Does ovarian stimulation for IVF increase gynaecological cancer risk? A systematic review and meta-analysis

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Abstract The aim of this study was to evaluate whether ovarian stimulation for IVF increases the risk of gynaecological cancer, including ovarian, endometrial, cervical and breast cancers, as an independent risk factor. A systematic review and meta-analysis was conducted. Clinical trials that examined the association between ovarian stimulation for IVF and gynaecologic cancers were included. The outcomes of interest were incidence rate of gynaecologic cancers. Twelve cohort studies with 178,396 women exposed to IVF were included; 10 studies were used to analyse ovarian (167,640 women) and breast (151,702 women) cancers, and six studies were identified in the analysis of endometrial (116,672 women) and cervical cancer (114,799 women). Among these studies, 175 ovarian, 48 endometrial, 502 cervical and 866 cases of breast cancer were reported. The meta-analysis found no significant association between ovarian stimulation for IVF and increased ovarian, endometrial, cervical and breast cancer risk (odds ratio [OR] 1.06, 95% confidence interval [CI] 0.85 to 1.32; OR 0.97, 95% CI 0.58 to 1.63; OR 0.43, 95% CI 0.30 to 0.60; OR 0.69, 95% CI 0.63 to 0.76, respectively). Ovarian stimulation for IVF, therefore, does not increase the gynaecologic cancer risk, whether hormone-dependent endometrial and breast cancer or non-hormone-dependent ovarian and cervical cancer.

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Introduction

Prevention and treatment of subfertility is an emerging public health priority (Wright et al., 2005; CDC, 2010), and an increasing number of infertile women are seeking and receiving subfertility treatment, particularly IVF (Connolly et al., 2009; Kimberly et al., 2012; Nyboe Andersen et al., 2004; Stephen and Chandra, 1998). Nowadays, a large proportion of these women undergo ovarian stimulation and IVF. In the USA alone, a figure between 5.4 and 7.7 million women aged between 15 and 44 years will have been estimated to seek medical advice for fertility problems by the year 2025 (Stephen and Chandra, 1998).

Ovarian stimulation exposes the ovaries to supraphysiological levels of gonadotrophins and results in multiple follicular developments for assisted conception. Gonadotrophins are administered to stimulate ovulation, and 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 (Konishi, 2006; Konishi et al., 1999; Risch, 1998), along with up to a five-fold increase in normal blood concentrations of oestradiol (MacLachlan et al., 1989). A study (Stewart et al., 2012) has critically approached the transient but sizeable increased level of oestrogen, which reaches nearly 3000–4000 pg/ml in an IVF cycle compared with only 300 pg/ml in a normal cycle (Joo et al., 2010; MacLachlan et al., 1989). To inhibit a premature rise in LH and prevent ovulation, gonadotrophin releasing hormone (GnRH) agonists and antagonists are the most frequently used components of the regimens; small continuous doses of agonists exert a reversible medically induced menopause by removing the overlay of gonadal steroids (Conn and Crowley, 1994), whereas antagonists directly prevent a premature rise of LH (Oliveira et al., 2006).

Gynaecological cancer epidemiology has made substantial progress in recent decades, revealing numerous risk factors for the disease; they include not only hormone-related factors, but also non-hormonal conditions. Hormone-related risk factors have traditionally meant the exposure to endogenous and exogenous oestrogens and progesterone.

The fundamental consideration for either ovarian stimulation, under either or both circumstances, increases the chance of gynaecological cancer as an independent risk factor. Reports on a tentative association between fertility medication received for subfertility, and several types of gynaecological cancers, notably ovarian, endometrial, cervical and breast cancers, have appeared since the mid-1960s, but sound scientific evidence is limited.

Earlier published papers (Akhmedkhanov et al., 2001b; Brinton et al., 2005; Rossing et al., 1994; Whitemore and Evers, 2003; Mahdavi et al., 2006; Vlahos et al., 2010a; Zreik et al., 2008). In fact, evidence of a tentative direct tumorigenic effect of fertility medication for ovarian stimulation is weak and controversial, and relies mainly on in vitro studies (Huhtaniemi, 2010).

