The link between female infertility and cancer: epidemiology and possible aetiologies

D.Meirow and J.G.Schenker

Department of Obstetrics and Gynecology, Hadassah University Hospital, Jerusalem, Israel

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Infertility has been suggested as a risk factor for various gynaecological cancers. Data analyses show that among infertile women, those with anovulation or polycystic ovarian syndrome (PCOS) have an increased risk of cancer. Clinical and laboratory data such as anthropometric measurements, endogenous hormones and growth factors may explain mechanisms which link tumorigenesis or tumour promotion to infertility. The possible association between ovulation induction and cancer is discussed both on theoretical grounds and based on epidemiological data. We conclude that according to epidemiological studies, laboratory data and on theoretical grounds, infertile patients have an increased lifetime risk of gynaecological cancer. The risk of cancer should be evaluated further for each subpopulation of infertile patients. Thus, more adequate means of monitoring these patients will become available. These data are necessary for a further evaluation of the possible cancer risks of infertility treatments.

Key words: anovulation/cancer/infertility/ovulation induction/sex hormones

Introduction

The possible relationship between sex hormones and genital cancers has received increasing attention in the last 20 years as it has become apparent that sex hormones can be linked to the development or promotion of genital cancers. Many infertile women suffer from hormonal disturbances; in addition, most of these women are exposed to fertility hormonal treatments which alter their endogenous hormonal milieu. Therefore, an important question which should be asked is whether there is an increased cancer risk among the various groups of infertile women. Furthermore, what are the possible explanations which link infertility and cancer, and do fertility treatments increase cancer risk or accelerate cancer progression?

Cancer and infertility: epidemiological studies

The aetiology of female reproductive cancer is still poorly understood, although reproductive performance and hormones are believed to play fundamental roles. Several epidemiological studies have consistently reported that nulliparity is a risk factor for carcinoma of the breast (Kelsey, 1979; Brinton et al., 1983; Dupont and Page, 1987; Mosee et al., 1993), endometrium (Kelsey et al., 1982; Henderson et al., 1983; Brinton et al., 1992) and ovaries (Stadel, 1975; Nasca et al., 1984). It is widely accepted that exogenous oestrogen administration unopposed by progesterone (unopposed oestrogen) promotes endometrial cancer development (Shapiro et al., 1980; Shushan et al., 1990). A promoting effect of unopposed oestrogens on the risk of breast cancer has been proposed (Korenman, 1980). However, there is some uncertainty as to its magnitude, and even a few factors contradict the view that oestrogen causes or promotes breast cancer (Brzezinski, 1995). Reports of ovarian tumours in women undergoing fertility treatment have raised questions about the potential neoplastic effects of ovulation-inducing agents used in the treatment of infertility (Atlas and Mencer, 1982; Bamford and Steele, 1982; Carter and Joyce, 1987; Fishel and Jackson, 1989; Kulkarni and McGarry, 1989; Dietl, 1991; Goldberg and Runowicz, 1992; Spirats et al., 1993). However, in many infertile women prior to the introduction of fertility medications, endogenous hormonal disturbances are already present. Therefore, the fundamental question that should be considered first and carefully answered is does being infertile cause an increased risk of cancer in these women and, if so, to what extent? Thereafter, it will be possible to determine the neoplastic potential of ovulation-inducing agents.

1To whom correspondence should be addressed. Telephone (97) 22 44 64 24; Fax (97) 22 43 44 34.
Table I. The risk of endometrial cancer in infertile patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Infertility</th>
<th>Infertility +anovulation</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coulam et al. (1983)</td>
<td>Cohort study</td>
<td>3.1a</td>
<td></td>
<td>1270b</td>
</tr>
<tr>
<td>Ron et al. (1987)</td>
<td>Cohort study</td>
<td>4.8a</td>
<td>10.3a</td>
<td>2632b</td>
</tr>
<tr>
<td>Brinton et al. (1989)</td>
<td>Cohort study</td>
<td>0.86a</td>
<td>1.05a</td>
<td>2335b</td>
</tr>
<tr>
<td>Escobado et al. (1991)</td>
<td>Case control</td>
<td>1.72</td>
<td>4.22c</td>
<td>399d</td>
</tr>
<tr>
<td>Brinton et al. (1992)</td>
<td>Case control</td>
<td>7.62c</td>
<td></td>
<td>405d</td>
</tr>
</tbody>
</table>

*a Relative risk of endometrial cancer among the patients in the study.
*b Number of patients with anovulation or infertility (see text).
*c The odds ratio of infertility among patients with endometrial cancer.
*d Number of patients with endometrial cancer (see text).

Endometrial cancer

Endometrial carcinoma is the most common malignancy of the lower female genital tract. In 1994, the estimated endometrial cancer incidence was 8% of all female cancers (Boring et al., 1994). Case reports and epidemiological studies identified an association between endometrial cancer and infertility. Coulam et al. (1983) evaluated 1270 women with chronic anovulation syndrome and showed a 3-fold increased risk of endometrial cancer. Many of these women may have been identified as infertile (after attempting to conceive for at least 1 year). Ron et al. (1987) evaluated 2672 women who were treated for infertility (primary or secondary) between 1964 and 1974 with >31 600 patient years of follow-up. The major infertility classifications were determined as hormonal (anovulation and menstrual disturbances) or other causes of infertility (male, mechanical, unclassified). There was a 4.8-fold increased risk of endometrial carcinoma in the infertile patients group and a 10.3-fold increased risk in infertile women with chronic anovulation. Brinton et al. (1992) evaluated endometrial cancer risk in a multicentre case control study. During 3 years of the study, 405 endometrial cancer cases and 297 population controls were selected. A major risk factor was the absence of a prior pregnancy, with a 2.8-fold relative risk. Moreover, among nulliparous women, those who sought medical work-up for infertility had a 7.6-fold increased risk compared with nulliparous women with no difficulty of conceiving.

