Introduction

It is well established that nulliparity is a risk factor for ovarian, breast and endometrial cancers, with many studies suggesting that the association is largely attributable to infertility. Despite the extensive literature on the topic, causes of infertility and treatment effects on cancer risk are poorly understood.

Increasingly, women are delaying their first childbirth, resulting in many more women seeking advice for infertility. In fact, it is estimated that, by the year 2025, between 5.4–7.7 million women aged 15–44 will be diagnosed in the USA with some form of infertility (Stephen and Chandra, 1998). Consequentially, ovulation-stimulating drugs are among the fastest growing groups of drugs, with prescriptions in the USA nearly doubling between 1973 and 1991 (Wysowski, 1993).

The two most commonly used medications, clomiphene citrate and gonadotrophins, are effective at stimulating ovulation, a factor implicated in the aetiology of both breast and ovarian cancers (Fathalla, 1971; Henderson et al., 1985). These drugs also raise both oestradiol and progesterone concentrations (Sovino et al., 2002), hormones which are recognized as affecting the development and growth of breast and gynaecological cancers. Finally, as elaborated below, some clinical and epidemiological studies have linked usage of these drugs with an increased incidence of various cancers.

Ovarian cancer

Numerous clinical reports have raised concern about a potential link between use of ovulation-stimulating drugs and ovarian cancer risk (Fishel and Jackson, 1989; Dietl, 1991; Goldberg and Runowicz, 1992; Nijman et al., 1992; Balasch et al., 1993; Lopes and Mensier, 1993; Willemsen et al., 1993; Adewole et al.,...
1997; Unkila-Kallio et al., 1997). The association has biological credibility, given that ‘incessant ovulation’ and associated alterations in endogenous hormones during reproductive years are plausible explanations for several factors that alter ovarian cancer risk, including nulliparity and oral contraceptive use (Fathalla, 1971; Cramer and Welch, 1983; Whittemore et al., 1992a). Results from two epidemiological studies that found marked elevations in ovarian cancer risk associated with exposure to ovulation-stimulating drugs (Whittemore et al., 1992b; Rossing et al., 1994) provide additional support for this hypothesis.

The earliest evidence of such a link derived from a meta-analysis of 12 case–control studies of ovarian cancer conducted by Whittiermore and coworkers (Whittemore et al., 1992b). Only three of these studies, with 526 cases and 966 controls, provided information regarding the use of fertility drugs and there was scant information about the type of drug or the extent of its use. Self-reported prior usage of fertility medications was associated with an odds ratio (OR) of 2.8 (95% CI 1.3–6.1) as compared with women who had no history of infertility. The increased risk was limited to nulligravid women, who experienced a 27-fold increase in risk associated with drug usage (95% CI 2.3–315.6). However, this risk was based on only 12 exposed cases and one exposed control.

Results from a retrospective cohort study involving 3837 women evaluated for infertility in a single Seattle practice between 1974 and 1985 also raised concern (Rossing et al., 1994). More details on this and other completed cohort studies are shown in Table 1. Information on drug exposures and indications for usage was obtained via linkage against a regional cancer registry. Effects of other risk factors were evaluated by abstracting information regarding the use of fertility drugs and there was limited to nulligravid women, who experienced a 27-fold increase in risk associated with drug usage (95% CI 2.3–315.6). However, this risk was based on only 12 exposed cases and one exposed control.

Use of clomiphene for less than 1 year was not associated with an increased risk, but five of the nine women with cancer had taken the drug for 12 or more monthly cycles, resulting in a relative risk of 11.1 (95% CI 1.5–82.3). An enhanced risk associated with long-term treatment was observed in both those with and without ovulatory abnormalities. A large proportion of the observed tumours were borderline (five of the 11 in the cohort).

Although the results of these two initial studies were alarming, subsequent results from a number of case–control studies were largely reassuring (Franceschi et al., 1994; Mosgaard et al., 1997; Parazzini et al., 1997). A meta-analysis of eight studies involving data on 1060 cases and 1337 controls (Ness et al., 2002) also showed no risk associations with fertility drug use. In this study, after adjustment for types of infertility, the risk associated with drug usage was somewhat higher among nulligravid women (1.8) and among those who had more than 4 months of exposure (relative risk (RR) 1.5–1.7), but none of these risks was statistically significant.