In the present study, published studies on the association between ovarian stimulation for IVF and risk of ovarian, endometrial cervical and breast cancers were systematically reviewed and meta-analysed by disentangling a variety of methodological notions that might modify the effect measures.

Materials and methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009) and in line with the a-priori protocol agreed by all authors.

Identification of the literature

The following electronic databases were searched: MEDLINE, Google Scholar and the Cochrane Library from inception until May 2014. The following medical subject and text words were used to search relevant studies: one including terms on gynaecological cancers (ovarian cancer or endometrial cancer or cervical cancer or breast cancer), and the other about reproductive techniques (ovarian stimulation or IVF). These subsets were combined with ‘AND’ to generate a subset of studies relevant to our research question. Only full articles published in English were searched. Two investigators independently reviewed the papers for eligibility, and discrepancies were resolved by group discussion.

Study selection and data extraction

Studies that evaluated the association between ovarian stimulation and gynaecological cancers in couples undergoing IVF using the general population or infertile women as reference population were selected. Case series and case reports, in-vitro and animal studies, narrative or systematic reviews and studies exclusively assessing the treatment of cancer or fertility preservation after cancer treatment were excluded. Studies examining precursor lesions were also excluded. Studies about ovarian stimulation not for IVF, as well as studies examining fertility drugs as a whole were not included. The primary outcome of interest was incidence rate of gynaecological cancers. For eligible studies, outcome data were extracted in 2 × 2 tables. Other information was also recorded. This included general information (title, author, year, journal, geographical and clinical setting), study characteristics (age, ascertainment of exposure and outcome, protocol of IVF, histology, type of infertility, stimulation drugs before IVF, matching factors) and results (i.e. number of participants, reference population). Two reviewers completed the quality assessment, and any disagreements about
inclusion were resolved by consensus or arbitration by a third reviewer.

Statistical analysis

The comparisons of study-by-study were synthesized by a standard meta-analytic approach applied to the relative risks of the individual 2 × 2 tables. Heterogeneity of the exposure effects was evaluated graphically using Forest plots and statistically using the I² statistic to quantify heterogeneity across studies. Fixed or random effect model for meta-analysis was applied to calculate an overall relative risk and its 95% confidence interval [CI]. As the chi-squared test for heterogeneity has low power in the situation of a meta-analysis when studies have small sample size or are few in number, a P-value of 0.10 rather than the conventional level of 0.05, was used to determine statistical significance. RevMan 5.0 (Cochrane Collaboration, Oxford, UK) was used for statistical analyses.

Results

Study selection and characteristics

The search strategy yielded 2683 records. Review of the titles and abstracts indicated that 2618 were not relevant. Of the 65 remaining publications, 43 were excluded for various reasons. A further four studies were excluded as all their data were duplicated in a later paper, which we have included in our meta-analysis. An additional six papers were excluded because a 2 × 2 table could not be constructed from the text (Supplementary Figure S1).

The study characteristics are presented in Table 1. The total number of eligible studies included in the review was 12 (10 studies for ovarian cancer and breast cancer, respectively; six studies for endometrial cancer and cervical cancer, respectively). The selected 12 studies included a total of 178,396 women exposed to IVF, yielding 175 reported cases of ovarian, 48 of endometrial, 50 of cervical and 866 of breast cancer.

Nine studies reported comparisons versus the general population, and four studies comparisons between infertile women directly or indirectly. Four studies reported two follow-up intervals (total follow-up or excluding first year after IVF).

Meta-analysis

The meta-analysis was conducted to address the question of a relative increased risk for specific cancer types after ovarian stimulation for IVF.