Escobado et al. (1991) studied 399 women aged 20–54 years with newly diagnosed epithelial endometrial cancer and 3040 controls. Women with proven infertility (those with physician-diagnosed infertility who reported at least 2 years of infertility) had an odds ratio for endometrial cancer of 1.7. In women who reported infertility resulting from ovarian factors (such as anovulation), the odds ratio for endometrial cancer rose to 4.2.

Most of these studies indicate (Table I) that infertile women are at an increased risk of contracting endometrial cancer. However, this increased risk is not equally distributed. When we grouped these women according to the cause of infertility, anovulation (‘progesterone deficiencies’ as defined by some authors) was clearly shown to be the main cause of the increased endometrial carcinoma risk in infertile patients.

Breast cancer

Epidemiological and clinical observations have implicated a variety of factors linking breast cancer and endocrine function. A number of established risk factors for breast cancer, such as age, early age of menarche and late menopause, late age at first birth and nulliparity, are related to endogenous hormone production (Paffenberg et al., 1980; Kelsey and Gammon, 1991). Nevertheless, most epidemiological studies conducted up to 1991 failed to show conclusive results (Table II). In a few studies, the diagnosis of infertility, whatever the cause, was not associated with a significantly higher risk of breast cancer. These include the studies of Ron et al. (1987) and Brinton et al. (1989) presented previously. Le et al. (1989) examined, in a case control study of young nulliparous women, the relationship between the causes of nulliparity and the risk of breast cancer. A total of 51 cases of breast cancer were compared with 95 matched controls. In the study of Le et al. (1989), the cause of nulliparity related to female infertility (mechanical, hormonal or any other problem) was not found to be associated with a significantly higher risk of breast cancer. In addition, Coulam et al. (1983) showed that chronic anovulation, in which continuous anopposed oestrogen stimulation is provided to the breast during the reproductive years, was not associated with an increased risk of breast cancer. A modest elevation in cancer risk (odds ratio 3.6), although in a small number of patients, was noted in women who were diagnosed as having carcinoma.
of the breast after the age of 55 years. On the other hand, Cowan et al.’s (1981) cohort study showed that anovulatory infertile women recruited from infertility clinics between 1945 and 1965 had a 1.8-fold greater risk of breast cancer than did women with other causes of infertility. As for the age of breast cancer diagnosis, the study of Cowan et al. (1981), in contrast to that of Coulam et al. (1983), found that the risk for pre-menopausal breast cancer was 5.4-fold greater in the anovulatory infertile group compared with non-hormonal causes of infertility. As for the incidence of post-menopausal breast cancer, it did not differ significantly between the two groups. In Table II the risk is compared with two cancer registry data as external data of comparison. Gammon and Thompson (1990) investigated whether a history of infertility affected a woman’s risk of developing breast cancer in pre- or perimenopausal women (aged 20–54 years). In their study, 4730 women with a diagnosis of breast cancer and 4688 controls were evaluated. Infertility was not found to be a risk factor in either nulligravid or gravid women (0.82 and 1.01 odds ratio respectively). Upon further evaluation of the data, Gammon and Thompson (1991) found that polycystic ovary syndrome (PCOS), as diagnosed by physicians, had an inverse association with breast cancer in this group of patients, with an odds ratio of 0.52.

Recently, Sellers et al. (1992, 1993) and Folsom et al. (1993) analysed data from a prospective study of >37 000 women aged 55–69 years. During 4 years of follow-up, 493 new cases of breast cancer were diagnosed. The group was divided into women with a positive family history of breast cancer (mother, grandmother, sister, aunt, daughter) and those with no family history (4368 versus 31 500 respectively). The results showed that an increased risk in breast cancer was associated with a high waist:hip (W:H) ratio [33 in 3547 (relative risk of 3.24) for a W:H >0.91 versus eight in 3340 (relative risk of 0.85) for a W:H <0.78] and a low parity [11 in 1457 (relative risk 2.24) in nulliparous women versus six in 3192 (relative risk 0.57) for multigravid patients] only in women with a family history of breast cancer and not in women with no family history of breast cancer. The analysis of Sellers et al. (1992, 1993) showed that among post-menopausal women who reported trying to become pregnant but with no success (infertile patients), a non-significantly elevated risk of breast cancer (relative risk 1.1.) was noted. However, a pronounced, statistically significant association was noted in patients with a positive family history (relative risk 2.1). Infertility explains the association of W:H with breast cancer. The association between high W:H and infertility was documented previously (Zaadstra et al., 1993), especially in a particular subgroup of infertile women, i.e. those with PCOS who show signs of hyperandrogenism.

Moseeseon et al. (1993) evaluated 354 breast cancer patients and 747 controls. In their study, an elevated cancer risk was present in infertile nulligravid patients (odds ratio 3.5). Patients with irregular menstruation or recurrent amenorrhoea had odds ratios of 2.4 and 3.5 respectively. Patients with an excess of body hair and persistent acne, which are signs of hyperandrogenism, had an odds ratio of 6.8. In the study by Moseeseon et al. (1993), >60% of patients were post-menopausal at the time of diagnosis, while >30% were between the ages of 22 and 54 years.