The results of case control studies are limited by the fact that information on prior drug use is based on patient histories. Most have been further limited by small numbers of ovarian cancer cases reporting prior drug usage. For example, in the largest case–control study (Parazzini et al., 2001), based on 1031 cases and 2411 hospital controls, only 1.1–1.5% of the subjects reported prior usage of fertility drugs, resulting in only 15 cases and 26 controls with relevant exposures for analysis.

Although results have also been published from additional cohort studies (Ron et al., 1987; Shushan et al., 1996; Modan

<table>
<thead>
<tr>
<th>Location</th>
<th>Reference</th>
<th>No. of subjects</th>
<th>Years evaluated</th>
<th>Average years of follow-up</th>
<th>Type of cancer</th>
<th>Ovarian</th>
<th>Breast</th>
<th>Endometrial</th>
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<tr>
<td>Israel</td>
<td>Ron et al., 1987</td>
<td>2575</td>
<td>1964–1974</td>
<td>12.3</td>
<td>4</td>
<td>15</td>
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<td>Venn et al., 1995</td>
<td>10,358</td>
<td>1978–1992</td>
<td>6.5</td>
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<td>Modan et al., 1998</td>
<td>2496</td>
<td>1964–1974</td>
<td>21.4</td>
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<td>1197</td>
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<td>17.9</td>
<td>2</td>
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<td>29,666</td>
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<td>8.5</td>
<td>13</td>
<td>143</td>
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<td>50</td>
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<td>1965–1988</td>
<td>18.8</td>
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et al., 1998; Potashnik et al., 1999; Dor et al., 2002; Doyle et al., 2002; Klip et al., 2002), most have involved small numbers of ovarian cancers, with the number of exposed cases ranging from two in the smallest study (Potashnik et al., 1999) to 12 in the largest study (Modan et al., 1998). These studies were also limited by lack of information on causes of infertility or on other factors that could independently influence ovarian cancer risk (including parity, oral contraceptive usage and socioeconomic status).

One of the most recently published studies was designed to overcome many of the limitations of previous studies (Brinton et al., 2004a). This retrospective cohort study followed 12,193 infertile women for a median of 18.8 years, and had detailed information on drug exposures and causes of infertility from medical records as well as questionnaire data on potential cancer risk factors for a substantial proportion of the patients. This study was unique in being able to identify subjects who underwent a bilateral oophorectomy and were thus no longer at risk for developing ovarian cancer. The number of ovarian cancers, 45, was larger than in other cohort studies, but this number was still too limited for analyses of small subgroups of women. The results were largely reassuring, showing no increase in risk associated with ever using either clomiphene or gonadotrophins. There were non-significant increases in risk (RR 1.5–2.5) associated with use of either clomiphene or gonadotrophins among the subjects followed for the longest periods of time (15 years or more).

While this study focused on women exposed to ovulation-stimulating agents prescribed during earlier times, a number of other studies have concentrated on exposures received during IVF. One other US study, published to date only in abstract form, found no evidence for an effect of ovulation-stimulating drugs on ovarian cancer risk. After 5.6 years of follow-up of 51,371 patients seen for conception or ovum donation in 15 California clinics, 50 ovarian cancers were diagnosed (Croughan-Minhane et al., 2001). The only significant associations with ovarian tumour risk observed in the study were with length of time in infertility treatment and nulligravidy. However, no associations of risk were found for ovulation-stimulating drugs and risk, even when dose, formulation and number of treatment cycles were considered.

Among 29,666 women referred to 10 Australian IVF clinics, 13 ovarian cancers were observed during a follow-up period averaging 7.8 years (Venn et al., 1999). The investigators had detailed information on indications for drug usage, but only limited information on patient characteristics. Comparing risks to the general population, the standardized incidence ratio (SIR) was 0.99, with no higher risk for the women who received at least one IVF treatment cycle (0.88) as compared with those who received no drug treatment (1.16). Women with unexplained infertility were at a significantly increased risk compared with the general population, but within this subgroup there was no difference in risk between treated and untreated women.

In a cohort of 25,152 women treated for subfertility in the Netherlands, 17 ovarian cancers developed during 5.6 years of follow-up (Klip et al., 2002). Strengths of this study included detailed information on causes of infertility and drug exposures from medical records, as well as on cancer risk predictors obtained through completed questionnaires from many of the study subjects. Thus, the study was able to assess risks associated with different parameters of drug exposures, while adjusting for other risk factors. Results showed no difference in risk between treated and untreated subjects, even when the number of cycles or ampoules received were considered.

