In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk

Louise M. Stewart a,⁎, C. D’Arcy J. Holman a, Patrick Aboagye-Sarfo a, Judith C. Finn b,c, David B. Preen a, Roger Hart d,e

a School of Population Health, Faculty of Medicine, Dentistry and Health Sciences, The University of Western Australia, M431, 35 Stirling Highway, Crawley, WA 6009, Australia
b School of Primary, Aboriginal and Rural Health Care, Faculty of Medicine, Dentistry and Health Sciences, The University of Western Australia, MS16, 35 Stirling Highway, Crawley, WA 6009, Australia
c Department of Epidemiology and Preventive Medicine, Monash University, The Alfred Centre, 99 Commercial Road, Melbourne, Vic 3004, Australia
d School of Women’s and Infant’s Health, Faculty of Medicine, Dentistry and Health Sciences, The University of Western Australia, King Edward Memorial Hospital, 374 Bagot Road, Subiaco, WA 6008, Australia
e Fertility Specialists of Western Australia, Bethesda Hospital, 25 Queenslea Drive, Claremont, WA 6010, Australia

HIGHLIGHTS

► Infertile women who remain nulliparous have an increased risk of ovarian cancer.
► In nulliparous, endometriosis increases risk and IVF may also be a risk factor.
► There is little or no increase in risk with IVF or endometriosis in parous women.

ABSTRACT

Objectives. To examine the risk of invasive epithelial ovarian cancer in a cohort of women seeking treatment for infertility.
Methods. Using whole-population linked hospital and registry data, we conducted a cohort study of 21,646 women commencing hospital investigation and treatment for infertility in Western Australia in the years 1982–2002. We examined the effects of IVF treatment, endometriosis and parity on risk of ovarian cancer and explored potential confounding by tubal ligation, hysterectomy and unilateral oophorectomy/salpingo-oophorectomy (USO).
Results. Parous women undergoing IVF had no observable increase in the rate of ovarian cancer (hazard ratio [HR] 1.01; 95% confidence interval [CI] 0.35–2.90); the HR in women who had IVF and remained nulliparous was 1.76 (95% CI 0.74–4.16). Women diagnosed with endometriosis who remained nulliparous had a three-fold increase in the rate of ovarian cancer (HR 3.11; 95% CI 1.13–8.57); the HR in parous women was 1.52 (95% CI 0.34–6.75). In separate analyses, women who had a USO without hysterectomy had a four-fold increase in the rate of ovarian cancer (HR 4.23; 95% CI 1.30–13.77). Hysterectomy with or without USO appeared protective.
Conclusions. There is no evidence of an increased risk of ovarian cancer following IVF in women who give birth. There is some uncertainty regarding the effect of IVF in women who remain nulliparous. Parous women diagnosed with endometriosis may have a slightly increased risk of ovarian cancer; nulliparous women have a marked increase in risk.

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Introduction

Sadly, ovarian cancer is often diagnosed too late. There remains a pressing need to identify early warning signs and groups of women at increased risk.

Subfertile women have been shown to be at increased risk of ovarian cancer [1,2], and women who undergo treatment with in vitro fertilization (IVF) may be at even greater risk. Only a small number of studies have examined the relationship between IVF treatment and ovarian cancer risk [3–9]. Of these, four did not find an association between IVF and risk of ovarian cancer [4–7], while three found an increased risk of ovarian cancer in IVF patients; one with extended follow-up [9], another in a comparison that was restricted to women who gave birth [3] and a third in women who purchased drugs for IVF, compared with general population controls [8]. Research in this field is limited by short periods of follow-up, small numbers of ovarian cancer cases and
comparisons with the general population which do not allow for adjustment for parity or other important risk factors.

