38.7 at end of follow-up</td>
<td>32.7 at first treatment 38.7 at end of follow-up</td>
<td>Exposed diagnosed with subfertility problems and had at least one cycle of IVF</td>
<td>NR</td>
<td>Medical records</td>
<td>Israel National Cancer Registry</td>
<td>NR</td>
<td>42.14% mechanical, 24.2% hormonal, 30.1% male, 3.55% unexplained</td>
<td>None</td>
<td></td>
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<tr>
<td>Study publication</td>
<td>Country, region</td>
<td>Study period (including follow-up)</td>
<td>Cancer site*</td>
<td>Total number of exposed women</td>
<td>Number of incident cases combined (ovarian; endometrial; cervical)</td>
<td>Number of exposed cases (ovarian; endometrial; cervical)</td>
<td>Mean follow-up in total cohort (years)</td>
<td>Mean follow-up in exposed women (years)</td>
<td>Study protocol for IVF</td>
<td>Effect estimates</td>
<td>Reference group</td>
<td>Adjusting factors</td>
<td>Excludes first year of follow-up</td>
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<tr>
<td>van Leeuwen et al. (2011)</td>
<td>Netherlands</td>
<td>48.0 at end of follow-up</td>
<td></td>
<td>47.5 at end of follow-up</td>
<td>VNY clinics registry (obligatory)</td>
<td>Netherlands Cancer Registry</td>
<td>NR</td>
<td>31.5% tubal, 10.3% endometriosis, 28.7% male factor, 6.7% male factor, 17.8% unexplained, 4.8% other factors, 17.3% missing</td>
<td>Follow-up, No. of cycles, Subfertility diagnosis, Previous FD use, Parity, Total hMG/FSH ampules, No of oocytes (total, mean, maximum)</td>
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<tr>
<td>Venn et al. (1999)</td>
<td>State population-based</td>
<td>30.7 at entry 39.9 at end of follow-up</td>
<td></td>
<td>31.0 at 0 at entry of follow-up</td>
<td>Medical records, computerized data for four clinics</td>
<td>State population-based Cancer Registies, National Cancer Statistics Clearing House and National Death Index</td>
<td>66.6% endometrial adenocarcinomas, 16.6% leiomyosarcomas, 16.6% leiomyosarcomas</td>
<td>33.1% tubal, 33.6% male factor, 13.3% male factor, 13.6% endometriosis, 4.0% ovarian defect, 3.2% other, 10.9% Unexplained, 11.4% missing</td>
<td>None of specialized cycles, Fertility drugs Mean number of oocytes per stimulated cycle</td>
<td></td>
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<tr>
<td>Venn et al. (1995)</td>
<td>Victorian Cancer Registry</td>
<td>31.5 at entry 39 at end of follow-up</td>
<td></td>
<td>32.0 at 38 at end of follow-up</td>
<td>Medical records, computerized data for four clinics</td>
<td>Victorian Cancer Registry (VCR), National Cancer Statistics Clearing House (NOSCH)</td>
<td>NR</td>
<td>43.4% tubal, 23.2% male factor, 13.3% endometriosis, 6.2% ovarian disorders, 18.7% unexplained, 3.5% other causes, 8.4% missing</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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\% \text{ CI: } 0.62–2.55, \text{ 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\% \text{ CI: } 0.86–1.64, \text{ 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\% \text{ CI: } 1.22–3.43, \text{ 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\% \text{ CI: } 0.18–1.14, \text{ fixed effects, Fig. 3b}). For studies treating the general population as the reference category, the subanalyses on SIRs (pooled effect estimate \(= 1.97, \text{ CI: } 1.15–3.40, \text{ fixed effects}) and ORs (pooled effect estimate \(= 2.86, 95\% \text{ CI: } 0.52–15.75, \text{ 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\% \text{ CI: } 0.49–1.49, \text{ 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\% \text{ CI: } 0.52–0.70, \text{ 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.

<table>
<thead>
<tr>
<th></th>
<th>Ovarian cancer</th>
<th>Endometrial cancer</th>
<th>Cervical cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n^a$</td>
<td>Effect estimate (95% CI)</td>
<td>$P$</td>
</tr>
<tr>
<td>Approach preferring estimates which excluded the first year of follow-up after IVF</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Analysis versus general population</td>
<td>6</td>
<td>1.50 (1.17–1.92)</td>
<td>0.001</td>
</tr>
<tr>
<td>Subanalysis on SIRs</td>
<td>4</td>
<td>1.19 (0.86–1.64)</td>
<td>0.293</td>
</tr>
<tr>
<td>Subanalysis on ORs</td>
<td>2</td>
<td>2.10 (1.43–3.10)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Analysis versus infertile women$^d$</td>
<td>2</td>
<td>1.26 (0.62–2.55)</td>
<td>0.521</td>
</tr>
<tr>
<td>Approach preferring estimates derived from total follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis versus general population</td>
<td>6</td>
<td>1.65 (1.07–2.55)$^R$</td>
<td>0.022</td>
</tr>
<tr>
<td>Subanalysis on SIRs</td>
<td>4</td>
<td>1.42 (0.74–2.76)$^R$</td>
<td>0.294</td>
</tr>
<tr>
<td>Subanalysis on ORs</td>
<td>2</td>
<td>2.13 (1.45–3.13)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Analysis versus infertile women$^d$</td>
<td>2</td>
<td>1.05 (0.55–2.01)</td>
<td>0.874</td>
</tr>
</tbody>
</table>

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.
- **$n^a$**: number of studies.
- **$P^b$**: $P$-value derived from Cochran Q statistic.
- **$R^c$**: 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.

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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 Leeuwen et al., 2011; Cetin et al., 2008) included studies provided adjusted effect estimates.

**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.
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

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**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.
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.,

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.
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 (Meirov 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/.

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**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 will act as a guarantor of the study. 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. 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. P.T. 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. 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. S.A. 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. 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, and gave final approval of the version to be published. B.W. 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.C. 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. L.O. 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.

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**Conflict of interest**

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