Ovarian cancer

Ten studies were included in our meta-analysis to evaluate the association between ovarian stimulation for IVF and the risk of ovarian cancer. The analysis of studies preferring estimates which included the first year of follow-up after IVF is presented as Figure 1. A significant increased ovarian cancer risk was not found in women undergoing ovarian stimulation for IVF. The results achieved good statistical homogeneity (I² = 0%). The fixed-effects model combined odds ratio was 1.06 (95% CI 0.85 to 1.32; P = 0.59) (Figure 1).

Endometrial cancer

In the present study, six were included to evaluate the association between IVF and increased endometrial cancer risk. The result of the meta-analysis indicated no significant increased endometrial cancer incidence rate in patients with IVF. The Q statistic P-value was above 0.1, indicating homogeneity of the studies (I² = 16%). The fixed-effects model was implied and the combined odds ratio (OR) was 1.97 (95% CI, 0.58 to 1.63) (Figure 2).

Cervical cancer

Six studies were included to evaluate the effect of IVF on cervical cancer. A significant increase was not found in incidence rate of cervical cancer in patients with IVF compared with reference women. The Q statistic P-value was above 0.1, indicating heterogeneity of the studies (I² = 83%; P = 0.0001). The random-effects model was implied and the combined OR was 0.43 (95% CI 0.30 to 0.60; P = 0.00001) (Figure 3).

Breast cancer

Eight studies were included to examine the association between IVF and breast cancer. The meta-analysis of studies used data derived from total follow-up. Studies treating the general population and the infertile women as reference group did not point to a statistically significant association between IVF and breast cancer risk. Similar to the evaluation of cervical cancer risk, the Q statistic P-value was above 0.1, indicating heterogeneity of the studies (I² = 87%; P = 0.00001). The random-effects model was implied and the combined OR was 0.69 (95% CI 0.63 to 0.76; P = 0.00001) (Figure 4).

The studies scored well on the Newcastle–Ottawa Quality Assessment Scale (not shown). The funnel plots of meta-analysis evaluating the effect of ovarian stimulation for IVF on ovarian, endometrial and breast cancer suggests a lack of publication bias owing to their symmetrical shape, although a small study may have been missed (Supplementary Figures S2 and 4). Studies showed, however, modest publication bias when the effect of ovarian stimulation was assessed for IVF on cervical cancer (Supplementary Figure S5).

Discussion

So far, only a few systematic reviews have evaluated the association between ovarian stimulation for IVF and gynaecological cancers, including ovarian, endometrial, cervical and breast cancer (Sergentanis et al., 2014; Siristatidis et al., 2013). The present study is, to the best of our
<table>
<thead>
<tr>
<th>Study publication</th>
<th>Country region</th>
<th>Study period</th>
<th>Mean follow-up in total cohort (years)</th>
<th>Mean follow-up in exposed women (years)</th>
<th>Cancer site</th>
<th>Study protocol for IVF</th>
<th>Reference group</th>
<th>Adjusting factors</th>
<th>Excludes first year of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venn et al. (1999)</td>
<td>Australia</td>
<td>1978-1993</td>
<td>8.5</td>
<td>7.0</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>None</td>
<td>No</td>
</tr>
</tbody>
</table>
| Dor et al. (2002) | Israel        | 1991-1996    | 3.6                                  | 3.6                                    | Yes         | Yes                  | (1) CC/HMG, FSH, LH; (2) HMG; (3) GnRH
                                                     |               |                          |                                      |             | Yes                  | General population |
| Lerner-Geva et al. (2010) | Israel | 1984-1996    | 6.5                                  | 6.5                                    | Yes         | –                   | None           | Both           | No                  |
| Kristiansson et al. (2007) | Sweden | 1981-2001    | 11.5                                 | 6.4                                    | Yes         | Yes                  | None           | None           | No                  |
| Pappo et al. (2008) | Israel        | 1986-2004    | 8.1 ± 4.3                            | 8.1 ± 4.3                              | Yes         | –                   | No mention    | Year of delivery, maternal age at delivery and smoking |
| Källén et al. (2011) | Sweden        | 1982-2006    | NR                                   | 8.3                                    | Yes         | Yes                  | No mention    | No             | No                  |
| van Leeuwen et al. (2011) | Netherlands | 1983-2007    | 14.8                                 | 14.3                                   | Yes         | –                   | Both          | Age at end of follow-up, endometriosis |
| Stewart et al. (2012) | Western Australia | 1983-2010    | 16.3 ± 5.6                           | 16.1 ± 4.8                             | Yes         | –                   | Infertile women |
| Yli-Kuha et al. (2012) | Finland       | 1996-2004    | 7.8                                  | 7.8                                    | Yes         | Yes                  | General population |
| Brinton et al. (2013) | Israel        | 1994-2013    | 8.1                                  | 8.1                                    | Yes         | Yes                  | Infertile women |
| Stewart et al. (2013) | Western Australia | 1982-2002    | 16.7 ± 5.9                           | 16.7 ± 5.9                             | Yes         | –                   | Classical IVF protocol |

