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Fertility drugs and cancer

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Introduction

The short-term risks of fertility drug treatment, such as ovarian hyperstimulation syndrome,[1,2] are well recognised by clinicians providing infertility treatment. There is uncertainty, however, about whether there are any long-term risks such as an increased risk of breast or gynaecological cancer. The possibility of such long-term risks is sometimes a concern for couples who are considering or receiving infertility treatment and their concerns need to be discussed using the best available evidence. The need for appropriate evaluation of long-term health effects of treatment with fertility drugs, including cancer, has been highlighted in major reviews of infertility treatments in Australia and Canada.[3,4]

In this review we focus on the methodological problems and difficulties encountered in this area of research, review the published research evidence, and discuss future directions. The methodological issues are central to our interpretation of the research findings published so far and to our ability to obtain answers in the future. Lessons learned from completed studies have implications for specialists in reproductive medicine and infertility as well as for epidemiologists. Ovarian cancer has been of particular concern because of the very direct effects of fertility drugs on the ovaries and ovarian hormones. Breast cancer, other gynaecological cancers and melanoma will also be discussed in this review.

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Methodological issues

Key methodological issues, from an epidemiologist's perspective, include selecting appropriate study populations, defining and measuring the exposures and outcomes of interest, estimating the effect of factors that could bias the association between exposure and outcome and defining the role of chance in producing the findings.

The study population: who and how many to study

Two types of observational study design have been used to look at the relationship between fertility drugs and cancer: case–control studies and cohort studies. Case–control studies measure exposures in people with a disease of interest (cases) and people without the disease (controls). Case–control studies have examined large groups of women with ovarian cancer but have often found very few with a history of fertility drug use.

Cohort studies of cancer after infertility have followed-up large groups of infertile women but have had few with the outcomes of interest. The number of cancer cases expected in a cohort study of women exposed to fertility drugs increases with the size of the study group, the duration of follow-up, age of the women and the general population incidence rate of the cancer. The level of evidence obtained from a well-designed cohort study is generally believed to be higher than that obtained from a case–control study.[5] Although cohort studies of cancer after infertility have been retrospective, data on infertility treatments were collected prior to any diagnoses of cancer.

Although the absolute number of women who have been treated with fertility drugs world-wide is large, there remain practical difficulties, whichever study design is used, in setting-up studies that have the statistical

power to detect a moderate or small increase in cancer risk with confidence. Multi-centre studies can generate large cohorts but present greater practical difficulties than single-centre studies and are more costly.

The exposure: defining and measuring exposure to fertility drugs

There have been significant changes to the types, combinations and doses of fertility drugs used over the last thirty years that could potentially affect cancer risk in different ways. Exposure assessment should, therefore, take these factors into account but, to date, studies have been limited in this respect.

Case reports[6–20] and case series[21–23] of cancer in infertile women have provided the most comprehensive descriptions of previous fertility drug treatments but only the weakest evidence for an association between the two.[5] Whilst alerting us to the possibility of an important association between a particular exposure and outcome, case series and case reports tell us little about the frequency of the association in the wider clinical or general population. Only three observational studies[24–26] have examined the relationship between different types of fertility drug treatment and ovarian cancer risk: the small number of cases in the different treatment sub-groups limited the findings in each study. Elucidating the relationship between cancer and different fertility drugs is particularly difficult when women have been exposed to different combinations of drugs over the course of their infertility treatment.

Practical considerations explain why many studies have been unable to make distinctions between different treatment regimens. Accurate data on all fertility drug treatments taken by women over their lifetimes, including drug types, combinations, doses and dates, are not usually available, either because of poor recall, if self-reported, or because of poor quality or missing medical records. In case–control studies, self-reported information on past use of fertility drugs is prone to recall bias: women with cancer are more likely to remember past exposures to agents that might be associated with their disease than women without cancer. Whilst manual retrieval of data from medical records is feasible in case–control studies, it is more problematic in cohort studies of several thousand women.

Few studies have looked at cancer risk in relation to the number of treatment cycles with fertility drugs. In a study of cancer incidence after infertility and *in vitro fertilization* (IVF),[27] we found that 77% of treated women had three or fewer stimulated assisted reproductive technique (ART) cycles. Only 2% of treated women had ten or more cycles: there was no correlation between number of cycles and cancer risk. In a study of women who sought infertility treatment in North America, largely before ART became available, Rossing *et al.*[24] showed that of women who had ever used clomiphene citrate, 22% had had 12 or more cycles. Exposure to 12 or more treatment cycles with clomiphene citrate was found to be associated with a significantly increased ovarian cancer risk [relative risk (RR) =11.1, 95% confidence interval (CI) 1.5–82.3]. No such association was found in an Israeli case–control study[25] of ovarian cancer which gave an odds ratio (OR) = 1.44 (95% CI 0.34–5.82) for women having 12 or more treatment cycles with fertility drugs.