While the results of the most recent studies are consistently reassuring when compared with the results of earlier studies, several observations indicate a need for further monitoring. These include the findings in the two most recent studies (Ness et al., 2002; Brinton et al., 2004a) of modest increases in risk estimates with either extended follow-up or increased exposure to ovulation-stimulating drugs. Given that these ovulation-stimulating drugs first became available beginning in the early 1960s, women who were exposed to them are just beginning to enter the ovarian cancer age range. Furthermore, less information is available on gonadotrophins than clomiphene, given that the latter was the drug of choice in earlier time periods. Thus, additional follow-up data are needed to fully evaluate effects of both exposures.

In addition, two recent investigations (Ness et al., 2002; Brinton et al., 2004a) and Whittemore’s early meta-analysis (Whittemore et al., 1992b) found drug effects to be greatest among nulligravid women, suggesting the possibility of an enhanced effect of the medications among women with certain indications for usage.

That ovulation-stimulating drugs might preferentially affect the risk of borderline ovarian tumours is also suggested by several studies. Both cohort (Rossing et al., 1994; Shushan et al., 1996) and case–control (Parazzini et al., 1998; Ness et al., 2002) investigations have shown risk ratios in the range of 3–4 associated with fertility drug usage. In one study, the relationship was restricted to nulligravid women (Ness et al., 2002) and in another specifically to gonadotrophins (Shushan et al., 1996). These findings, in conjunction with case reports of ovarian neoplasms developing in women during or shortly after treatment with ovulation-stimulating agents (Dietl, 1991; Goldberg and Runowicz, 1992; Nijman et al., 1992; Willemsen et al., 1993; Hull et al., 1996; Adewole et al., 1997; Bayar et al., 2006), have led to speculations that ovarian stimulation may induce growth in existing highly differentiated indolent tumours. Alternatively, the findings simply could reflect more intensive medical surveillance among infertile women.

### Breast cancer

The epidemiology of breast cancer has been extensively studied, with many investigations supporting the notion of an important aetiological role for endogenous as well as exogenous hormones (Bernstein, 2002). Specific concerns regarding the effects of fertility drugs have been raised by the recognized effects on breast cancer risk of ovulation and hormonal patterns (Henderson et al., 1985; Parazzini et al., 1993). Furthermore, there are a number of clinical reports of breast cancer occurring among users of such drugs (Arbour et al., 1994; Brzezinski et al., 1994; Jourdain et al., 1996; Unkila-Kallio et al., 1997).

Many cohort (Ron et al., 1987; Venn et al., 1995; Modan et al., 1998; Venn et al., 1999; Doyle et al., 2002; Klip et al.,
2002; Lerner-Geva et al., 2003) and case–control (Braga et al., 1996; Weiss et al., 1998; Ricci et al., 1999) studies have failed to find any remarkable associations between fertility drug use and breast cancer risk. Most, however, were limited by small numbers of cancers, imprecise information on patterns of, or indications for, drug usage, and incomplete ability to control for other related risk factors, including well-recognized reproductive risk factors.

Several studies have suggested links between fertility drugs and breast cancer risk, but the results are conflicting, with some suggesting potential increases in risk and others decreases. A recent case–control study involving over 4500 breast cancer cases was able to carefully control for potential confounding variables but had to rely on self-reports of infertility and had few women exposed to fertility drugs (Burkman et al., 2003). Although this study found no association of risk related to use of clomiphene, there was some indication of a risk elevation among women with long-term use of menopausal gonadotrophins. Use for at least 6 or more months or at least six cycles was associated with RR ranging from 2.7–3.8. The finding was somewhat unexpected given that neither of the constituents of human menopausal gonadotrophin – FSH and LH – are thought to have direct effects on breast tissue (Healy and Venn, 2003). Since gonadotrophin therapy increases both serum oestrogen and progesterone concentrations, the investigators suggested this as a possible explanation for their findings. Whether the increases in hormones that would be associated with six or more cycles of exposure would be sufficient to substantially affect the subsequent risk of breast cancer is questionable (Healy and Venn, 2003).