In view of this conflicting evidence and the limitations described and in light of the poor prognosis for women diagnosed with ovarian cancer (only around 40% of women survive more than 5 years beyond diagnosis) [10], we believe this important issue warrants further investigation. The aim of the present study was to examine the risk of invasive epithelial ovarian cancer in a cohort of women seeking infertility treatment, comparing the risk in women who had IVF with those who did not, whilst at the same time considering the impact of infertility diagnosis, in particular endometriosis, and parity, surgical sterilization, hysterectomy, unilateral oophorectomy or salpingo-oophorectomy, age and socio-economic status.

Materials and methods

The study cohort

The study cohort included all women in Western Australia (WA) seeking hospital investigation or treatment for infertility during the years 1982–2002. We have previously described a similar cohort established using the same methods for a study on IVF and breast cancer [11]. Women in the study cohort had at least one hospital diagnosis of infertility or procreative management (ICD-9 628.0 to 628.9 or ICD-10 N97.0 to N97.9 or ICD-9 V26.1 to V26.9 or ICD-10 Z31.1 to Z31.9), with the first such diagnosis occurring when they were aged between 20 and 44 years inclusive.

Data sources

The study cohort and outcomes of interest were identified using the resources of the WA Data Linkage System [12]. Data on exposures and outcomes was collated in de-identified format from 1980 to 2010 (covering the recruitment period plus 2 years before and 8 years after). Information was extracted from the Hospital Morbidity Data System to identify the cohort and also to identify relevant diagnoses and surgical procedures. The Hospital Morbidity Data System collates information on all inpatient admissions at all hospitals in WA. We retained information on diagnoses of endometriosis and pelvic inflammatory disorders (PID – ICD-9 codes 614.0 to 614.9; ICD-10 codes N70.1, N70.9, N73.0 to N73.9), and the following procedures: hysterectomy, unilateral oophorectomy or salpingo-oophorectomy (USO), bilateral oophorectomy or salpingo-oophorectomy (BSO), tubal ligation and IVF treatment as these factors were believed to potentially influence the risk of ovarian cancer. IVF cycles were identified using the Hospital Morbidity Data System and the Reproductive Technology Register. Linkage to the Midwives Notification System enabled us to identify births; deaths were identified from the Deaths Register and cancer diagnoses from the WA Cancer Registry. We attempted to minimise loss to follow-up by restricting the cohort to women known to be resident in WA. Women who moved interstate after 1988 (when linkage commenced) were excluded from the WA Electoral Roll; these were excluded from the study population as were women who had an interstate or overseas address on their hospital records. Socio-economic status using location of residence was derived from the address recorded on the woman’s hospital record at the first infertility diagnosis. The Index of Education and Occupation was chosen to represent socio-economic status [13].

Explanatory variables

We explored the potential relationship between IVF and ovarian cancer risk, and considered the variables identified above as possible confounders in this relationship. All variables were first examined separately in univariate and age-adjusted models and then, where appropriate, were included in the final model, according to methods described by Hosmer, Lemeshow and May [14]. Variables under consideration included IVF, age, socio-economic status, PID, endometriosis, birth, USO, tubal ligation and hysterectomy. Variables that were set at the start of follow-up (age, socio-economic status, diagnosis of PID or endometriosis) were entered into the model as fixed covariates; variables that could change status during follow-up (birth, tubal ligation, USO, hysterectomy and IVF) were entered as time-dependent variables. In this way, follow-up time was correctly apportioned into time before and time after exposure. Age was divided into quartiles (20–27, 28–31, 32–35, 36–44 years) and entered into the model as a categorical variable. Socio-economic status was entered into the model as a binary variable with the upper quartile compared to the lower three quartiles combined.

We captured all births in WA during 1980–2010, as well as previous births in women confined in WA during this time period, but the small proportion of births occurring either out of the state or prior to 1980 in women who did not also give birth in WA were unknown to us. In addition, we found that a small proportion of women had a reversal without prior mention of a tubal ligation. We were able to correctly classify these women, however it is likely there would also be women who had a tubal ligation that was unrecorded and no later reversal, opting instead simply to have IVF. We were unable to classify this small proportion of women correctly. Women with PID or endometriosis had these diagnoses recorded in their hospital records at or before the start of follow-up. It was possible that other women in the cohort also suffered from these conditions, though they remained undiagnosed, or were diagnosed later during follow-up.