Variation in responsiveness to fertility drugs between individuals is well recognised and may be important in any relationship between exposure and cancer. Markers of an individual's response to fertility drugs could be a useful, and possibly more sensitive, measure of exposure. Measures of responsiveness that are widely used and well documented in medical records are most useful for epidemiologists. The number of oocytes collected in a stimulated ART cycle is an obvious choice and one that we are examining in our current Australia-wide follow-up of cancer incidence in women in IVF programmes. The data from Australian IVF clinics so far indicate that the number of oocytes collected in a stimulated ART cycle can range between 0 and 61.

No completed studies of fertility drugs and cancer have reported on the doses of fertility drugs used or any biological measurements of the response to stimulation that was achieved. Peak serum oestradiol concentrations are typically twice normal in patients undergoing ovulation induction for chronic anovulation and five times normal in women having multiple folliculogenesis for ART. Such levels, of course, persist for only 1–3 days before administration of human chorionic gonadotrophin (hCG).

The outcome: ascertaining cancer incidence

Cohort studies describing the relationship between fertility drugs and cancer have determined cancer incidence by record-linkage with population-based cancer registries. Cancer registries have also been the source of women with cancer for two case–control studies.

Several factors contribute to the reliability of cancer incidence data: the completeness of cancer registry records; the accuracy of data for women in the cohort; the availability of unique identifiers for matching; the matching process itself; and the proportion of women lost to follow-up due to change of name or change of residence outside the region covered by the registry. Epidemiologists have used a range of strategies to maximise the ascertainment of cancer cases. These strategies include the use of social security numbers and national identity numbers to trace women and to use as additional matching variables with the cancer registries. Mandatory notification of cancers to cancer registries is especially helpful in achieving complete ascertainment of cancers in a study population.

Cohort studies of cancer in groups of women who have been exposed to fertility drugs have had, as their comparison, groups of either infertile women who have not been exposed to fertility drugs or women in the general population. Any differences in the way cancer cases are ascertained between the groups of exposed and unexposed women could lead to biased estimates of the risk of cancer associated with fertility drug treatment. Earlier ascertainment of cancer might be expected in women who have used fertility drugs if they have more ongoing gynaecological investigations or screening for breast and gynaecological cancer than women who have not used fertility drugs. Earlier ascertainment might also occur if the cause of infertility is associated with pre-existing early stages of ovarian or uterine cancer or if fertility drugs act as promoters of pre-existing tumours leading to earlier recognition and diagnosis of disease. The question of whether ovarian tumours might be pre-existing in some women having fertility drug treatment was debated when Willemsen *et al.*[22] reported a case series of twelve patients in whom granulosa cell ovarian tumours were detected after ovarian stimulation with clomiphene citrate or gonadotrophins. Eight of the twelve patients returned to normal ovulatory cycles after surgical removal of their tumours and five conceived spontaneously during the follow-up period. This report emphasises the need for a thorough investigation of the cause of infertility before fertility drug treatment is commenced.

Defining and measuring covariates

As well as exposure to fertility drugs, several other factors could be predictive of cancer in women seeking infertility treatment. These factors or covariates should be considered in the design and analysis of studies of fertility drugs and cancer. Nulliparity and late age at first birth are known to be more common in infertile women and are well established risk factors for breast cancer: both can be assumed to be confounding variables. Confounding variables are factors that are independently associated with both the exposure and outcome of interest; they can bias study results by either giving the appearance of an association between exposure and outcome where none exists, or, conversely, by masking a true association.

There is less certainty about how some other covariates might affect the relationship between fertility drugs and cancer. These include infertility itself, use of oral contraceptives and oestrogen replacement therapy, age at menarche and menopause, lactation, hysterectomy, oophorectomy, tubal ligation, socioeconomic status, obesity, and family history of cancer. The potential importance of some of these covariates is discussed in the following sections.

Parity

Women seeking treatment for infertility include those with secondary infertility but overall tend to be of lower parity and are more likely to be nulliparous than women of the same age in the general population. Nulliparous women are at an increased risk of cancer of the breast, ovary and uterus. Therefore, in the long term, we would expect infertile women to have a higher incidence of these cancers irrespective of their infertility or fertility drug treatment.

The size of the effect of parity on breast cancer risk differs by age. The short-term effect of full-term pregnancy is to increase the risk of breast cancer.[28, 29] There is also some evidence to suggest that recent pregnancy is an indicator of poor prognosis in women with breast

cancer.[30] The potential confounding effect of parity on breast cancer risk, therefore, is likely to depend on the age of women being studied and the time since last term pregnancy. Late age at first birth is associated with a small increase in breast cancer risk; women aged over 30 at their first birth have been shown to have a greater breast cancer risk than women aged less than 20.[31] Studies of the effects of birth spacing, age at last birth, spontaneous and induced abortions and multiple births have been inconsistent and their relationships with breast cancer risk remain uncertain.[31]

Several studies have shown a decreasing risk of ovarian cancer with an increasing number of full-term pregnancies for both invasive and borderline ovarian cancers.[32, 33] Findings on the effect of age at first birth on ovarian and endometrial cancer risk have been inconsistent.[34, 35]

Studies of cancer after fertility drug treatment have had varying degrees of success in measuring and adjusting for parity and infertility, as discussed elsewhere.[36] Case–control studies that have used self-reported information on reproductive history are likely to have more accurate data on parity than studies using records from infertility clinics. Information held by infertility clinics can be incomplete, especially when women have treatment with more than one doctor or clinic, or when they conceive normally after completing unsuccessful infertility treatments.