BMI = body mass index; CC = clomiphene citrate; GnRH = gonadotrophin-releasing hormone; GnRHa = gonadotrophin-releasing hormone agonist; HMG = human menopausal gonadotrophin; ICSI = intractoplasmic sperm injection; NR = not relevant.
knowledge, the largest in sample size, with 178,396 women having undergone IVF treatment. In the present systematic review, 10 studies evaluated the association between IVF and ovarian cancer, 6 studies evaluated the association between IVF and endometrial cancer, 6 studies evaluated the association between IVF and cervical cancer, and 6 studies evaluated the association between IVF and breast cancer.

Enlarging the perspective, the results of the present meta-analysis showed that ovarian stimulation for IVF was not associated with increased risk for endometrial, ovarian, cervical and breast cancer, which is in line with the evidence from previous reviews on ovarian stimulation drugs. Most found no relationship between medication and ovarian cancer (Brinton, 2007; Brinton et al., 2005; Devesa et al., 2010; Impicciatore and Tiboni, 2011; Källén, 2008; Kanakas and Mantzavinos, 2006; Kashyap et al., 2004; Lerner-Geva et al., 2010; Mahdavi et al., 2006; Ness et al., 2002; Venn et al., 2003; Vlahos et al., 2010a, 2010b), endometrial cancer (Brinton, 2007; Källén, 2008; Kanakas and Mantzavinos, 2006; Kashyap et al., 2004; Lerner-Geva et al., 2010; Mahdavi et al., 2006; Ness et al., 2002; Venn et al., 2003; Vlahos et al., 2010a, 2010b), cervical cancer (Källén, 2008; Kashyap et al., 2004; Venn et al., 2003; Vlahos et al., 2010a, 2010b), and breast cancer (Brinton, 2007; Källén, 2008; Kanakas and Mantzavinos, 2006; Kashyap et al., 2004; Lerner-Geva et al., 2010; Mahdavi et al., 2006; Ness et al., 2002; Venn et al., 2003; Vlahos et al., 2010a, 2010b).
2008; Kanakas and Mantzavinos, 2006; Vlahos et al., 2010a) or breast cancer (Sergentanis et al., 2014; Zreik et al., 2010), whereas in other studies, the results were inconclusive (Ayhan et al., 2004; Glud et al., 1998; Impicciatore and Tiboni, 2011; Lerner-Geva et al., 2010; Meirow and Schenker, 1996; Zreik et al., 2008). In two studies, a direct relationship was attributed (Bukovic et al., 2011; Whittemore et al., 1992), 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 assisted reproduction techniques than the expected reproductive benefits (Kashyap et al., 2004).

Ten earlier studies were included that assessed the relationship of IVF to ovarian cancer risk in our meta-analysis, involving 167,640 women with IVF and 175 ovarian cancer cases. The meta-analysis of studies showed a combined OR of 1.06 (95% CI 0.85 to 1.32).

Infertile women undergoing IVF may have supraphysiological levels of oestrogen, and often involves repeated ovarian punctures and resultant trauma to the ovarian surface epithelial cells (Fishel and Jackson, 1989; Merviel et al., 2009). Theoretically, all of these could lead to the incidence of ovarian cancer. We did not find such an association. Some possible explanation are as follows.