Outcome variable

The outcome of interest was invasive epithelial ovarian cancer. Borderline ovarian tumours and non-epithelial tumours were excluded as outcome events, but women who were diagnosed with these were still included in the study population. Follow-up was censored in women who were diagnosed with borderline ovarian tumours only if they underwent a BSO. Otherwise they were considered to be still at risk of invasive epithelial ovarian cancer and were treated as such in the analysis.

Data analysis

Hazard ratios (HRs) were estimated using Cox regression models. Follow-up commenced at the date of first infertility admission and continued until the date of epithelial ovarian cancer diagnosis, date of BSO, date of death or censor date (15 August 2010), whichever came first. Data were analysed using SPSS version 19.

Ethics approval

This study received ethics approval from The University of Western Australia Human Research Ethics Committee and the Department of Health WA Human Research Ethics Committee.

Results

The cohort

A total of 22,045 women had a first diagnosis of either infertility or procreative management between 1982 and 2002 when they were aged between 20 and 44 years inclusive, and were eligible for inclusion in the cohort. Of these, 379 were identified as having an interstate address or having moved out of the State and were excluded. A further 20 women were excluded because they were considered not to be at risk of a diagnosis of ovarian cancer after the start of infertility treatment. These included 13 women who had a BSO before their first infertility admission and 7 women who were diagnosed with ovarian cancer...
prior to or within 6 months of their first infertility admission. The final cohort therefore comprised a total of 21,646 women.

The mean and median ages at the start of follow-up were both 31 years; the mean and median ages at the end of follow-up were both 48 years. The total duration of follow-up was 366,041 person-years with a mean of 17 years. Ovarian cancer was diagnosed in women in the cohort when they were aged between 33 and 61 years; the mean age at diagnosis was 46 years. There were 38 cases of ovarian cancer in the cohort: 16 in women undergoing IVF and 22 in women not undergoing IVF (Table 1).

**Ovarian cancer risk factors**

The association between IVF, potential confounding factors and ovarian cancer rate was examined in age-adjusted analysis (Table 2) and then in multivariate analysis (Table 3).

The age-adjusted rate of ovarian cancer in women in the cohort undergoing IVF, compared with women seeking infertility treatment but not IVF, was 1.40 (95% confidence interval [CI] 0.73–2.68) (Table 2).

Women who gave birth had a reduced rate of ovarian cancer (Table 2).

The most common diagnoses at baseline in women seeking infertility investigation and treatment were PID and endometriosis. We did not find an association between PID and ovarian cancer, but we did note an increased age-adjusted rate of ovarian cancer in women diagnosed with endometriosis (Table 2).

Women in the upper quartile of socio-economic status, as measured by the Index of Education and Occupation, had a reduced rate of ovarian cancer (Table 2).

Of the surgical procedures we identified, we found that tubal ligation was associated with a reduced rate of ovarian cancer. Hysterectomy performed with or without USO also appeared protective, though CIs around all these estimates included one. In contrast, USO performed without hysterectomy was associated with an increased rate of ovarian cancer (Table 2).

We retained the following variables in the final model: IVF, birth, endometriosis, age and socio-economic status. We examined the relationship between these variables and the rate of ovarian cancer firstly in the whole cohort, and then separately in women who gave birth and women who did not. Results of the multivariate analyses are presented in Table 3.

Consistent with the age-adjusted results presented in Table 2, in the multivariate model we found that having given birth was protective, undergoing IVF was associated with a slightly increased rate of ovarian cancer and the diagnosis of endometriosis was associated with an increased rate of ovarian cancer (Table 3, first column of results).