Cause of infertility

As well as there being heterogeneity in the use and effects of fertility drugs, there is considerable heterogeneity in the types of infertility being treated. It is not yet certain whether infertility in its own right is associated with cancer risk but it should be treated as a potential confounder in the relationship between fertility drugs and exposure.

Studies of infertility and cancer[37–41] have produced inconsistent findings. They have been limited by imprecise measures of infertility, the lack of appropriate comparison groups, the difficulty in separating the effects of infertility from the effects of treatment or nulliparity, and small numbers of women with both cancer and a history of infertility. Important questions remain about the relationship between infertility and cancer. If infertility is associated with cancer, which types of infertility are important? What is the biological plausibility of an increased cancer risk associated with ovulation disorders compared with tubal obstruction, endometriosis or unexplained infertility? Which cancers are associated with which types of infertility?

Even within the group of women with abnormal ovulation, there may be sub-groups who have quite different risks of cancer irrespective of any treatment they receive. Women with polycystic ovary syndrome (PCOS) have been shown to have an increased incidence of endometrial cancer[42] thought to be associated with the high levels of unopposed oestrogen characteristic of the disorder. Conversely, several studies of breast cancer incidence in women with PCOS have shown no increase in risk.[40, 43, 44]

Women hospitalised with endometriosis were shown to have a significantly increased incidence of breast and ovarian cancer compared with the general population in a recent Swedish record-linkage study of 20,686 women.[45] The standardised incidence ratio (SIR) for breast cancer was 1.3 (95% CI 1.1–1.4). The incidence of ovarian cancer was overall greater than expected, SIR=1.9 (95% CI 1.3–2.8), and particularly increased in women with a long history of ovarian endometriosis (SIR=4.2, 95% CI 2.0–7.7). Paulson[46] has suggested that the inflammatory peritoneal exudate associated with endometriosis might act on the ovarian epithelium and increase the likelihood of malignant changes. He proposes that the presence of vascular adhesions would be expected to further increase the risk of ovarian cancer.

The incessant ovulation hypothesis for the pathogenesis of ovarian cancer[47, 48] predicts that anovulation, whether due to pregnancy, oral contraceptive use, lactation or infertility, should be protective against ovarian cancer. Women who are anovulatory or oligo-ovulatory, therefore, might have a lower risk of ovarian cancer. The net effect of fertility drug exposure would be difficult to ascertain without a large group of women with equivalent ovulation disorders and no fertility drug treatment. The majority of women having ART treatment for male factor infertility are likely to have normal fertility themselves. Therefore the relationship between fertility drug exposures and cancer in these patients is less likely to be

confounded by factors associated with the underlying causes of infertility. Male infertility is an increasingly common indication for ART, especially since the development of intracytoplasmic sperm injection (ICSI).[49].

In order to clarify whether infertility itself is associated with an increased cancer risk, future studies will need careful ascertainment and recording of data on the type of infertility, large numbers of women with each type of infertility and the statistical power to adjust for the effects of parity and treatments.

Other covariates

There are several other covariates that might act as confounding variables in the relationship between fertility drug exposure and cancer, though their importance is much less certain than parity or cause of infertility. Not all have been considered in studies of fertility drugs and cancer to date.

Oral contraceptives. Oral contraceptive use is associated with reduced risks of ovarian and endometrial cancer.[34, 35] The relationship with breast cancer has been less clear though a recent re-analysis of pooled data from studies of oral contraceptive use and breast cancer risk[50] suggests that there is a small increase in breast cancer risk among current users which decreases with years since last use. It might be expected that women having fertility drug treatment would have fewer years of oral contraceptive use than normally fertile women.

Measuring past oral contraceptive use is difficult with self-reported data, especially if recall is sought many years after use. Infertility clinics and gynaecologists vary greatly in their recording of previous oral contraceptive use, hence medical records are often an unreliable source of data for this covariate.

Hormone replacement therapy (HRT). Whether or not HRT increases the risk of breast cancer is a controversial issue,[51] but HRT appears to have little effect on the risk of ovarian cancer.[52] However, there is good evidence for an increased risk of endometrial cancer in women who take oestrogen replacement therapy without progestogen. It is not clear whether women who have been exposed to fertility drugs are more or less likely to be users of HRT later in life. Women having ART treatment tend to be of higher socioeconomic status (SES) than the general population. There has been some evidence from the United States[53] and Australia[54] that the use of HRT is positively associated with SES. A history of medical intervention for reproductive problems might increase the likelihood of HRT being offered to some infertile women. On the other hand, HRT is less likely to be offered to infertile women for whom it is contraindicated, for example those with a history of problems such as abnormal uterine bleeding.

Future studies of cancer in fertility drug users that wish to measure HRT use will have to rely on self-report or medical records held by doctors providing care to women often many years after their infertility treatment.