### Table II. The risk of breast cancer in infertile patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Anovulation</th>
<th>Infertility</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coulam et al. (1983)</td>
<td>Cohort study</td>
<td>1.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1270&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cowan et al. (1981)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Cohort study</td>
<td>2.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1083&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Le et al. (1989)</td>
<td>Case control</td>
<td>0.5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>51&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ron et al. (1987)</td>
<td>Cohort study</td>
<td>1.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2632&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brinton et al. (1989)</td>
<td>Cohort study</td>
<td>0.92&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.94&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2335&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Gammon and Thompson (1990)</td>
<td>Case control</td>
<td>1.26&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4730&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sellers et al. (1992)</td>
<td>Prospective cohort study</td>
<td>I.R.&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>493&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Moseeseon et al. (1993)</td>
<td>Case control</td>
<td>3.5&lt;sup&gt;d&lt;/sup&gt;&lt;sup,g&lt;/sup&gt;</td>
<td>3.5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>354&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Relative risk of breast cancer among the patients in the study.

<sup>b</sup>Number of patients with infertility (see text).

<sup>c</sup>The relative risk of infertility is compared with two different cancer registries' data as external standards of comparison.

<sup>d</sup>The odds ratio of infertility among patients with breast cancer.

<sup>e</sup>Number of patients with breast cancer (see text).

<sup>f</sup>Increased risk.

<sup>g</sup>Recurrent amenorrhoea and not anovulation per se.
Based on all these data it seems that the interrelationship between hormonal conditions, infertility and breast cancer is complex. However, the most recent studies show that women who suffer from infertility are at increased risk of breast cancer. In particular, this holds true for infertile nulligravid patients at their peri- and post-menopausal periods. Obese infertile patients in whom anthropometric measurements show a high W:H ratio, and according to Sellers et al. (1992, 1993) those with a positive family history of breast cancer, have an increased risk of breast cancer. Moreover, patients affected by the triad of obesity, hypertension and diabetes, which is common in PCOS patients, have a three times increased risk of breast cancer (Coulam et al., 1983). In only one study (Gammon and Thompson, 1991) was PCOS shown to have a protective effect on breast cancer risk during the pre-menopausal years, but it is difficult to assess the relevance of this study at present. We suggest that PCOS patients should be monitored carefully with repeated breast examinations. A liberal policy should be taken in their submission for mammography, and whenever a suspicious mass is observed, tissue sampling and pathological examinations are mandatory. Further studies should address the question of the role of PCOS in the development and progression of breast cancer during the pre-menopausal years.

**Ovarian cancer**

Ovarian cancer is the sixth most common malignancy in women. In 1994, 4% of estimated cancer incidence was caused by ovarian cancer. This cancer is the fifth leading cause of death in women (Heintz et al., 1985), and in 1994 it was estimated that 5% of cancer deaths in women were caused by this disease (Boring et al., 1994).

Epithelial tumours comprise 90% of all ovarian cancers. Currently, no single aetiological factor can be incriminated for this group of tumours. Nevertheless, the striking differences among various populations strongly suggest that several risk factors, such as diet and hormones, may play a role in its aetiology. There is growing evidence that the reproductive history, such as an impaired ability to conceive, is associated with an increased risk of ovarian cancer. Several reports have shown that nulligravid women are more at risk of developing ovarian carcinoma than are women who have been pregnant (Franceschi et al., 1982; Cramer et al., 1983; Nasca et al., 1984). Women with ovarian cancer have an increased incidence of nulliparity. In the study of McGowan et al. (1979) of 197 women with ovarian cancer, nulligravid women were 2.45 times more likely to develop ovarian cancer than were women who had been pregnant three or more times. Among women who had been pregnant at least once, the risk was reduced to 1.27 times. The negative association between ovarian cancer and increasing parity is well established for both ovarian cancer (Joly et al., 1974; McGowan et al., 1979; Franceschi et al., 1982; Nasca et al., 1984) and borderline tumours (McGowan et al., 1979; Harlow et al., 1988).

Several studies have evaluated the association between a history of infertility and the risk of ovarian cancer. As Table III shows, most of these studies found a positive association between infertility and malignant ovarian tumours for both ovarian carcinoma and carcinoma of low malignant potential.

### Table III. The risk of ovarian cancer in infertile patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Ovarian cancer</th>
<th>Borderline carcinoma</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Case control</td>
<td>a</td>
<td></td>
<td>400b</td>
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<tr>
<td>McGowan et al. (1979)</td>
<td>Case control</td>
<td>2.45c</td>
<td>2.9c</td>
<td>197b</td>
</tr>
<tr>
<td>Nasca et al. (1984)</td>
<td>Case control</td>
<td>a</td>
<td></td>
<td>403b</td>
</tr>
<tr>
<td>Ron et al. (1987)</td>
<td>Cohort study</td>
<td>2.1d</td>
<td>6.0c</td>
<td>2632a</td>
</tr>
<tr>
<td>Harlow et al. (1988)</td>
<td>Case control</td>
<td></td>
<td></td>
<td>116b</td>
</tr>
<tr>
<td>Brinton et al. (1989)</td>
<td>Cohort study</td>
<td>1.28d</td>
<td></td>
<td>2335a</td>
</tr>
<tr>
<td>Whittemore et al. (1992)b</td>
<td>Case control</td>
<td>2.1c</td>
<td>1.9c</td>
<td>2197b</td>
</tr>
<tr>
<td>Harris et al. (1992)</td>
<td>Case control</td>
<td></td>
<td></td>
<td>327b</td>
</tr>
<tr>
<td>Rossing et al. (1994)</td>
<td>Cohort study</td>
<td>1.8 (infertility)</td>
<td>3.7 (anovulation)</td>
<td>3837b</td>
</tr>
</tbody>
</table>

*a*Increased risk, figures not available.

