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DOES OVARIAN STIMULATION INCREASE THE RISK OF OVARIAN CANCER?

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INTRODUCTION

Ovarian cancer is the commonest cause of death from gynaecological malignancy in the Western world. About 5000 new cases of this cancer are diagnosed each year in England and Wales (5% of all cancers), and it is the fourth commonest cancer in all women up to 85 years (after cancers of the breast, lung and large bowel).¹ The life-time risk of developing ovarian cancer, in England and Wales, is 1 in 56, or 1.8% by the age of 85.² Ovarian cancer incidence in England and Wales has increased gradually in the last two decades.^{1,3} Mortality rates are only slightly lower than the incidence rates^{1,3} – a reflection of its poor prognosis. In England and Wales, only 29% of women with the malignancy survive as long as five years after diagnosis although younger women do survive longer: 69% of those who are under 40 years old at diagnosis survive for five years compared to less than 20% for those aged 70 or more.⁴ Because of its high incidence and poor prognosis, ovarian cancer also represents the fourth most common cause of death from cancer among women in England and Wales, accounting for about 3600 deaths per year (7% of all cancer deaths).¹

The incidence of ovarian cancer shows marked geographical variation. The age-adjusted annual incidence for England and Wales is about 18 per 100,000 women,¹ compared with 24 per 100,000 in Sweden, 8 per 100,000 in Spain and even lower figures in Japan, South America and India.^{5,6} It seems unlikely, however, that this variation between countries can be explained solely by genetic differences, as migrants from low- to high-risk areas shift their risk to that of the host country. For instance, women of Chinese and Japanese origin who live in the USA tend to have higher rates than their Asian counterparts, although the disease is still less common in them than in the US white population.⁷

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The large majority of ovarian cancers are epithelial in origin (about 90%), while germ cell tumours account for less than 5%, and stromal cell tumours for an even smaller percentage. Unlike ovarian germ cell tumours, epithelial ovarian carcinoma is extremely uncommon at young ages, with 90% of cases occurring after the age of 45 years. This review will concentrate on epithelial ovarian carcinoma only.

RISK FACTORS FOR EPITHELIAL OVARIAN CANCER

Epidemiological research has consistently shown that high parity, late age at first birth, use of combined oral contraceptives, tubal ligation and hysterectomy (with conservation of the ovaries) are associated with a reduction in the risk of ovarian cancer, whereas a family history of breast and ovarian cancers is associated with an increase in risk. Dietary factors (e.g. intake and/or metabolism of galactose⁸), exposure to ionizing radiation⁹ and to certain chemical carcinogens (e.g. talc¹⁰) have also been found to be associated with an excess risk in some studies, but not in others. There is also some evidence that infertility and ovulation-induction drugs may increase the risk of ovarian cancer and this will be discussed in detail later in this paper.

Pregnancy exerts a strong protective effect against ovarian cancer. Cramer *et al.*¹¹ showed that women with one or two children have half the risk, those with three or four children have one-third the risk, and those with five or more children, one-quarter the risk of ovarian cancer in nulliparous women. Kvale *et al.*¹² estimated that the risk in women with five or more children was only 0.46 (95% confidence interval [CI] = 0.30–0.72) of that in women with just one child after adjustment for age, place of residence (urban/rural) and occupational class. This study also suggested that uncompleted pregnancies (abortions) were protective. In a case-control study nested within a large Swedish cohort,¹³ increasing parity was found to be associated with a progressive decrease in ovarian cancer risk, a protective effect that persisted for decades. It is unlikely that the increased risk of ovarian cancer among nulliparous women could reflect an independent association between ovarian cancer and infertility. First, the risk declined progressively with each additional birth, even among women who already had several children. Thus it is improbable that there is an appreciable frequency of some condition (e.g. endometriosis or a hormonal abnormality) that can cause both infertility and ovarian cancer in these women. Second, some studies (e.g. Booth *et al.*¹⁴) found that there remained a steadily declining risk of ovarian cancer with increasing number of pregnancies even after adjusting for the number of contraceptive-free years of sexual activity.