Age at menarche and menopause. Women seeking infertility treatment include those with a history of primary amenorrhoea, late menarche and early menopause. Late menarche and early menopause have each been shown to have a moderately protective effect against breast,[31] ovarian and endometrial cancer.[52] It is not clear to what extent women having fertility drug treatment differ from the rest of the female population in this regard.

Hysterectomy and oophorectomy. In the long-term, women having fertility drug treatment might be more likely to have a hysterectomy or oophorectomy than other infertile or normally fertile women. An increased rate of hysterectomy in women who have had fertility drug treatment would reduce the risk of uterine and cervical cancer. Some studies have shown the risk of ovarian cancer to be reduced in women who have had a hysterectomy with their ovaries left intact.[55, 56] Several case–control studies of fertility drugs and cancer have accounted for hysterectomy and oophorectomy using data collected by self-report: hysterectomy is usually more reliably ascertained in this way than oophorectomy.

Socioeconomic status. Socioeconomic status, or social class, has been shown to be positively associated with breast cancer risk[31] and, less consistently, with ovarian and endometrial cance.[34, 35] Women seeking ART treatment tend to be of relatively high SES, at least partly explained by the high costs often associated with ART. Not all women who experience infertility seek treatment[57, 58]; any difference in SES between those who do and do not seek treatment has the potential to be a confounding variable in the relationship between fertility

drugs and cancer when comparisons are made with control groups of infertile women who have not had fertility drug treatment.

Measures of SES can be estimated using family income, education level or area of residence. Case–control studies of breast and ovarian cancer have often adjusted for SES in their analysis of cancer risk associated with past fertility drug use but they have not described SES in fertility drug users compared with infertile women who have not used fertility drugs.

Other covariates that might warrant further investigation in future studies of the relationship between fertility drugs and cancer include: family history of breast and ovarian cancer, benign breast disease, history of medical and surgical treatment for endometriosis, other gynaecological and endocrine disorders, height and weight, breastfeeding, diet and alcohol use. As discussed earlier, information on women's use of cancer screening methods would help determine whether women who have had exposure to fertility drugs are more or less likely to have cancers detected at an earlier stage.

Summary of published findings

This section summarizes the published data on fertility drugs and cancer.

Ovarian cancer

Ovarian cancer is the most studied cancer in women exposed to fertility drugs. The findings of studies published since 1992 have been summarised in Table 1.

The study by Whittemore, Harris and Itnyre[33] combined raw data from 12 United State case–control studies conducted in the thirty years prior to 1987 to evaluate the relationship between invasive epithelial ovarian cancer and reproductive and menstrual characteristics. Cases were women who had had a hospital diagnosis of invasive epithelial ovarian cancer in the United States. Data were obtained from cases and controls using personal interviews with structured questionnaires. Three of the twelve studies had data on infertility in ever-married women. Infertility was defined as physician diagnosed, and excluded male causes. The findings suggested that only a small excess of ovarian cancer risk in nulliparous women was due to infertility but that the fertility drug use might be an important factor in the increased risk for infertile women.

Data on fertility drug use was available for 622 cases and 1101 controls. Of these, 76 cases had a history of infertility and 20 used fertility drugs. Of the controls, 135 had a history of infertility and 11 used fertility drugs. An increased risk associated with fertility drug use was seen relative to women with no clinical history of infertility (OR = 2.8, 95% CI 1.3–6.1). The risk was higher among nulligravid women (OR = 27.0, 95% CI 2.3–315.6) than gravid women (OR = 1.4, 95% CI 0.52–3.6). Fertility drugs had been used by 12/34 nulligravid infertile cases compared with 1/23 nulligravid infertile controls, hence the broad confidence intervals. The analysis adjusted for age, oral contraceptive use, the study from which data were derived, and, in gravid women, parity and breastfeeding.

There were some important limitations with this study, recognised by the authors. These included problems with pooling data from studies of different origins and from different times, the relatively small number of cases and controls exposed to fertility drugs, poor quality of data on fertility drug use, no distinction between ovulatory and anovulatory patients, and no information on the types, combinations or doses of fertility drugs or number of treatment cycles. The estimates of association between fertility drugs and ovarian cancer were based on infertile women exposed to fertility drugs compared with normally fertile women who were not exposed. No comparison was made of infertile women who had and had not been exposed to fertility drugs. Despite its limitations, this study was provocative, stimulating much useful discussion and a wider recognition of the need for further work in this area.

The risk of borderline ovarian tumours in fertility drug users was examined in a pooled reanalysis of the same three case–control studies.[32] A statistically significant increase in risk was found in fertility drug users compared with normally fertile women who had not used fertility drugs (OR=4.0, 95% CI 1.1–13.9).