First, oestrogenic drugs are known to stimulate cell proliferation in cells containing oestrogen receptors, and use of oestrogen replacement after IVF has been suggested to cause an increased risk of ovarian cancer in several studies (Clinton and Hua, 1997; Garg et al., 1998). Contrary to oestrogen, progesterone receptors seem to exert a protective role against ovarian cancer (Risch, 1998). Decreased progesterone receptor is found in ovarian malignancies (Noguchi et al., 1993). The increased endogenous oestrogen-to-progesterone ratio in women with oligo-ovulation may explain the increased incidence of ovarian cancer in the reference group of infertile women (Bu et al., 1997).

Second, now extensive clinical and epidemiological data link endometriosis to an increased risk of ovarian cancer. Ness (2003) has discussed similarities between the proposed cause of ovarian cancer and the observed pathophysiology of endometriosis. The synchronous occurrence of endometriosis with endometrioidal, clear cell, and mixed subtypes of ovarian cancers suggests transformation of endometriosis constituents into cancer cells. Ness et al. (2002) have demonstrated an association between alterations in bcl-2 and p53 proteins with malignant transformation of endometriotic cysts. All known, bcl-2 and p53 proteins are important factor to the cell apoptosis. Endometriosis as a common cause of infertility can provide another possible explanation for ovarian carcinogenesis in this population.

On the basis of several studies addressing pre-IVF exposures on endometrial cancer risk (Althuis et al., 2005; Calderon-Margalit et al., 2009a; dos Santos Silva et al., 2009; Jensen et al., 2009a; Liat et al., 2012), we had hypothesized increased in risk, but the observed associations were fairly modest and not statistically significant. Owing to the relative rarity of endometrial cancer and the relatively few events, only six earlier studies that assessed the relationship of IVF to endometrial cancer risk were included in our meta-analysis, involving 116,672 women with IVF and 48 endometrial cancer cases. The meta-analysis showed a combined OR 0.97 (95% CI 0.58 to 1.63).

Endometrial cancer is the most common cancer of the lower female reproductive system, accounting for 8% of all cases (Akhmedkhanov et al., 2001a; Bamberger et al., 1998; Boring et al., 1994); most of the cases were hormone-dependent cancer. In fact, a hyper-oestrogenic milieu and changes in endometrial secretory profiles through higher concentrations of various molecules caused by supraphysiological gonadotrophin levels during ovarian stimulation (Boomsma et al., 2010; Fishel and Jackson, 1989) represent risk factors. Of note, polycystic ovary syndrome and unexplained infertility have also been linked directly to endometrial cancer (Escobedo et al., 1991; Gregory et al., 2002; Homburg, 1996; Navaratnarajah et al., 2008; Venn et al., 1999).

Earlier studies that have observed elevated endometrial cancer risks in relation to fertility drugs have mainly focused on clomiphene, a selective oestrogen receptor modulator with chemical properties similar to tamoxifen (Sovino et al., 2002), a drug linked with endometrial cancer risk increases (Varras et al., 2003). One study (Brinton et al., 2013), in which the
most drug exposure was for gonadotrophins routinely used for IVF, showed that the highest endometrial cancer risks were among women receiving one to three IVF cycles, although small numbers were involved. In the present systematic review and meta-analysis, however, no significant association was found between ovarian stimulation and endometrial cancer.

Six studies on cervical cancer, with 502 cases, were included in the meta-analysis and the analysis of odds ratios pointed to a rather inverse association with a combined OR of 0.43 (95% CI 0.30 to 0.60; \( P < 0.00001 \)), namely a protective role of IVF.