The opposite relationship, namely a non-significantly reduced risk of invasive and in situ breast cancer associated with clomiphene (adjusted RR 0.5, 95% CI 0.2–1.2) was found in Rossing’s retrospective cohort study (Rossing et al., 1996). This estimate was based on only 12 exposed cases and there was no indication of any further risk reduction with extended duration of use. A chemopreventive effect of clomiphene would be of interest given that it is a selective oestrogen receptor modulator (SERM), and thus could have properties similar to another SERM, tamoxifen (Fisher et al., 1998). Additional epidemiological support of a reduced risk of breast cancer associated with clomiphene use was provided from The Nurses Health Study II (Terry et al., 2006), which showed a RR of 0.40 (95% CI 0.2–0.7) associated with use of clomiphene among women treated for ovulatory infertility. Risk decreased significantly with duration of use of clomiphene, with users of 10 or more months having a RR of 0.25 (95% CI 0.09–0.75) compared with non-exposed women. The findings were based on self-reports of both drug usage as well as causes of infertility.

On the other hand, the recent multi-centre US cohort study, involving 292 breast cancer cases, failed to find any substantial alterations in risk related to ever using either clomiphene or gonadotrophins (Brinton et al., 2004b). However, there were small non-significant increases in risk after extended follow-up periods (>15 years), with the RR in the range of 1.4–2.5, similar to the long-term risks observed for ovarian cancer in this same cohort study. When analyses were restricted to invasive breast cancers, the RR after 20 years of follow-up became statistically significant (RR 1.6, 95% CI 1.0–2.5).

More recent results are now beginning to emerge regarding the effects on breast cancer risk among IVF exposed cohorts. In a study of 5788 women attending an Israeli clinic in whom 131 breast cancers developed, a significantly elevated risk was found related to clomiphene exposure (SIR 1.4, 95% CI 1.0–1.8) (Lerner-Geva et al., 2006). Even stronger results were found when internal analyses were conducted through a nested case–control study within the cohort (OR 2.7, 95% CI 1.3–5.7).

However, in a large cohort study in France, involving 92,555 women and 2571 invasive breast cancers, there was no evidence of any increases in risk, regardless of the exposure considered (Gauthier et al., 2004). This included overall treatment for infertility, IVF treatment, exposure to specific drugs (e.g., clomiphene), and specifics of exposures (duration of treatment, age at first use). The exposure information, however, was self-reported and no information was available on indications for drug usage, including causes of infertility. The only evidence of any increased risk associated with fertility treatment was among women with a family history of breast cancer (RR 2.32–2.77), with estimates based on fairly small numbers of affected women.

Two other epidemiological investigations of IVF-exposed women, one conducted in Australia (Venn et al., 1999) and the other in the Netherlands (Klip et al., 2002), did not find differences in risk between exposed and unexposed subjects. However, in the Australian study, an approximately two-fold increased risk of breast cancer was observed within 1 year of last treatment. This prompted the suggestion that ovulation-stimulating drugs might promote the rapid growth of pre-existing tumours, similar to the short-term transient increase in breast cancer following a recent pregnancy (Lambe et al., 1994). However, several other studies, which assessed detailed timing effects of last drug usage, found no support for a promotional effect by either clomiphene or gonadotrophins (Klip et al., 2002; Brinton et al., 2004b).

In the Australian study, Venn and coworkers also assessed causes of death among their cohort of infertile women, observing non-significant decreases in mortality for most causes as compared with the general population (Venn et al., 2001). Deaths due to breast cancer showed no appreciable differences between those who did and did not receive IVF. The data therefore provided little support for another report that demonstrated poor prognostic features among breast cancer patients with recent histories of exposure to fertility drugs (Siegelmann-Danieli et al., 2003).

Endometrial cancer

Endometrial cancers are well recognized as hormonally sensitive (Akhmedkhanov et al., 2001). There is a clinical report of three cases of adenomatous hyperplasia of the endometrium, a precursor condition, occurring among women exposed to ovulation-stimulating agents (Miannay et al., 1994). Few analytical studies, however, have assessed the relationship between endometrial cancer and use of fertility drugs.

One small case–control study that assessed the relationship found no association, but, with only seven exposed cases, the investigation had limited power to detect an effect (Benshushan
et al., 2001). Most cohort studies have not observed an association, but the majority had follow-up times of less than 10 years and few associated cases of endometrial cancer (between two and 14) (Venn et al., 1995, 1999; Potashnik et al., 1999; Klip et al., 2002).