In 1994, Rossing *et al.*[24] reported findings from a case–cohort study of cancer in women who had been evaluated for infertility at clinics in Washington State between 1974 and 1985. A case–cohort study is a cohort study with the

Table 1. Summary of findings on the risk of ovarian cancer in fertility drug users (see text for description of strengths and limitations of individual studies)

Study	Design	Comparison	Fertility drug users with cancer*	SIR	OR or RR	95% CI
Rossing *et al.* 1994[24]	Case–cohort	Infertile fertility drug (CC) users vs infertile non-users	9 Borderline & invasive epithelial‡		2.3	0.5–11.4
		Fertility drug (CC) users vs general population		3.1		1.4–5.9
Venn *et al.* 1995[27]	Cohort	Infertile fertility drug users vs infertile non-users	3 Invasive epithelial		1.45	0.28–7.55
		Fertility drug users vs general population		1.70		0.55–5.27
Whittemore *et al.* 1992[33]	Pooled, reanalysed case–control	Fertility drug users vs non-users†	20 Invasive epithelial 4 Borderline		2.8 4.0	1.3–6.1 1.1–13.9
Franchesci *et al.* 1994[59]	Case–control	Fertility drug users vs non-users†	2 Invasive epithelial		0.73	0.16–3.30
La Vecchia *et al.* 1995[60]**	Case–control	Fertility drug users vs non-users†	4 Invasive epithelial		1.1	0.4–3.6
Shushan *et al.* 1996[25]	Case–control	Fertility drug users vs non-users†	24 Invasive epithelial 10 Borderline		1.31 3.52	0.63–2.74 1.23–10.09
Mosgaard *et al.* 1997[26]	Case–control	Parous infertile fertility drug users vs parous infertile non-users	10 Invasive		0.56	0.24–1.29
		Nulliparous infertile fertility drug users vs nulliparous infertile non-users	18 Invasive		0.83	0.352.01

*Ovarian tumours as described in paper: invasive epithelial, invasive (various) or borderline
‡Number of each tumour type amongst fertility drug users not given (see text)
**Report of supplementary data from study described by Franchesci *et al.*[59]
†Non-users were fertile and infertile non-users

addition of more detailed data collection and analysis for a sub-cohort comprising individuals with the outcome of interest (ovarian cancers in this instance) and a sample of individuals who do not have the outcome of interest. The case–cohort design, like the nested case–control study, has many of the advantages of both cohort and case–control studies.

The cohort included 3837 women who had made at least two visits to participating infertility clinics for evaluation of infertility between 1974 and 1985. Cases of cancer that had occurred up until the end of 1991 were determined by record-linkage with a population-based cancer registry. Linkage was based on name, date of birth and social security number. Driver's licence records, credit bureau tracing and the National Death Index were used to determine the last known whereabouts of women who were lost to follow-up and the person-years were adjusted accordingly. The sub-cohort included all women with invasive and borderline ovarian tumours and 135 women without cancer randomly selected from the cohort within strata matched to the cases on age at enrolment and time period of enrolment with the infertility clinic. Data on the cause of infertility and exposure to fertility drugs were abstracted from infertility clinic medical records for the women in the sub-cohort. Data on additional covariates, including weight, menstrual, contraceptive and reproductive history, were also abstracted from records.

Eleven ovarian tumours were identified in the cohort: four invasive epithelial, two granulosa cell, and five borderline epithelial tumours. The observed number of cancers was compared with the expected number of 4.4 cancers, derived from age-standardized general population rates, to give a standardized incidence ratio (SIR) of 2.5 (95% CI 1.3–4.5). Women who had been treated with the fertility drug clomiphene citrate (CC) had significantly more tumours than expected with a SIR=3.1 (95% CI 1.4–5.9), as did women with ovulatory abnormalities (SIR=3.7, 95% CI 1.4-8.1). The observed number of cases did not significantly exceed the

expected number for women with any other cause of infertility.

Analysis of cases and the sub-cohort of controls gave relative risk (RR) estimates, adjusted for age and year at enrolment and gravidity, for ovarian cancer according to fertility drug exposure. Exposure to clomiphene citrate was not significantly associated with an increased ovarian cancer risk (RR=2.3, 95% CI 0.5–11.4), however, examination of a dose-response effect showed that exposure to twelve or more treatment cycles with clomiphene citrate was associated with a significantly increased risk (RR=11.1, 1.5–82.3) compared with women who had not had clomiphene citrate. The broad CI reflects the uncertainty around this estimate of the effect of multiple treatment cycles with fertility drugs.

The main limitations with this study are the difficulties that most studies of fertility drugs and cancer have to face. These include relatively small numbers of cancer cases with the exposures of interest, ascertainment of cancers being affected by loss to follow-up, or differential ascertainment of borderline tumours in infertile women compared with women not seeking infertility treatment, and potential misclassification of exposure to fertility drugs, in this case because exposure that might have occurred after treatment at the participating infertility clinics was not known.

Franceschi *et al.*[59] reported on the relationship between fertility drugs and ovarian cancer in a case–control study conducted in four areas of Italy. Cases comprised 195 women admitted to hospital with invasive epithelial ovarian cancer during 1992–1993; 1330 hospital controls were selected from women admitted for a range of conditions excluding malignant, hormonal and gynaecological diseases. Data were collected from cases and controls using personal interview. This study found no association between ovarian cancer and the use of fertility drugs: two cases and fifteen controls had ever used fertility drugs giving an OR=0.73 (95% CI 0.16–3.30) adjusted for age, residence, education, use of oral contraceptives and number of pregnancies. Cases were more likely to be nulliparous than controls but were not more likely to have had a medical diagnosis of infertility. The very small number of women who had had fertility drug treatment meant this study was unable to look at the effects of different types of fertility drugs or the effect of cause of infertility. Updated data for one of the regions in the Italian study were reported in 1995.[60] Fertility drugs had been used by 4 out of 208 cases and 13 out of 873 controls giving an OR=1.1 (0.4–3.6). None of the 34 nulliparous cases and only 2 of the 135 nulliparous controls had ever used fertility drugs.