*b*Number of patients with ovarian cancer (see text).

*c*The odds ratio of infertility among patients with ovarian cancer.

*d*Relative risk of ovarian cancer among the patients in the study.

*e*Number of patients with infertility (see text).
In their group study, Whittemore et al. (1992a,b,c) and Harris et al. (1992) analysed the data from 12 case control studies of ovarian cancer conducted during 1956–1986, representing some 3000 cancer cases and 10 000 controls. They found a 2.1 odds ratio for invasive epithelial ovarian cancer in nulligravid patients with a history of female infertility. For epithelial tumours of low malignant potential, the odds ratio was 1.9 (Harris et al., 1992; Whittemore et al., 1992b). Recently, Rossing et al. (1994) evaluated the potential neoplastic effects of medications used in infertility treatment. In their group of 3837 infertile women, the relative risk of ovarian cancer was 1.9 for the whole group. For patients who did not use ovulation-inducing agents, the relative risk was 1.6. There were substantial differences in the relative risks of ovarian tumours with infertility type. The standardized incidence ratio for ovulating abnormalities was higher than that for non-ovulating abnormalities (3.7 versus 1.8).

Most studies show a link between infertility and ovarian cancer. This holds true especially for former works when ovulation-inducing agents were not used extensively. (The possible role of these agents in the initiation or promotion of epithelial ovarian cancer will be discussed later.) However, today, after more than four decades of extensive infertility evaluation and treatment in thousands of infertility clinics, the time has come to evaluate the net effect of ovulation-inducing agents were not used extensively. (The possible role of these agents in the initiation or promotion of epithelial ovarian cancer will be discussed later.) However, today, after more than four decades of extensive infertility evaluation and treatment in thousands of infertility clinics, the time has come to evaluate the net effect of infertility (separately for each cause of infertility) on the risk of ovarian cancer.

**Other tumours**

The incidence of malignant melanoma is rising sharply. In 1994, the estimated incidence of melanoma of the skin was 3%. More than 40% of melanoma patients were found to be in the pre-menopausal status, and up to 10% of all disease was first discovered during gestation (George et al., 1960; Houghton et al., 1981; Garbe, 1993). Pregnancy has been incriminated in the induction or exacerbation of melanoma. It has been proposed that there may be a hormonal influence on survival from malignant melanoma. Among the reasons given were a more favourable prognosis in females than in males, different courses of disease in the prepubertal period and during menopause, and that pregnancy and oestrogen administration may alter the natural course of the disease (Shaw et al., 1978). However, recent results have contradicted previous data. Pregnancy and oestrogen administration are no longer contra-indicated in melanoma patients because it became apparent that survival rates for pregnant patients were compared with the rates in women without pregnancies.

Epidemiological studies have revealed that the occurrence of malignant melanoma in infertile patients is slightly higher than the expected incidence. When melanoma risk was evaluated in relation to various causes of infertility (Ron et al., 1987; Brinton et al., 1989), the group with hormonal disturbance (‘progesterone deficiency’) had a significantly higher cancer incidence, with a standardized incidence ratio of 2.6 in both studies. However, these data were based on only a small number of patients (four cases in each study). A larger volume of data is mandatory to confirm these observations.

Virilizing adrenal tumours in females during the reproductive years cause infertility. However, hirsutism is the first clinical sign and menstrual disorders are common. Oligomenorrhoea appears first and can be followed by amenorrhoea. Other endocrinopathies, such as Cushing syndrome, cause menstrual disturbances, anovulation and infertility. Epidemiological studies have found a standardized incidence ratio for cancer of the endocrine glands in general (Brinton et al., 1989). The standardized incidence ratios for thyroid cancer were 1.7 and 2.6 in two epidemiological studies (Ron et al., 1987; Brinton et al., 1989).

**Possible mechanisms which link cancer and infertility**

In many infertile patients, hormonal status, anthropometric measurements and growth factors (composition and concentration) are disturbed. Epidemiological, clinical and experimental studies have proved the association between these aberrations and a higher cancer risk.

**Hormones**

**Gonadotrophins**

*Breast cancer:* Several reports about gonadotrophin positivity in the serum or tissue of patients with breast cancer show divergent results. Borkowski et al. (1984) found that in post-menopausal women with breast cancer, the concentration of a human chorionic gonadotrophin (HCG)-like substance was much increased. Ayala et al. (1983) found a high frequency of immunoactive HCG in patients with carcinoma of the breast. The HCG concentrations decreased corresponding to the therapeutic response. Gunasegaram et al. (1985) showed a high immunoreactivity of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and HCG in mammary tumour tissues of human infiltrating breast carcinoma. On the other hand, Wachner et al. (1984) could not demonstrate tissue HCG positivity in >10% of breast cancer patients, and only a few of the malignant cells gave a positive staining. Few studies have addressed the role of gonadotrophin-releasing hormone analogues agonists (GnRHa) in the treatment of
breast cancer patients. GnRHa effects on mammary carcinoma could be mediated by the suppression of gonadotrophins and gonadal steroids, or they may also act directly on tumour cells. Kiesel et al. (1988) showed that in >40% of cases, specific GnRH binding sites were present in breast tumour cells. For this reason, GnRHa therapy was suggested in the treatment of post-menopausal patients with breast cancer. However, such GnRHa treatment in post-menopausal patients with advanced breast carcinoma showed no response (Vici et al., 1991).