The two largest cohort studies both raise some concern regarding effects of ovulation-stimulating agents on the endometrium. In an Israeli cohort, in which 21 uterine cancers were diagnosed during an average of more than 20 years of follow-up, a significant two-fold increase in risk was associated with fertility drug usage (Modan et al., 1998). Similarly, the multi-centre US cohort study, which detected 39 cases of endometrial cancer among cohort members, found clomiphene usage associated with a non-significant increase in risk (RR 1.8, 95% CI 0.9–3.3) (Althuis et al., 2005). Further, increases in risk were found among subjects with higher dosages of exposure or longer follow-up periods, with trends in risk for the latter variable being statistically significant. Drug effects were also more apparent among nulligravid and obese women (RR of 3.5 and 6.0, respectively).

Because tamoxifen, a SERM which bears structural similarities to clomiphene (Sovino et al., 2002), has been repeatedly linked with increases in endometrial cancer risk (Varras et al., 2003), these two studies raise concern despite the fact that they were based on fairly small numbers of cancers.

Future research needs

Given that clomiphene was first approved for clinical use in 1967 and gonadotrophins in 1969, the women who first used these drugs during their late twenties and early thirties have only recently reached the age when hormonally-related cancers are common. Most studies to date are reassuring in not showing a strong association between use of these medications and risks of most cancers. On the other hand, several studies have found increasing risks with greater exposures or extended follow-up, indicating that complacency is not warranted and that long-term effects should be further monitored, especially in view of changes in reproductive technology.

There has been little attention focused on the long-term effects of assisted reproductive technologies, which often involve much higher exposures to gonadotrophins than were received by women in previous eras. In addition, most IVF protocols include luteal phase support for several weeks with supplemental progestogens, which raises concern since these agents have been linked in several studies to increases in breast cancer risk (Key and Pike, 1988; Beral, 2003). Since in-vitro techniques have become common only in the last couple of decades, it may be some time before epidemiological studies can amass the follow-up times required to fully address long-term effects.

There is some consistency across studies of a modest enhancement of ovarian cancer risk associated with use of fertility drugs among women who remain nulligravid (Whittemore et al., 1992b; Ness et al., 2002; Brinton et al., 2004c). This may indicate an interactive effect of the drugs with the underlying causes of infertility, including those reflecting unique hormonal perturbations. On the other hand, it may be that women who continue to remain infertile may have received larger doses and longer durations of fertility or other medications than other women.

There are other issues of interest that have not been widely pursued. First is the question of whether women at particularly high risk of cancer, including those with a genetic predisposition, experience unusual risks from the use of fertility medications. Secondly, it is of interest whether fertility drugs have unusual effects among women who have used other hormones. This includes oral contraceptives, which have been shown to be associated with reduced risks of endometrial and ovarian cancers (Deligeroioglu et al., 2003) and somewhat increased risks of breast cancers (CGHFRB, 1996), and menopausal hormone replacement therapy, which has been linked with increases in the risk of all three cancer sites (Akhmedkhanov et al., 2001; Lacey et al., 2002; Beral, 2003).

Some (Rossing et al., 1994; Shushan et al., 1996; Parazzini et al., 1998; Ness et al., 2002, Brinton et al., 2004a), although not all (Brinton et al., 2004a), studies suggest an unusual occurrence of borderline ovarian cancers among women exposed to fertility medications. Whether this reflects a biological effect or is merely the result of more intensive surveillance of women treated with these drugs by ultrasound and clinical examination warrants further scrutiny. Biologically, it is of interest that oestrogen receptor expression is a common feature of borderline ovarian tumours. Thus, further study of the relationship of fertility medications to ovarian, as well as breast cancers, according to hormone receptor status would appear warranted. In addition, investigations of cancer associations by tumour histologies should also be undertaken, given clinical reports of several unusual types of ovarian cancer (e.g., clear cell, germ cell, granulosa cell tumours) occurring among fertility drug users (Willemens et al., 1993; Tewari et al., 1998; Makrydimas et al., 2003).

Although most attention has focused on effects of fertility drugs on ovarian cancer risk, more recent investigations support the need for further attention on breast and endometrial cancers. This need is supported by the recognition that ovulation-stimulating drugs are effective at increasing both oestrogen and progesterin concentrations, alterations that have been linked with both of these cancers. Further, a relationship with breast cancer would parallel findings of an increased risk of this tumour among mothers exposed to diethylstilbestrol during pregnancy (Titus-Ernstoff et al., 2001). The preliminary findings regarding an increased risk of endometrial cancer following exposure to clomiphene, a drug closely related to tamoxifen, especially warrants further follow-up in well-designed epidemiological investigations.

References


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