When we examined women separately according to whether they had given birth, we found that the effect of both IVF and endometriosis were more pronounced in women who did not give birth than in women who did (Table 3, second and third columns of results). In women who remained childless, IVF treatment was associated with a 76% increase in the rate of ovarian cancer which was not

**Table 2** Potential ovarian cancer risk and protective factors: age-adjusted analysis.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVF</td>
<td>1.40 (0.73–2.68)</td>
</tr>
<tr>
<td>Birthb</td>
<td>0.48 (0.25–0.93)</td>
</tr>
<tr>
<td>PIDc</td>
<td>1.02 (0.42–2.43)</td>
</tr>
<tr>
<td>Endometriosisd</td>
<td>2.23 (0.97–5.12)</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>0.66 (0.26–1.68)</td>
</tr>
<tr>
<td>Hysterectomyd</td>
<td>0.55 (0.13–2.32)</td>
</tr>
<tr>
<td>Hysterectomy with USOd</td>
<td>0.72 (0.10–5.27)</td>
</tr>
<tr>
<td>USOd</td>
<td>4.23 (1.30–13.77)</td>
</tr>
<tr>
<td>High socioeconomic statusg</td>
<td>0.52 (0.22–1.25)</td>
</tr>
</tbody>
</table>

Legend:

- a Hazard ratios derived from separate Cox regression models, adjusted for age at the start of follow-up and including only the variable listed. Each hazard ratio compares women in the exposed group with all other women in the cohort who did not have the exposure.
- b Women who gave birth to at least one child were compared with women who did not give birth.
- c PID and endometriosis were both diagnosed at, or prior to the first infertility admission.
- d Women who had a hysterectomy without USO in the same or any other admission.
- e Women who had both a hysterectomy and a USO in the same or separate admissions.
- f Women who had a USO without hysterectomy in the same or any other admission.
- g Women in the upper quartile of the Index of Education and Occupation were compared with women in the lower three quartiles combined.

**Table 1** Characteristics of the study population.a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All women in the cohort</th>
<th>Women undergoing infertility treatment but not IVF</th>
<th>Women undergoing IVF treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women</td>
<td>21,646</td>
<td>14,098</td>
<td>7,548</td>
</tr>
<tr>
<td>Number of women who gave birth</td>
<td>14,907</td>
<td>10,012</td>
<td>4,875</td>
</tr>
<tr>
<td>Number of women diagnosed with ovarian cancer</td>
<td>38</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Mean length of follow-upb (years)</td>
<td>16.9±5.9</td>
<td>17.0±5.9</td>
<td>16.7±5.9</td>
</tr>
<tr>
<td>Total length of follow-up (years)</td>
<td>366,041</td>
<td>240,203</td>
<td>125,837</td>
</tr>
<tr>
<td>Mean age at start of follow-up (years)</td>
<td>31.2±5.2</td>
<td>30.8±5.3</td>
<td>32.1±4.8</td>
</tr>
<tr>
<td>Mean age at first birth (years)</td>
<td>29.6±6.0</td>
<td>28.3±5.8</td>
<td>32.2±5.4</td>
</tr>
<tr>
<td>Mean age at ovarian cancer diagnosis (years)</td>
<td>46.0±7.0</td>
<td>46.7±8.2</td>
<td>44.9±4.8</td>
</tr>
<tr>
<td>Mean age at end of follow-up (years)</td>
<td>48.0±7.1</td>
<td>47.7±7.2</td>
<td>48.7±6.9</td>
</tr>
<tr>
<td>Number of women diagnosed with PIDc</td>
<td>3,890</td>
<td>2,576</td>
<td>1,314</td>
</tr>
<tr>
<td>Number of women diagnosed with endometriosisd</td>
<td>2,978</td>
<td>1,914</td>
<td>1,064</td>
</tr>
<tr>
<td>Number of women who underwent tubal ligation</td>
<td>3,740</td>
<td>2,856</td>
<td>884</td>
</tr>
<tr>
<td>Number of women who had a hysterectomyd</td>
<td>2,188</td>
<td>1,599</td>
<td>589</td>
</tr>
<tr>
<td>Number of women who had a hysterectomy with USOd</td>
<td>696</td>
<td>488</td>
<td>208</td>
</tr>
<tr>
<td>Number of women who had a USOd</td>
<td>500</td>
<td>276</td>
<td>224</td>
</tr>
<tr>
<td>Number of women in the highest quartile of socioeconomic status (%)</td>
<td>5,268 (24%)</td>
<td>2,928 (21%)</td>
<td>2,340 (31%)</td>
</tr>
</tbody>
</table>