Ovarian cancer: Gardner (1961) and Stadel (1975) hypothesized that exposure of the ovarian epithelium to persistently high circulating concentrations of pituitary gonadotrophins increased the likelihood of malignancy. This hypothesis was supported by several animal experiments which confirmed the presence of gonadotrophin receptors in ovarian tumours (McGowan and Davis, 1970; Cramer and Welch, 1983; Shirama and Hokano, 1992). Furthermore, the development of certain animal ovarian tumours depended upon the hypersecretion of gonadotrophins. However, these experimentally induced tumours originated from the stromal cells of the ovary and are either uncommon or non-existent in humans, and their relevance to the epithelial cancers that comprise the majority of human malignancies is unclear (Scott, 1984). The issue as to whether or not ovarian cancer contains LH and FSH receptors is open to considerable debate. Several workers (Kammerman et al., 1981; Rajaniemi et al., 1981) found LH and FSH receptors in epithelial ovarian cancers, although in a low amount. These findings were disputed by Stouffer et al. (1984), who failed to find gonadotrophin receptors in epithelial cancers. In-vitro studies have shown that gonadotrophins stimulate DNA synthesis and proliferation in a number of ovarian cancer cell lines and also significantly increase protein kinase C activity in these tumours (Simon and Holzel, 1979; Simon et al., 1983). Recent experiments have shown the growth-promoting effects of castration (high gonadotrophin concentrations) on hetero-transplanted human ovarian cancer in the nude mouse. On the other hand, inhibition of cancer cell proliferation in the same model was achieved by the suppression of gonadotrophins by GnRH agonists (Pour et al., 1988; Peterson and Zimniski, 1990).

However, FSH receptors are present in human stromal ovarian tumours. The possibility that gonadotrophins may induce stromal ovarian tumours was further supported by a clinical study and animal models. The case study by Willemsen et al. (1993) showed an increased incidence of granulosa cell tumours in patients exposed to high concentrations of gonadotrophins. The study presented 12 infertile patients in whom a granulosa cell tumour was diagnosed. These infertile patients were treated with either human menopausal gonadotrophin (HMG) or clomiphene citrate, which resulted in increased serum gonadotrophin concentrations. The frequency of granulosa cell tumours in the infertile population that underwent ovulation induction treatment in the study of Willemsen et al. (1993) was much higher than that in the general population (0.05–1.70 per 100 000 women). Nevertheless, these data do not prove the existence of a causal relationship between iatrogenic raised serum gonadotrophin concentrations and the development of granulosa cell tumours (other explanations are possible, e.g. tumour presence before infertility treatment initiation or the onset of the tumour during infertility treatment was coincidental). Animal models and in-vitro studies of human ovarian cancer cell lines have shown the direct influence of gonadotrophin concentrations on stromal ovarian cancer. All these data suggested that, indeed, gonadotrophin administration can alter the natural course of this disease. Because these tumours are rare, an effort should be made to collect data in such cases so as to correctly assess the influence of gonadotrophin administration on these tumours. As for epithelial ovarian cancer, there are contradictory findings that have to be taken into account. First, does epithelial ovarian cancer contain receptors for gonadotrophins and, if so, what is the influence of gonadotrophin suppression on the natural course of the disease? Both the influence of gonadotrophin suppression on tumour progression by GnRHa and the role of gonadotrophin administration on ovarian cancer incidence should be investigated further. In a recent multicentre study (called ‘Decapeptyl Depo in the Treatment of Ovarian Cancer’) conducted in Europe and Israel, the therapeutic value of GnRHs in ovarian cancer patients was evaluated. In addition to receiving conventional treatment, patients were treated with either GnRHs or a placebo. However, the study results after the treatment of >300 patients could not demonstrate a beneficial effect of GnRH administration compared with placebo with regard to survival rates or chemotherapy administration (personal communication). According to Rossing et al. (1994), the highest relative risk of ovarian tumours associated with ovulatory abnormalities was in PCOS patients. Although these data were based on a small number of patients, it is tempting to relate this additional risk to the disturbed gonadotrophin concentrations and ratios which exist in many PCOS patients.

Oestrogens and progestins

Breast cancer: Epidemiological and experimental evidence elucidates the role of sex hormones in breast malignancy. In the regulation of breast tissue growth and functional activity, oestrogens and progestins are major
determinants. With the onset of puberty and sex steroid hormone production, ductal epithelium in the breast proliferates and mitotic activity is prominent. Early pregnancy is associated with the extensive proliferation of ductal, lobular and alveolar tissue under the stimulus of high concentrations of oestrogen and progesterone. These hormones act upon stem cell differentiation in the terminal ducts and lobules (Kampert et al., 1988). Oestrogen and progesterone receptor formation are influenced by oestrogen and progesterone concentrations. Oestrogen induces both oestrogen and progesterone receptors, while progesterone down-regulates this receptor formation. A higher oestrogen receptor content was observed in obese than in non-obese women (Markopoulous et al., 1988). However, progestins did not oppose the effects of oestrogen on breast epithelium. Oestrogen binding to its receptor results in an oestrogen receptor complex which stimulates the transcriptional activity by binding with specific sites on the DNA molecule (Gronemeyer et al., 1988).

In cell lines, oestrogen has been shown to have a variety of actions, specifically to increase concentrations of transforming growth factor (TGF) and insulin-like growth factor-1 (IGF-1) (Barrett-Lee, 1991).