The relationship between age at first birth and ovarian cancer is less clear, but there is now evidence for an effect of decreasing risk with increasing age at first birth.^{13,15} A 10% decrease in the risk of epithelial ovarian cancer for each five-year increment in age at first childbirth was observed in the large Swedish cohort described above, this effect being independent of that of parity.¹³

Oral contraceptives "mimic pregnancy" by suppressing ovulation and reducing the secretion of pituitary gonadotrophins. As a result, one would expect oral

contraceptives to reduce the risk of ovarian cancer. This relationship has now been assessed in a large number of case-control and cohort studies. Risk in ever-users is, on average, about 50% of that in never-users, with the degree of protection increasing with duration of use.¹⁵⁻¹⁷ The protective effect of oral contraceptive use seems to persist for 15 years or more.¹⁵⁻¹⁷ In some studies (e.g. Franceschi *et al.*¹⁷), the protective effect was more marked for women who reported their first use before 25 years of age but this finding has not been confirmed by others.^{15,16} However, the separate effects of age at first use, time since first and last use, and duration of use are not easy to disentangle. There is also evidence that oral contraceptives may reduce the risk of ovarian cancer in carriers of mutations of the BRCA1 or BRCA2 genes, the protective effect increasing with duration of use.¹⁸ More recent studies have shown that modern low-dose pills are also associated with reductions in risk.¹⁹

Many studies have suggested that tubal ligation or hysterectomy (with ovarian conservation) reduce the risk of subsequent ovarian cancer.^{15,20-22} These observations may be a result of bias, in that early ovarian disease may be detected during surgery and the diseased ovary removed. However, not all surgery allows a view of the ovaries, and another explanation may be that surgery in some way impairs ovarian blood supply and, hence, reduces ovulation.^{15,22,23}

Early hypotheses about the aetiology of epithelial ovarian cancer implicated ovulation and gonadotrophins. Fathalla postulated that "incessant ovulation" led to frequent disruption of the ovarian surface epithelium, with subsequent neoplasia.^{24,25} His arguments were supported by the observation that the domestic hen, which was bred for egg-laying, developed ovarian cancer. Cruickshank²⁶ added support to the ovulation theory by showing that ovarian cancer was more likely to occur on the right side – in women ovulation occurs significantly more often on the right.^{26,27} However, while a single pregnancy and subsequent lactation reduced the total number of ovulations by only 3%, the impact of a single pregnancy was to reduce the risk of ovarian cancer by half.²⁸

The gonadotrophin theory appears to originate from a letter by Stadl in the *American Journal of Obstetrics and Gynecology*,²⁹ pondering why the incidence of epithelial ovarian cancer remained high after the menopause, proposing that this was due to rising pituitary gonadotrophin levels, and suggesting that menopausal estrogen therapy would decrease the risk. But subsequent studies did not find higher gonadotrophin levels in women who went on to develop ovarian cancer compared to those who did not.³⁰

The observed decline in the risk of ovarian cancer with increasing parity, oral contraceptive use and lactation, all of which suppress ovulation, fits with the incessant ovulation hypothesis (although this hypothesis cannot account for the magnitude of the decline in risk associated with pregnancy). Perhaps surprisingly, published data on early menarche and late menopause do not show a consistent pattern of increasing risk,¹⁵ as would be predicted by the incessant ovulation hypothesis, but this may partly reflect the difficulty in recalling accurately age at menarche and of determining precisely the age of onset of menopause. Also, starting or finishing menstruation may not accurately reflect ovulation patterns.²³ The suggested increased risk with

use of fertility drugs, which stimulate the ovary to produce multiple ovulations, and the protective effect of tubal ligation or hysterectomy also support the incessant ovulation hypothesis. Parity, oral contraceptives and fertility drug use also fit the high gonadotrophin hypothesis, but the associations with lactation, tubal ligation and hysterectomy do not. The high gonadotrophin hypothesis would predict a reduced risk for women taking hormone replacement therapy, but what little data there are do not show a convincing association.²³ It is possible that both hypotheses, and possibly others, may be valid, with each explaining a proportion of all epithelial ovarian cancers.