We used record-linkage with population-based cancer registries to determine the incidence of cancer in an Australian cohort of 10,358 women who had been in an IVF programme.[27] Cancer incidence was compared between women in the IVF programme and women of the same age in the general population and between women in the IVF programme who had and had not been treated with fertility drugs. Women who had not been exposed to fertility drugs were those who had been referred for IVF treatment but who chose not to continue for a range of reasons such as pregnancy occurring without IVF, financial constraints, relationship difficulties, and risks associated with treatment. Women in the unexposed group tended to have joined the IVF programme in its earlier years. Exposure to fertility drugs in this cohort was characteristic of the regimens used routinely to induce 'superovulation'; relatively few women exposed to fertility drugs had ovarian disorders (6.2 %).

Three cases of ovarian cancer were observed in the women exposed to fertility drugs compared with 1.77 expected (SIR=1.7, 95% CI 0.55–5.27). In the unexposed group (n=4794), 3 cases were observed and 1.85 expected (SIR=1.62, 95%CI 0.52–5.02). All IVF patients combined gave a SIR=1.66 (95% CI 0.75–3.69). Fertility drugs did not appear to be associated with an increased risk of ovarian cancer; RR=1.45 (95% CI 0.28–7.55) adjusted for age and infertility type. The proportional hazards model used to derive the RR estimate proved to be unstable due to the small number of ovarian cancer cases.[61] Examination of the relationship between cause of infertility and cancer risk showed significantly more cases of ovarian cancer in IVF patients with unexplained infertility than expected from age-standardised general population rates (SIR=6.98, 95% CI 2.90–16.8).

Our study was limited by the small number of ovarian cancer cases observed, the relatively short follow-up time after exposure to fertility

drugs and the lack of data on important covariates including parity. Data on reproductive history were kept by referring doctors and not routinely held in the clinic records. Loss to follow-up and incomplete ascertainment of cancer cases in the unexposed group might have been greater than in the exposed group due to the longer follow-up time, poorer quality clinic records, and possibly more name changes due to break down of relationships.

An Israeli case–control study of ovarian cancer was reported by Shushan *et al.* in 1996.[25] Cases included living women aged 36–64 with invasive or borderline ovarian tumours reported to the Israel cancer registry. Controls from the general female population were selected by random digit dialling with matching for area of residence. Women who had had a bilateral oophorectomy were excluded from the controls. Of all ovarian cancer cases reported to the registry, 25% of women had died and 30% of those living were lost to follow-up or were unable to participate. Data were collected from the 200 cases (164 invasive and 36 borderline tumours) and 408 controls using personal interview. Assessment of exposure to fertility drugs came from women's self-report, with second interviews being conducted for women who could not remember the type of fertility drug they had used. The prevalence of fertility drug use was higher in this study than in the Italian case–control study described above: 22 cases and 24 controls had used clomiphene citrate alone or in combination with hMG. Exposure to fertility drugs was not significantly associated with ovarian cancer (invasive and borderline combined), OR=1.3 (0.63–2.74) adjusted for age, parity, body mass index, region of birth, education, family history and interviewer. A significant association was found, however, for borderline ovarian tumours, adjusted OR=3.52 (1.23–10.09). Analysis by type of fertility drugs suggested that exposure to hMG had the largest effect, adjusted OR=3.19 (0.86–11.82), but the finding was not statistically significant. Exposure to twelve or more cycles with clomiphene citrate was not associated with ovarian cancer (crude OR=1.44, 95%CI 0.34–5.82). Some of the limitations with this study include the exclusion of cases who had died, reliance on self-report of fertility drug exposures without verification using medical records and the lack of data on cause of infertility.

The most recent study to examine fertility drugs and ovarian cancer came from Mosgaard *et al.*[26] This Danish case–control study used a postal questionnaire to obtain data from living women with invasive ovarian cancer identified in population-based hospital and cancer registries and controls selected from the National Person Register with matching for area of residence and age at time of cancer diagnosis in the matched case. The analysis was based on 746 cases and 1721 controls who returned useable questionnaires. To help establish the type of exposure to fertility drugs, women were asked about the route of drug administration and were asked to give permission for the investigators to contact the treating physicians; it is unclear whether fertility drug treatments were verified from medical records.

Fertility drugs had been used by 20.7% of the cases and 23.8% of the controls. Odds ratios were adjusted for age, residence, use of oral contraceptives and intrauterine devices, menopausal status, previous cancer, familial cancer, use of HRT and body mass index. Parity and infertility were also included in the model according to the association being examined. Among infertile women, fertility drugs were not associated with ovarian cancer in either nulliparous women (OR=0.83, 95% CI 0.35–2.01) or parous women (OR=0.56, 95% CI 0.24–1.29). No significant association was found with ovarian cancer for any particular fertility drug type.