The beneficial effect of removing the primary source of oestrogen and progesterone production by surgical oophorectomy on the risk of breast cancer has been known for several decades (Lilienfeld, 1956). Obesity increases the risk of breast cancer in post-menopausal women, an effect which is thought to be mediated by increased oestrogen stimulation of the breast. Adipose tissue is a major site of aromatization of androgens to oestrogens in post-menopausal women (Cauley et al., 1989). However, there is no correlation between serum oestrogen concentrations and oestrogen content within the breast tumour tissue (Mehta et al., 1987). Body mass index (measured at age 18 years) was negatively associated with the relative risk of breast cancer (Sellers et al., 1992). On the other hand, the oestrogen and progesterone receptor content is significantly higher in tumour tissue than in normal breast tissue (Ricketts et al., 1991). Oestrogen stimulates DNA synthesis and increases mitotic activity in the breast epithelium, and thus may accelerate the growth of oestrogen-dependent breast cancer. In-vitro studies have shown that oestrogens stimulate the proliferation of breast cancer cell lines and enhance the mRNA transcriptional activity of oestrogen receptor, epidermal growth factor (EGF) and IGF-1 receptor genes (Dotzlaw et al., 1990; Stewart et al., 1990). An imbalance in ovarian oestrogen and progesterone production in anovulating patients, and an increased peripheral conversion of androgens to oestrogens in obese patients, alter oestrogen and progesterin concentrations and may increase the risk of breast cancer (as shown by several epidemiological studies). Follicular stimulation by the administration of ovulation-inducing drugs to infertile patients is associated with an exposure to excessive oestrogen and progesterone concentrations which may also alter the risk of breast cancer.

Endometrial cancer: As early as 1947, clinical and morphological evidence forced the conclusion that the prolonged stimulation of the uterus by oestrogen without progestational modification was an endometrial cancer precursor (Gusberg, 1947). Long-term exposure to oestrogen should always be regarded as causing an increased cancer risk. An increased incidence of endometrial carcinoma has been reported in anovulatory women. In patients with PCOS, endometrial cancer has been reported to occur in up to 25% of patients as the endometrium is exposed to anopposed oestrogen (Sommers et al., 1949; DiSaia and Creasman, 1989), although in actuality this number is considerably smaller. Oestrogen and progesterone receptors have been found in endometrial carcinoma cells. Oestrogen increases the concentration of both oestrogen and progesterone receptors, while progesterone down-regulates the level of both receptors (McCarty et al., 1983). Although the mitogenic action of oestrogen is well known, the mechanism of action is still unresolved. There is no direct evidence that natural oestrogens are carcinogenic in humans. Gusberg (1994) has pointed out a gap in our knowledge of the critical phase of the hormone-tumour relationship. Although the proliferative activity of oestrogen and its action as a tumour promoter have been demonstrated, the evidence that oestrogen can immortalize cells is still elusive. Moreover, a group of endometrial cancers which are highly virulent and lethal are autonomous, non-hormone-related tumours. Recent cellular and molecular oncological evidence has revealed that oestrogens act by genetic mechanisms on cancer cells, and a close relationship between oestrogens, growth factors and oncogenes is important for human cancer (Lupulescu, 1993). Oncogenes, such as c-myc, c-neu and erb-b, express proteins that ultimately act in transformation. It is suggested that oestrogen induces growth factors, such as EGF, which in turn activate phosphorylation, protein reactions and transduction. However, this scientific field is beyond the scope of this paper and should be investigated thoroughly in the coming years.

Androgens

In post-menopausal women and in many anovulatory PCOS patients, androgens, chiefly androstenedione, are the main sources of oestrogens (Grodin et al., 1973). In obese patients and especially in those with high W:H ratios,
sex hormone-binding globulin concentrations are low (Kaye et al., 1991), thus increasing the free androgen concentrations. Obesity accelerates the peripheral conversion of androgens to oestrogens, and anopposed oestrogens contribute to increased endometrial and breast cancer risk, as described previously. As for breast cancer, increased testosterone secretion by the ovaries is a major steroid abnormality shown to be associated with an increased risk of both pre- and post-menopausal breast cancer (Secreto et al., 1989, 1991; Gordon et al., 1990). A pattern of high W:H ratio which represents the hyperandrogenic state is also associated with an increased risk of breast cancer (Kelsey and Berkowitz, 1988; Schapira et al., 1990). A relationship between these factors and familial breast cancer has been proposed previously (Sellers et al., 1993). Androgens can directly increase the risk of cancer by increasing the proliferation of cells after binding to androgen receptors (Bryan et al., 1984). One hypothesis that has been offered claims that the hormonal promotion of mammary carcinogenesis is likely to be greatest between puberty and the first full-term pregnancy. The presence of hyperinsulinaemia can increase the ovarian production of androgens, and the abnormal hormonal profile may stimulate proliferative activity in mammary epithelium, which in turn increases the risk of epithelial atypia and carcinogenesis (Stall and Secreto, 1992). Hyperandrogenaemia at puberty and during the reproductive years interferes with the normal ovulatory cycle and may cause infertility as well. However, another possibility is that hyperinsulinaemia and IGF cause both hyperandrogenaemia during the reproductive years and an increased risk of breast cancer in pre- and post-menopausal women.