It must also be recognized that epithelial ovarian cancer is not a single pathological entity, but may be divided on histology into serous, endometrioid, mucinous, clear cell and other types. Each histological type may have a different aetiology although this has not been properly examined in epidemiological studies. Similarly, epithelial borderline malignant tumours (also called epithelial tumours of low malignant potential), although sharing some of their histological characteristics with invasive tumours, may differ in some of their aetiological risk factors.³¹

INFERTILITY, OVULATION INDUCTION AND OVARIAN CANCER

Case reports

In the 1980s case reports of ovarian cancer in women undergoing assisted conception raised concerns about the use of ovarian stimulants in infertility treatment.³² Bamford and Steele³³ documented the history of a 32-year-old woman with primary infertility who had undergone eight cycles of ovulation induction with menopausal gonadotrophins plus human chorionic gonadotrophin injections with a further three cycles two years later. A 4-cm left-sided ovarian cyst was then found. Within one month the ovary had increased to 25 cm diameter and surgery removed what was found histologically to be an endometrioid tumour of the ovary, plus hyperplasia and a well differentiated adenocarcinoma of the endometrium.

Land³⁴ conducted a literature review to search for reports of ovarian neoplasms arising in patients who had undergone ovulation induction. The first reported case in the literature was that from Bamford and Steele³³ described above. A further nine cases had been published between 1982 and 1992 with ages at diagnosis ranging between 22 and 38 years. Seven of these nine cases were borderline or low malignant potential tumours of serous histological type. Another review by Hull *et al.*³⁵ reported 13 cases published in the literature and added a further case of stage-3 poorly differentiated serous carcinoma diagnosed eight months after Caesarean section – conception had occurred after five cycles of gonadotrophin treatment. Unkila-Kallio *et al.*³⁶ reported on a case series of 11 women who developed malignant tumours of the ovary after investigation or treatment of infertility. Two patients had granulosa cell tumours, one a malignant teratoma and eight epithelial ovarian cancers (seven being invasive serous papillary in type, and one mucinous). Of these eight women, four had used

clomiphene for more than 12 cycles, but two had the diagnosis of carcinoma made during investigations and before receiving any treatment.

A common feature of these case reports is the relatively short interval between use of fertility drugs and the diagnosis of ovarian tumours (less than one to two years). This would suggest that either fertility drugs stimulate the growth of pre-existing lesions or more cases were diagnosed because of increased medical surveillance of women who underwent investigation and treatment for infertility.

Epidemiological studies

Most early epidemiological studies used surrogate measures to investigate the relationship between infertility and ovarian cancer with little information available on physician-diagnosed infertility or its treatment. For example, ovarian cancer occurrence was noted to be higher among childless women who tried to conceive (presumably infertile) than among childless women who did not (most of whom were presumably fertile), with the risk increasing with number of years of unprotected intercourse (e.g. Booth *et al.*¹⁴).

One of the first studies to examine the relationship between infertility, its treatment and ovarian cancer was a cohort study of 2632 Israeli women treated for infertility between 1964 and 1974 and followed through the National Cancer Registry to the end of 1981.³⁷ The causes of infertility were defined as infertility of the male partner, mechanical infertility (where there was evidence of ovulation but mechanical factors were demonstrated at hysterosalpingography or laparoscopy), hormonal infertility (with anovulation, amenorrhoea, oligomenorrhoea or irregular periods) or infertility of unclassified origin. Analysis by type of infertility showed a significantly increased risk of endometrial cancer and nonsignificantly elevated risks of breast cancer and malignant melanoma for the hormonal group. Among women with nonhormonal infertility, there was a suggestion of an increased risk of cancer of the ovary but the number of cases was far too small to be conclusive. There was no evidence of an association between ovulation-inducing drugs (i.e. clomiphene citrate or human menopausal gonadotrophins) and cancer, but the paper does not provide details on numbers of women to whom such drugs were prescribed. A recent re-analysis of data from this cohort,³⁸ with almost twice the length of follow-up (mean = 21.4 years), showed an overall excess risk for endometrial cancer, but not for ovarian cancer, and no relationship between site-specific cancer risks and treatment with ovulation-inducing drugs.