This study had some important advantages as well as limitations. The study was able to estimate the effect of a wide range of covariates and to compare the odds of ovarian cancer in infertile women who had had fertility drug treatment with infertile women who had not had fertility drug treatment; something few other studies have achieved. Although no association was found between fertility drugs and ovarian cancer, the data suggested that infertility was significantly associated with ovarian cancer in nulliparous women (OR=2.71, 95% CI 1.33–5.52) when compared with nulliparous women with no history of infertility. The effect of infertility was not seen for parous women (OR= 1.14, 95% CI 0.6–2.17).

The exclusion of women who had died of ovarian cancer (37% of all cases identified) limited the findings of this study. Other limitations were the lack of data on cause of in-

fertility and a difference in the way exposure was ascertained for cases and controls. Exposure and covariate measurement in the controls was matched to the cases for age at diagnosis of cancer, but was later in calendar time; it is not clear what effect this difference might have had.

Breast cancer

Three studies[27, 62, 63] have addressed the relationship between exposure to fertility drugs and the incidence of breast cancer; two have been described in the previous section.[27, 62] Our study of cancer in women referred to an IVF programme compared the incidence of invasive breast cancer in women exposed and unexposed to fertility drugs with IVF with general population incidence rates. In the exposed group, 16 cases were observed and 17.9 expected (SIR=0.89, 95% CI 0.55–1.46); in the unexposed group 18 cases were observed compared with 18.3 expected (SIR=0.98, 95%CI 0.62–1.56). The within cohort comparison of IVF patients showed no increase in breast cancer risk with exposure to fertility drugs (RR=1.11, 95% CI 0.56–2.20, adjusted for age and cause of infertility). No significant association was found between breast cancer risk and number of stimulated IVF treatment cycles or cause of infertility.

The case-cohort study conducted by Rossing *et al.*[62] found 27 cases (*in situ* and invasive tumours combined) of breast cancer in 3837 women with infertility compared with 28.8 cases expected (SIR=0.9, 0.6–1.4). Women who had had treatment with clomiphene citrate appeared to have a reduced risk of breast cancer (RR=0.5, 95%CI 0.2–1.2), after adjusting for age, weight and calendar year at entry into the cohort, though the difference was not statistically significant. Cases and women in the sub-cohort were very similar in terms of parity and a range of other covariates that were described.

Braga *et al.* (63) reported the results of an Italian multi-centre case–control study of breast cancer that also showed no increase in breast cancer risk in women exposed to fertility drugs. Cases were 2569 women who had been hospitalised for breast cancer; it was not specified whether they included women with *in situ* cancers. The controls were 2588 women who had been hospitalised for acute, non-neoplastic and non-gynaecological conditions. Information on the exposures and covariates of interest was collected by personal interview and included ever having a medical diagnosis of infertility and infertility treatment. As found in the Italian case–control study of ovarian cancer,[59] only a small proportion of cases (1.8%) and controls (1.2%) had ever used fertilty drugs giving an OR=1.43, adjusted for age, centre, education, parity, age at first birth, menopausal status, age at menopause, age at menarche, hysterectomy, benign breast disease, family history of breast cancer and use of oral contraceptives. Women who had had any form of infertility treatment were at no greater risk of breast cancer than women who had not been treated (adjusted OR= 1.08, 95% CI 0.8–1.5).

Although this study collected data on a range of covariates that might have affected the relationship between exposure to fertility drugs and breast cancer risk, there were no data on number of treatment cycles using fertility drugs or the types of drugs used. Due to the low prevalence of fertility drug treatment in the study population, there was limited statistical power for subgroup analyses.

Uterine cancer

To our knowledge, ours is the only study to have reported on the risk of uterine cancer in women exposed to fertility drugs. We observed five cases of uterine cancer in our cohort of IVF patients compared with 1.76 cases expected (SIR=2.84, 95% CI 1.18–6.81). The risk of uterine cancer did not differ significantly between women exposed and unexposed to fertility drugs (RR=0.65, 95% CI 0.11–3.94), but was greater in women with unexplained infertility compared with women with known causes (RR=6.34, 95% CI 1.06–38.0). These findings await confirmation in other studies.

Cervical cancer

Two studies[27, 64] have reported on the incidence of invasive and *in situ* cancer of the cervix in women seeking infertility treatment; both showed a significantly lower than expected incidence compared with women in the general population. This finding might be explained by differences in risk factors for cervical cancer in infertile women compared with the general population and/or greater prevention of *in situ* and invasive cancer of the cervix in infertile

women due to a higher level of cervical screening.