**Growth factors**

Recently, the subject of growth factors has gained much attention. Adipose tissue and stromal ovarian cells following hormonal triggering synthesize a substantial amount of growth factors such as IGF-1, TGF and tumour necrosis factor. Ovarian homeostasis is mediated not only by gonadotrophins and steroid hormones, but also by several growth factors. Moreover, in certain types of anovulation, as in obese PCOS patients, IGF concentrations are elevated (high W:H ratio is also common in these patients; Conover et al., 1992). Growth factors can stimulate tumorigenesis and tumour progression. IGF-1 has been detected in a variety of in-vivo and in-vitro experimental systems. In mice, growth factors have malignant transforming potential (Besmer et al., 1983; Robbins et al., 1983). IGF-1 bioactivity in neoplastic tissue is determined by several factors, including the circulatory IGF-1 concentration, the local IGF-1 gene expression and the local and systemic concentrations of IGF binding proteins. Growth factors also increase the degree of cellular autonomy and can be chemotactic to blood vessels (Yee et al., 1989; Aaronson, 1991; Cross and Dexter, 1991). Receptors for IGF-1 are expressed in breast tumour cells, while IGF-1 promotes the proliferation of breast cancer cell lines. For these cells, its mitogenic activity is more potent than that of oestradiol. Tamoxifen, a commonly used anti-oestrogen anti-neoplastic agent, significantly suppresses IGF-1 gene expression and serum IGF-1 concentrations (Pollak et al., 1992).

In the uterus, the local expression of the IGF-1 gene is stimulated by oestrogens, and the positive trophic effect of oestradiol on this organ is thought to be mediated at least in part by IGF-1 (Murphy and Ghahary, 1990). In recent years, the role of growth factors in the ovulatory process in general and in infertility in particular has been investigated enthusiastically, as has the role of growth factors in tumorigenesis. In the future, such efforts should be aimed at the mutual interactions between the roles of these growth factors.

**Genes and protein products**

Numerous oncogenes, tumour suppressor genes (such as P-53) and their expression products have been demonstrated in tumour tissues and cell lines. Genomic alterations, such as amplification, point mutation and deletions, are associated with cancer. Endogenous and exogenous hormone administration have an influence on oncogenes, as demonstrated by Olsson et al. (1991) who showed that the oncogene HER-2/neu amplification in malignant breast tumours was related to reproductive factors and exposure to oral contraceptives. Comprehensive studies on the inter-relationships between protein and steroid hormones, growth factors and DNA alterations are needed in the near future.

**Superovulation theory**

Another hypothesis that may link infertility, infertility treatment and superovulation with ovarian tumorigenesis was presented by Fathalla in 1971. This hypothesis suggested that ovarian carcinogenesis results from mechanical trauma or mitotic activity in the ovarian epithelium as a consequence of ovulation. Therefore, increasing ovulation by ovulation induction medication will increase the frequency of ovarian tumour, while any factor which suppresses ovulation, such as pregnancy, oral contraception, the longer duration of lactation and an early menopause, will reduce the risk of cancer. This theory on the pathogenesis of epithelial ovarian cancer is commonly used to explain the association, demonstrated recently, between ovarian cancer and superovulation with fertility drugs.
Fertility medication recruits many oocytes which simultaneously mature and ovulate during one cycle. This in turn increases the mechanical trauma and increases the number of epithelial inclusions in the surface epithelium of the ovary. However, some epidemiological data and comments contradict such a link (Scott, 1984; Ron et al., 1987; Booth et al., 1989; Brinton et al., 1989; Whittemore et al., 1992b; Rossing et al., 1994). The risk of ovarian cancer in these studies was increased in women with ovulatory disturbances (either anovulation or oligo-ovulation), while, according to the ‘incessant ovulation’ theory, these women would have been expected to have a reduced risk of ovarian cancer.

Another hypothesis frequently suggested is that an undiagnosed early ovarian cancer causes, in some manner, infertility. This hypothesis was based upon the epidemiological data which showed an increased rate of infertility in patients with ovarian cancer (Harlow et al., 1988; Harris et al., 1992). Few large studies have focused on this issue. In their study, Ronford and Steele, 1982; Ben-Hur et al., 1986; Carter and Joyce, 1987; Goldberg and Runowicz, 1992). Few large studies have focused on this issue. In their study, Ron et al. (1987) did not demonstrate an association between ovulation-inducing drugs (clomiphene citrate, HMG, HCG) and cancer.

As for breast cancer, Brzéinski et al. (1994) reported 16 new cases of breast cancer from among 950 patients who had been treated previously with ovulation-inducing agents. The subjects were relatively young (mean age 40 years) at the time of diagnosis of their breast tumours. Of the 16 cases, 13 cancers tested positive for oestrogen receptors. All these patients were subjected to potent follicular stimulation for a prolonged period of time. Recently, a case was reported of the early onset of familial cancer (aged 41 years) after the fourth cycle of ovulation induction and in-vitro fertilization (Arbour et al., 1994). It has been proposed that hormonal stimulation may increase the rate of progression of existing lesions in hereditary breast cancer syndromes. Did hormonal fertility treatments per se with excessive and prolonged oestrogen and progesterone stimulation increase the risk of breast cancer in infertile patients, particularly in those with familial breast cancer syndromes? As reported previously, it should be emphasized that many of these nulliparous infertile patients are already at a high risk of contracting breast cancer. Until now there has been no published scientific study to answer this question.

Whittemore et al. (1992a,b,c) and Harris et al. (1992) caused much concern with their finding that infertile nulligravid women had a 2.1 odds ratio for epithelial ovarian cancer. These conclusions were based on only three of their 12 studies and presented only 20 cancer cases. For nulligravid women with a history of infertility who used fertility drugs, the odds ratio (based on only 12 cancer cases) was 27.0 (although the initial study design was of 12 case control studies and 2197 ovarian cancer patients). The odds ratio for fertility drugs on borderline tumours was 4.0, but these data were also based on small numbers — only four cases (the study of women with ovarian cancer of low malignant potential was based initially on 327 tumours). The data presented by Whittemore et al. (1992a,b,c) have prompted world-wide concern, and in the last 2 years much attention has been focused on this subject. Articles and letters, such as those of Cohen et al. (1993), Spirats et al. (1993) and Darder (1993), have analysed and debated the results of Whittemore et al. (1992a,b,c). Recently, Whittemore (1994) pointed out several obstacles in interpreting her findings: (i) only a few of the women in her study used fertility medications, and hence the estimates of risk were imprecise; (ii) there was inadequate information on the reason for infertility; (iii) no information was available about the type of medication or the duration of treatment; and (iv) patients with ovarian cancer are more apt to recall bias than the controls. Based on her own study, Whittemore (1994) concluded that the existence of a causal link between fertility medications and ovarian cancer remains an open question.