Legend:

- a The study cohort comprised a total of 21,646 women commencing hospital investigation and treatment for infertility between 1982 and 2002. Information on exposures and outcomes was collected over a period of 30 years, from 1980 to 2010.
- b All means expressed±SD.
- c PID and endometriosis were both diagnosed at, or prior to the first infertility admission.
- d Women who had a hysterectomy without USO in the same or any other admission.
- e Women who had both a hysterectomy and a USO in the same or separate admissions.
- f Women who had a USO without hysterectomy in the same or any other admission.
statistically significant (HR 1.76; 95% CI 0.74–4.16) while a diagnosis of endometriosis was associated with a three-fold increase in the rate of ovarian cancer (HR 3.11; 95% CI 1.13–8.57) (Table 3, third column of results).

**Discussion**

The results of this study suggest that IVF treatment has no effect on the risk of ovarian cancer in women who give birth, but uncertainty still surrounds the question of whether IVF contributes to an increased risk in women who remain childless. Parous women diagnosed with endometriosis may have a slight increase in the risk of ovarian cancer; nulliparous women face a three-fold increase in risk.

Women in our study who had IVF and gave birth had the same risk of ovarian cancer as women who had non-IVF infertility treatment (HR 1.01; 95% CI 0.35–2.90). Nulliparous women observed in our study may have had a modest increase in the risk of ovarian cancer after IVF (HR 1.76); however, there is uncertainty over statistical inference and interpretation. With the small numbers of ovarian cancer cases typical of such studies, this estimate was imprecise and potentially consistent with a wide range of true values including the null value of 1 (95% CI 0.74–4.16). Parous women diagnosed with endometriosis may have had a slight increase in the risk of ovarian cancer (HR 1.52; 95% CI 0.34–6.75); nulliparous women had a three-fold increase (HR 3.11; 95% CI 1.13–8.57).

Previous studies have rarely examined nulliparous women separately from parous women, despite the clear association between parity and ovarian cancer risk. None of the published papers on IVF and ovarian cancer considered parous and nulliparous women separately; indeed, none adjusted for confounding by parity, perhaps because it was not possible in studies that involved comparisons with the general population and had only small numbers of ovarian cancer cases (between 1 and 13) [4–8]. Even in a recent study of a similar size to this [9], which compared women undergoing IVF with a historical cohort of unexposed women, the authors did not adjust for parity in their analysis of invasive epithelial ovarian cancer. With regard to fertility drug exposure and ovarian cancer risk [15], three studies identified an increased risk in women who did not give birth [2,16,17], though another large study did not [18]. Studies of endometriosis and ovarian cancer have sometimes adjusted for parity [19]; to our knowledge none have considered nulliparous women as a separate group, though Brinton et al. [20] found a four-fold increase in risk of ovarian cancer in women with primary infertility and a diagnosis of endometriosis, compared with the general population.