Brinton *et al.*³⁹ reviewed 2335 women evaluated for infertility at the Mayo Clinic between 1935 and 1964, for cancer risks; most cancers occurred at frequencies similar to those observed in the general population. The risk of ovarian cancer was 60% higher (although this was not statistically significant) in women who had progesterone deficiency (an indication of anovulation or luteal phase defect) but not in those with other causes of infertility. Some information on the effect of treatment was available (primarily estrogen or progestogen concentrations), and it did not seem to affect the risk of ovarian cancer.

A pooled analysis of data from 12 US case-control studies conducted by the Collaborative Ovarian Cancer Group and including 2197 cases of invasive epithelial ovarian cancer showed no overall association between physician-diagnosed female infertility and ovarian cancer.^{15,23} Three of the studies included in this pooled analysis collected information on use of fertility drugs. Infertile women who had used fertility treatment were at an increased risk of invasive epithelial ovarian cancer (relative risk (RR) = 2.8; 95% CI = 1.3, 6.1), and of borderline ovarian tumours (RR = 4.0; 95% CI = 1.1, 13.9) compared to women without a history of infertility. The risk for the smaller subgroup who never got pregnant was 27 times (95% CI = 2.3, 315.6) that of nulligravid women who did not report infertility, whereas the risk for those who took drugs but did achieve a pregnancy was not raised. The results generated a great deal of interest because of the potentially serious implications for the rapidly expanding assisted conception programmes throughout the world.^{40,41} Several possible explanations could account for the association between failed infertility treatment and ovarian cancer. As with all case-control studies, there is a possibility that recall bias might have led to an overestimation of the magnitude of these associations.⁴² Even if the observed association between infertility treatment and ovarian cancer risk were real, women may have taken drugs for longer periods and in greater doses because they had a certain type of infertility that predisposed them *a priori* to both infertility and ovarian cancer.

This latter possibility was assessed by Rossing *et al.*⁴³ in a cohort of 3837 women from Seattle who had been evaluated for infertility between 1974 and 1985. The authors found an increased risk of invasive or borderline ovarian tumours in infertile women who took clomiphene relative to infertile women who had not taken this drug (RR = 2.3; 95% CI = 0.5, 11.4). This risk was particularly high among women who had taken clomiphene for more than 12 cycles (RR = 11.1; 95% CI = 1.5, 82.3).

Other small case-control studies have also reported on the relationship between fertility treatment and ovarian cancer. Sushan *et al.*⁴⁴ compared past use of fertility drugs among 200 women with invasive or borderline epithelial ovarian cancer identified through the Israel Cancer Registry with 408 healthy control women resident in the same geographical areas. Twenty-four women with cancer (12%) and 29 healthy controls (7.1%) reported ever-use of fertility drugs, yielding a statistically nonsignificant relative risk of 1.31 (95% CI = 0.63, 2.74). Twenty-two cancer cases and 24 controls had used gonadotrophins alone or in combination with clomiphene (RR = 1.42; 95% CI = 0.65, 3.2) and 11 cancer cases and 6 control women had used gonadotrophins alone (RR = 3.19; 95% CI = 0.86, 11.82). The risk was particularly increased in the group of women with borderline tumours who had used gonadotrophins (RR = 9.38; 95% CI = 1.66, 52.08).

A recent pooled analysis of data from eight population-based case-control studies conducted between 1989 and 1999 in the US, Canada, Denmark and Australia, which included over 5000 cases and 7000 controls, showed that among nulligravid women, those who tried to become pregnant for more than five years had a 2.67-fold (95% CI = 1.91, 3.74) increase in the risk of developing ovarian cancer.⁴⁵ Fertility drug use in nulligravid women, but not in nulliparous women, was associated with an increased

risk of borderline serous tumours ($RR = 2.43$; 95% CI = 1.01, 5.88), but not with any invasive histologic subtype. These findings are rather consistent with those reported by the large pooled analysis of US case-control studies described above.¹⁵