Recently, Shushan et al. (1996) performed a case control study of patients with ovarian cancer and matched controls to determine whether women with epithelial ovarian cancer were more likely to have been exposed to fertility drugs than the healthy population. They found that the risk of ovarian cancer was increased in women who had used HMG (odds ratio 1.97, 95% confidence interval 1.03–3.77), and the risk was particularly increased in the

**Induction of ovulation**

Follicular stimulation in the treatment of infertility exposes patients and their ovaries to high concentrations of gonadotrophins and sex steroids. In addition, the ovaries are induced to superovulate in each treatment cycle. Does infertility treatment raise the risk of cancer? In the last few years much attention has been focused on this issue mainly for two reasons. The first is the increased use of ovulation-inducing medications. In the past decade, millions of women have reported previous exposure to fertility drugs, and the number of exposures is growing continuously. Second, several case reports of women undergoing infertility treatment have focused on the potential carcinogenic effects of these preparations, especially in terms of malignant epithelial ovarian tumours (Atlas and Mencer, 1982; Bamford and Steele, 1982; Ben-Hur et al., 1986; Carter and Joyce, 1987; Goldberg and Runowicz, 1992). Few large studies have focused on this issue. In their study, Ron et al. (1987) did not demonstrate an association between ovulation-inducing drugs (clomiphene citrate, HMG, HCG) and cancer.
subgroup of women with borderline ovarian tumours who had used HMG (odds ratio 14.58, 95% confidence interval 3.82–55.91).

Willemsen et al. (1993), who described 12 patients in whom a granulosa cell tumour was discovered after ovarian stimulation treatment with clomiphene citrate and/or gonadotrophins, showed that the prevalence of a granulosa cell tumour in this population was 0.23%, much higher than the incidence of that tumour in the female population as a whole. Although these data did not prove the existence of a causal relationship between ovulation induction treatments and the development of granulosa cell tumours, the possibility of such an association exists and the authors recommend further wide-ranging investigations by registered authorities.

Based on all these data, it can be concluded that to determine whether treatment with ovulation-inducing drugs raises the risk of cancer, we must first discover to what degree there is a risk of cancer development in the various subgroups of infertile patients, particularly among women suffering from anovulation. Balasch and Barri (1993), who critically reviewed the literature concerning follicular stimulation and ovarian cancer, concluded that even if an association between ovulation induction and ovarian cancer was found, it would not necessarily indicate an effect of ovarian stimulation. A more likely explanation is that an underlying ovulatory disorder or the absence of pregnancy predisposes the woman to cancer of the ovary. There is still insufficient data on these groups. Only when such data have been gathered for each group separately can we then determine whether ovulation-inducing drugs raise the risk of cancer.

Such data were published recently by Rossing et al. (1994). They examined the risk of ovarian tumours in infertile women. In this study, 3837 infertile women were evaluated. Data concerning infertility causes, treatment duration and drugs were available. Out of 11 malignant ovarian tumours diagnosed, nine of the women had taken clomiphene citrate. The adjusted relative risk was 2.3, whereas in the women who used the drug for ≥12 months the adjusted relative risk was 11.1. In the presence of ovulatory abnormalities, the adjusted relative risk of clomiphene citrate was reduced from 11.1 to 7.7. They concluded that the risk of ovarian tumours associated with the long-term use of clomiphene citrate was increased. Patients with ovulatory abnormalities had a higher cancer risk than the rest of the infertile patients, but both women with ovulatory abnormalities and those with no known ovulatory abnormalities had an increased risk of cancer. These results suggest that the increased risk associated with the use of clomiphene citrate is not merely a reflection of the presence of ovarian abnormalities that are the indication for treatment with this drug, but rather that the prolonged use of clomiphene citrate per se may increase the risk of ovarian tumours.

Cancer is a multifactorial disease. Genetic and environmental factors are important, as are cellular correcting mechanisms (such as P-53). The female reproductive system, as other tissues, is continually exposed to hormones, growth factors and different metabolites during a woman’s lifetime. As laboratory and clinical studies have shown, the imbalanced secretion of these hormones and growth factors can induce tumorigenesis. The hypersecretion of growth factors and the imbalanced secretion of hormones are also common in women with anovulation, especially those with polycystic ovaries. However, women who do not conceive due to male factor infertility have a normal hormonal milieu. Infertile women should not be lumped together as one group. According to the data presented here, investigators and clinicians need to distinguish between infertility subpopulations prior to conducting epidemiological studies and monitoring their patients.

The question of causal relationships between infertility drugs and cancer can be answered only after we conclude what are the cancer risks among the different groups of infertile patients. This review clearly shows that despite the fact that there is a trend that shows that anovulation and polycystic ovaries predispose to gynaecological cancers, there are insufficient data on these populations. Only after such data become available will we be able to evaluate the risk of infertility medications. These data are important not only for the management and follow-up of our patients in the infertility clinic, but also in the diagnosis of those who are at increased cancer risk so that we can find the proper way to monitor this population.

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