Our data also confirm previous findings of a reduction in risk of ovarian cancer with tubal sterilization and with hysterectomy, with or without USO. Tubal ligation is known to protect against ovarian cancer and in recent meta-analyses, Cibula et al. [21] estimated the relative risk (RR) of ovarian cancer after tubal ligation to be 0.66 (95% CI 0.60–0.73) while Rice et al. [22] derived a RR of 0.70 (95% CI 0.64–0.75). The estimate from our study was 0.66 (95% CI 0.26–1.68). Hysterectomy with or without USO has generally been shown to protect against ovarian cancer [21] and our results were consistent with this. We found a HR of 0.55 (95% CI 0.22–1.25) for hysterectomy alone, and 0.72 (95% CI 0.10–5.27) for hysterectomy with USO; very similar to the estimates reported in Rice et al.’s meta-analysis [22] of 0.62 (95% CI 0.49–0.79) and 0.60 (95% CI 0.47–0.78). We had also expected to find a protective effect from USO performed without hysterectomy, but this was not the case, and we were surprised to find the exact opposite. Women who underwent USO without hysterectomy had a four-fold increase in ovarian cancer risk, with ovarian cancer diagnosed more than 10 years after USO. This observation derives some support from a paper published in 1997 by Krieger et al. [23]. These authors also found an increased risk of ovarian cancer in women who had undergone USO without hysterectomy; however, in their study, most of the increased risk was concentrated in the first few years after USO. Nevertheless, we believe this is an important observation that warrants further investigation. It may be that the reason for performing a USO is tied with an inherent risk of ovarian cancer in some women, and hence they are more likely to be subsequently diagnosed with ovarian cancer, and it may be possible to target these women at increased risk of disease many years before it would normally be diagnosed.

Our study had a number of limitations. Our estimates were imprecise due to the relatively small number of ovarian cancer cases, and their confidence intervals frequently included one [24,25]. Nevertheless, where possible we verified our estimates by comparison with the literature and found good agreement between our results and other published estimates. Even though we recruited women from 1982, when IVF was in its infancy, and followed them for up to 29 years through to 2010, the mean age at the end of follow-up was only 48 years, well short of the average age at ovarian cancer diagnosis of 63 years. Future studies, which could take advantage of longer periods of follow-up, would likely see more ovarian cancer cases diagnosed and consequently more precise estimates of risk. The fact that follow-up ended at an average age of 48 years may explain why the average age at ovarian cancer diagnosis was only 46 years. However, it is also conceivable that this infertile population had a higher incidence of BRCA1 mutations with possibly an increased risk and earlier development of ovarian cancer [26].

A further limitation of our study was our inability to categorise IVF exposure according to types and doses of fertility drugs used, as this information was unavailable to us. In addition, we had no information on the use of fertility drugs, which may influence the risk of ovarian cancer, other than those used as part of an IVF cycle. We also had no information on the use of oral contraceptive preparations prior to infertility treatment. Oral contraceptive use is known to lead to a reduction in the risk of ovarian cancer [27].

Our study had a number of strengths. We were able to examine the risk of ovarian cancer in a large population-based cohort of women seeking infertility treatment, with information on exposures and outcomes available over a period of 30 years. We made comparisons within the cohort, rather than comparing infertile women with the general population, thus reducing the potential for confounding by unknown variables. We had minimal loss to follow-up as the cohort was restricted to women known to be resident in WA. Accurate information on exposures and outcomes was obtained from hospital and registry data, thus eliminating the possibility of non-response. The diagnosis of endometriosis was recorded at the start of follow-up, so there was a clear
temporal relationship between the earlier diagnosis of endometriosis and later diagnosis of ovarian cancer, with ovarian cancer diagnosed, on average, 14 years after the diagnosis of endometriosis. A further strength was that we were able to measure time at risk accurately and censor follow-up in women who had a BSO who afterwards experience a dramatic reduction in the risk of ovarian cancer.

We suggest two avenues for future research. Both involve a narrowing of focus. Firstly, that known and potential risk factors are investigated separately in parous and nulliparous women, and secondly that women who require a USO without hysterectomy are investigated further to determine if the conditions that underlie the need for this procedure can predict early-stage ovarian cancer.

Conflict of interest statement

LMS, CDJH, PAS, JCF and DBP have nothing to declare. RH is a member of the Medical Advisory Board of Schering-Plough, Australia and the Medical Advisory Board of Merck-Serono, Australia and has received travel and accommodation support from the above to attend conferences. RH is a Medical Director of Fertility Specialists of Western Australia and holds shares in Western IVF.

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