In our cohort of IVF patients, 18 cases of cervical cancer (invasive and *in situ* combined) were observed in women exposed to fertility drugs compared with 30.5 cases expected (SIR=0.6, 95% CI 0.4–0.9), and, in the unexposed group, 16 cases were observed compared with 34.0 expected (SIR=0.5, 95% CI 0.3–0.8). Cervical cancer incidence was not significantly associated with exposure to fertility drugs (RR=1.64, 95% CI 0.85–3.15) or tubal causes of infertility (RR=1.25, 95% CI 0.58–2.69). Although the incidence of cervical cancer was lower in IVF patients than in the general population from the time they entered the cohort, the number of cases found in the cancer registry for the same women prior to joining the IVF programme was the same as the number expected from general population incidence rates (64 cases observed, 64 expected). This could suggest that infertility treatment reduces the risk of cervical cancer but the difference was the same for all women who joined the IVF programme, irrespective of whether they went on to have treatment. If cervical cancer screening is more frequent in women seeking infertility treatment, then early detection and treatment of abnormalities such as CIN I and II, which are not notified to Australian cancer registries, might be preventive for the later development of CIN III, which is notified.

The case–cohort study reported by Rossing *et al.*[64] found 36 cases of cervical cancer (*in situ* and invasive combined) compared with 67.8 cases expected (SIR=0.5, 95% CI 0.4–0.7). They found a significantly reduced risk of cervical cancer in women who had used clomiphene citrate (RR=0.4, 95% CI 0.2–0.8) and a greater, but not statistically significant, risk in women with tubal causes of infertility (RR=1.8, 0.8–4.0). The authors postulated that clomiphene citrate might have a protective effect against cervical cancer. Women with tubal causes of infertility might be expected to have a higher incidence of previous sexually transmitted infections, including infection with human papilloma virus, and also, therefore, a higher incidence of cervical cancer than women with other causes of infertility. There was little evidence to support that hypothesis from these studies.

Melanoma

Findings on the incidence of melanoma in women seeking infertility treatment differed between our study and Rossing's case–cohort study.[65] We found that Australian IVF patients had the same incidence of melanoma as the general population with 16 cases observed compared with 14.92 expected (SIR=1.07, 95% CI 0.66–1.75). Exposure to fertility drugs was not associated with a significantly increased risk (RR=0.91, 95% CI 0.33–2.50). Rossing's study, on the other hand, suggested a greater than expected incidence compared with the general population (12 cases observed, 6.8 expected; SIR=1.8, 95% CI 0.9–3.1) and an increased risk among women who had had twelve or more treatment cycles with clomiphene citrate (RR=2.2, 95% CI 0.5–10.2). Neither association was statistically significant.

Future research needs

The question of whether fertility drugs are associated with an increased risk of cancer remains largely unresolved. The epidemiological studies that address the question are now outnumbered by the articles that review them[36, 66–72] and all have important limitations. The greatest challenge facing epidemiologists is to conduct studies that have large enough numbers of women with both the exposure and outcome of interest.

Australia's role in the development of ART has given it a high profile, the public is well informed and has a high level of acceptance of the technology as well as more affordable and accessible treatment than most other countries. We are currently working with ten Australian IVF clinics to follow-up 30,000 ART patients. Even with a cohort of this size, only 14 cases of invasive ovarian cancer and 144 cases of breast cancer are expected from general population incidence rates. Once again, analyses by treatment regimen, type of infertility, parity, and other potential confounders will be limited by the small numbers of cases in the sub-groups. Collaboration between those services and clinicians who provide infertility treatment will be important in assembling large study populations. International collaboration, perhaps with re-analysis of pooled original data such as that used to examine the relationship between oral contraceptive use and breast cancer,[50] could also be valuable.

What can be done at the level of individual infertility clinics that might contribute to good research in this area in future? Epidemiologists often need medical records as their source of information on the characteristics of women in a study population and the treatments they received. Well organised, complete and accurate medical records therefore make an extremely important contribution to the reliability of a study's results. Some infertility clinics in Australia have had a practice of providing IVF patients with a written record of the fertility drug regimen used in their treatment cycles. In the course of pilot testing a questionnaire to elicit self-reported information on fertility drug use by IVF patients, we have heard that women appreciate these records and have referred to them to give us information about their past treatments.

Record-linkage of patient records with population-based cancer registries is another key method that epidemiologists use to study relatively rare outcomes in large populations. This method requires adequate safeguards to protect individual privacy and a proper process of review by institutional ethics committees is essential. There is a danger, however, that this type of research can be severely hindered by the lengthy process of seeking ethics approval from many collaborating centres, inconsistencies in the way ethical issues are reviewed, and a trend, at least in Australia, for ethics committees and clinics to let fears of litigation prevent them from allowing researchers to access identifiable patient information for record-linkage follow-up studies. Infertility clinics need to be aware of the important role that record-linkage can play in studies of long-term health after infertility and could consider informing their patients that their records might be used for studies of the long-term outcomes of infertility treatment.

Finally, irrespective of what is found in future studies of fertility drug use and cancer, we have a responsibility to provide clear and accessible information to couples who are considering fertility treatment or who are concerned about risks associated with past treatment. Such information should acknowledge the uncertainties that remain. It is to be expected that couples will differ in the degree of short and long-term risk they are prepared to accept with fertility treatment.[73] Good information on what is known about the risks associated with treatment is a useful resource for informed decision-making.

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