The largest cohort study so far to have examined the association between ovarian stimulation and risk of subsequent cancers consisted of 10,358 Australian women who were referred for *in vitro* fertilization (IVF).⁴⁶ Half of the cohort underwent ovarian stimulation to induce multiple follicles ("exposed" group) whereas the remaining women were untreated or had natural cycles without ovarian stimulation ("unexposed" group). There was no evidence that ovarian stimulation was associated with an increased risk of ovarian cancer but the follow-up of the cohort was short (median length of follow-up for the exposed group was only five years). This cohort was subsequently enlarged to include 20,656 IVF women who were exposed to fertility drugs and 9044 who were not.⁴⁷ The incidence of breast and ovarian cancers was no higher than expected. The incidence of uterine cancer was significantly higher than expected ($RR = 2.47$; 95% CI = 1.18, 5.18) in the unexposed group but not in the exposed one. Women with unexplained infertility, regardless of their exposure to ovarian stimulation, had a higher incidence of uterine ($RR = 4.59$; 95% CI = 1.91, 11.0) and ovarian ($RR = 2.64$; 95% CI = 1.10, 6.35) cancers than expected. The main advantages of this study are its large sample size and the availability of data on type of infertility and type of treatment administered in the participating IVF centres. The main weaknesses are the relatively low exposure levels (59% of the women in the exposed group had less than three cycles of treatment, with only 11% having had six or more cycles), the possibility of misclassification as information on exposure to fertility drugs outside the participating centres was not available, the lack of data on potential confounding factors such as gravidity and oral contraceptive use and the still relatively short follow-up (median of seven years for women exposed to ovarian stimulation).

Klip *et al.*⁴⁸ reviewed papers published between 1966 and 1999 that included information relevant to a link between sub-fertility, ovulation induction, and cancers of the ovary, breast, endometrium, thyroid and malignant melanoma. Many of the papers discussed above were included in this review. They concluded that methodological defects might have accounted for most of the observed inconsistencies. Lack of valid and standardized definitions of infertility and its types and lack of information on lifetime exposure to fertility drugs may have played a role. Potential for recall and selection bias was greater in case-control than in cohort studies. In contrast, lack of control for confounding was a main limitation of cohort studies as most of them relied on record linkage. Of the four cohort studies described above,^{37-39,43,46,47} all were able to adjust for age at diagnosis, but only one⁴³ was able to take into account gravidity at enrolment, and none was able to adjust for oral contraceptive use, family history or pelvic surgery, factors known to affect the risk of ovarian cancer. In addition, many cohort studies were based on relatively small sample sizes and short duration of follow-up.

OUR FOLLOW-UP STUDY

With funding from Cancer Research UK, we have assembled a large cohort of 8799 women who were referred to the Royal Free and the University College Hospitals, since the early 1960s, because of amenorrhoea or menstrual irregularity, infertility, hirsutism, thyroid or other endocrine disorders. This cohort is unique in that detailed clinical notes were kept not only of the reasons for infertility, but also of any diagnostic procedures performed on the patients, and of the type and doses of any treatments prescribed, including number of cycles with fertility drugs and their outcome (i.e. pregnancy and hyperstimulation). Clomiphene citrate was taken by 3419 (40%) patients in the cohort, with doses ranging from 250 mg to 1400 mg per cycle, and for 1 to 55 cycles per patient (mean number of cycles per patient = 4, with 40% of these patients having had more than six cycles). Gonadotrophins (usually human menopausal gonadotrophins plus human chorionic gonadotrophin) were given to 886 (10%) patients in the cohort for 1 to 31 cycles (mean cycles per patient = 5), with a total dose ranging from 4 to 1349 ampoules (mean 118) per patient. Administration of a postal questionnaire via the patient's current general practitioner has allowed us to complement the information available in the clinical notes with more up-dated information on the reproductive history of these women. Patients have been flagged at the National Health Service Central Register (NHSCR) to provide long-term follow-up, with ascertainment of incident cancer cases and deaths (with information on cause of death) among cohort members. It is hoped that this long-term follow-up study will help to clarify whether there is any true association between infertility and/or its treatment, and the development of ovarian and other cancers.

CONCLUSIONS

The evidence reviewed here seems to indicate that there is an association between infertility and ovarian cancer risk, but it is uncertain whether this association is causal or likely to be due to a common underlying mechanism. The association of ovarian cancer risk with fertility treatment is more difficult to evaluate. Data from both cohort and case-control studies seem to suggest that either there is no association, or if there is one the magnitude of the treatment effect is relatively small. However, this does not exclude the possibility that certain groups of patients may be at a particular high risk. Further research is required to clarify these issues.

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