A lower incidence of cervical cancer among infertile women attending infertility clinics has also been reported in other studies (Doyle et al., 2002; Jensen et al., 2008; Silva Idos et al., 2009). The incidence of cervical cancer depends on sexual behaviour, and it is possible that women who seek IVF are considered to have stable sexual relations and hence could be at a low risk for this type of cancer. Furthermore, this difference could be explained by surveillance bias, as it is likely that IVF women are used to visiting their gynaecologists regularly and thus more Pap smears are taken, which enable earlier treatment of suspicious cell atypia (Raz et al., 2012). Additionally, women diagnosed with cervical intra-epithelial neoplasia were not included in most of the selected primary studies.

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. 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 before developing cervical cancer. Additionally, parity (International Collaboration of Epidemiological Studies of Cervical Cancer, 2006) and socioeconomic status (SES) (Parikh et al., 2003) have been associated with decreased cervical cancer risk; in the study by Yli-Kuha et al. (2012), SES adjusted for, and in the study by Källén et al. (2005), women who gave birth without adjustment for SES were included. None of the studies in this analysis, however, controlled for both factors.

Hormonal factors are increasingly being recognized as important in the progression and persistence of human papillomavirus infection (González et al., 2010), the causal agent for cervical cancer.

The meta-analysis currently available for studies on IVF and breast cancer risk pointed to an overall lack of association between ovarian stimulation for IVF and subsequent breast cancer risk. Ten earlier studies that assessed the relationship of IVF and breast cancer risk were included in the meta-analysis, involving 151,772 women with IVF and 866 breast cancer cases. The meta-analysis showed a combined OR of 0.69 (95% CI 0.63 to 0.76; \( P < 0.00001 \)). A variety of explanations have been attributed to the protective association that emerged in the analysis of studies presenting odds ratios versus the general and infertile population.

First, it has been postulated that some pregnancy-related risk factors that seem to protect from breast cancer, such as pre-eclampsia (Calderon-Margalit et al., 2009b; Nechuta et al., 2010; Opdahl et al., 2012) and multiple birth (Hsieh et al., 1993; Ji et al., 2007), may occur more frequently in IVF pregnancies (Källén et al., 2005), and thus mediate the protection that the latter may offer (Källén et al., 2011).

Second, the relatively transient period of increased circulating oestrogens associated with an IVF cycle (Joo et al., 2010; MacLachlan et al., 1989) may not be sufficient to substantially modify breast cancer risk in quantitative terms.

Additionally, other intriguing explanations have been suggested, such as the ‘healthy patient effect’, according to which women seeking fertility treatment may be relatively healthier or from privileged socioeconomic status than their general population counterparts (Yli-Kuha et al., 2012).

As expected, ovarian stimulation for IVF does not seem to increase the risk both for the non-hormone-dependent cervical cancer and for hormone-dependent ovarian, breast and endometrial cancer. The associations examined in this meta-analysis, however, should be interpreted with caution owing to the limitations of this meta-analysis.

The limitations of this meta-analysis may partly reflect the inherent limitations of the constituent studies, including small number of study subjects in the literature, imprecise information on drug exposures, risk of treatment, meaningful confounders and relatively short follow-up periods. Only one study (Stewart et al., 2012) encompassed a follow-up period of over 10 years among exposed women; given that exposure to IVF mainly occurred during the woman’s reproductive years, an adequate follow-up period seems indispensable to effectively assess particularly the risk of post-menopausal breast cancer. Additionally, the primary studies included for cervical and breast cancer analyses were shown to be heterogeneous, which was also a limitation.

Notwithstanding these limitations, the present systematic review and meta-analysis provides a useful summary of the results of scientific publications so far, because of clear definitions of exposures (ovarian stimulation for IVF) and outcomes.

In summing up the results of published studies, ovarian stimulation for IVF is not associated with elevated ovarian or endometrial cancer risk, nor seems to be associated with cervical or breast cancer. To disentangle the sole effect of ovarian stimulation for IVF on gynaecological cancers, further cohort studies should preferably use infertile population as the reference group, adjust for a variety of meaningful confounders and adopt relatively longer follow-up periods in order to draw sound conclusions.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.rbmo.2015.03.008.

References


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