OVARIAN CANCER AND REPRODUCTION

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SUMMARY

Ovarian cancer is one of the most common malignancies to affect women, and is the fifth leading cause of female cancer deaths. The risk of ovarian cancer is altered by a number of factors relevant to fertility and reproductive health. The recent puplication by Whittemore et al suggested that relative risk of ovarian cancer was increased in infertile women who had used fertility drugs. Although a causal relationship between fertility drugs and ovarian cancer could not be excluded, it clearly has not been demonstrated at the present time.

INTRODUCTION

Ovarian cancer, which occurs in 1.4% of the general population is one of the most common malignancies to affect women. More than 21000 cases are diagnosed and about 13000 deaths occur annually in the USA. Among all gynecologic malignancies it is the most fatal, having a five year survival rate of about 40%. This neoplasm is the fifth leading cause of female cancer deaths (1). Despite improvements in imaging techniques, the development of sensitive biochemical markers and more aggressive surgical and chemotherapeutic treatment modalities, long term survival rates are poor.

Epidemiology of Ovarian Cancer

Familial factors:

Among the variety of factors that have been linked to an increased frequency of ovarian cancer, a positive family history may be the most significant. Although the overall lifetime probability of developing ovarian cancer is 1.4%, it is 5% among women who have one relative with this type of malignancy, and it is up to 9% if two relatives are afflicted. It is estimated that between 5 and 10% of ovarian cancer cases are familial with two or more first or second degree relatives having ovarian cancer also (2). This familial pattern suggests an autosomal dominant type of inheritance. Familial ovarian cancer has important characteristics that distinguish it from ovarian cancer of sporadic occurrence: the onset is earlier (47.7 years vs 59 years), it is a preponderance of serous cancers, it is bilateral and it has more poorly differentiated adenocarcinomas.

Although identification of an individual at risk for familial versus sporadic ovarian cancer is not yet possible, interest has focused upon the 17 q chromosome (2). Identification of individuals at risk for familial ovarian cancer might lead to prophylactic measures to reduce risk including oophorectomy at the conclusion of child bearing (3). However, abdominal carcinomatosis histologically indistinguishable from ovarian cancer has been reported many years after removal of normal ovaries (4).

Environmental Factors:

Because the incidence of ovarian cancer in highly developed countries is two to four times greater than in developing countries, environmental factors have been suggested as having an etiologic role in the genesis of ovarian cancer (5). This hypothesis is supported by the increased risk of ovarian cancer among certain groups after emigration from lesser to more highly developed countries. Most of the focus of possible environmental factors has centered upon high intake of animal fat and high intake of caffeine. (6, 7) Galactose has also been incriminated in the genesis of ovarian cancer (8). However, no supporting data are available as yet to incriminate these or other dietary additions of deletions.

Both talcum powder and asbestos have also been suggested as carcinogens (9,10). Evidence also includes documentation that transport of particles from the perineum to the peritoneal cavity is possible and that particles similar to talc have been found in the ovaries of women with ovarian cancer. Mumps infection has also been linked to ovarian cancer perhaps because of a primary mumps oophoritis or because of a primary immunodeficiency that hinders a response to the virus and permits carcinogenesis (11).

Reproductive Factors:

The number of pregnancies, number of abortions, duration of breast feeding, infertility, and age of menopause have all been associated with changes in the risk of ovarian cancer (12).

Many studies have demonstrated a protective effect of pregnancy, even those that do not progress to term, against the development of ovarian cancer (13). Depending upon the number of pregnancies, nulligravidas have been shown to have between 1.3 and 2.5 times the risk of those who have conceived before (14). Breast feeding has also been shown to afford some protection against the development of

ovarian cancer. Similarly the data correlating risk with age of menopause are conflicting and no trends have been demonstrated with age of menarch. The most striking evidence of a protective benefit is from the use of oral contraceptives. Estimates of a protective effect range between 20% and 70%. In many studies, increased duration of use is associated with an increased benefit (15, 16). Because the frequency of ovarian cancer rises dramatically with the onset of menopause and because levels of FSH and LH increase markedly after menopause, investigators have questioned whether or not gonadotropin levels contribute to the development of ovarian cancer (17,18).

Many authors have demonstrated that infertility is a risk factor for the development of ovarian cancer independent of nulliparity (19). These data might be explained by the presence of a single abnormal ovarian factor causing both infertility and ovarian cancer. The risk of ovarian cancer among infertile women has been judged to be between 1.8 and 6.5 times that of parous and nulliparous controls (19).

Biology of Ovarian Cancer:

The normal epithelium consists of a single layer of cells that vary in configuration being squamous, cuboidal and low columnar. Prior to ovulation, these cells produce lysosomal bodies that migrate to their basal regions. It is believed that enzymes from these lysosomes affect the tunica albuginea to cause follicular rupture. The resulting injury to the ovarian surface is healed by the rapid growth of epithelial cells. Frequently this healing process results in the development of surface epithelium inclusion cysts. These cysts develop because the rapidly proliferating epithelial cells are either trapped below the surface or because they directly invade the surface layer. Ovarian epithelial cancers are beleived to begin with these inclusion cysts (20,21).

The interactions of hormones and various growth factors to induce malignant transformation are unclear. With greater mitotic activity the risk of mutation, which would stimulate an oncogene or inactivate an antioncogene, increases. Receptors for epidermal growth factors that have been shown to be mitogenic in ovarian surface epithelial cells have been found in both normal and malignant human ovarian surface epithelium (22, 23). Other growth factors such as IGF 1, IGF 2 have also been detected in human follicular fluid and appear to act synergistically with FSH to facilitate aromatase activity during the follicular phase (24). Growth hormone (GH) may also play a regulatory role. In some studies, serum GH levels have been shown to rise in a fashion parallel to estradiol levels during superovulation (25). In other studies supplemention with GH has reduced the gonadotropin requirements for ovulation induction (25). The rates of neoplasia have been demonstrated to be increased markedly in both men and women with acromegaly (26). Although the most significant increase is in the incidence of GI neoplasms, ovarian cancers are also increased in frequency (26).

Incessant ovulation as a casue of ovarian carcinoma was proposed originally by Fathalla (27). The greater the risk of malignancy in never pregnant women, the greater frequency of ovarian inclusion cysts in those with repetitive ovulation and those with cancer, and the greater exposure of the surface epithelium to mitogens among those who ovulate repetitively all suggest a link. The protection against ovarian cancer afforded by tubal ligation is confusing because these women would have more ovulatory activity. Although some reports have suggested that luteal phase defects and other types of ovulatory dysfunction occur after tubal sterilization, large controlled studies show no such association (28). Perhaps tubal sterilization isolates the ovary from a carcinogen that ascends from the lower genital tract.

With this background, the question of "fertility drug" treatment can be addressed. Agents that may be classified as such, include clomiphene citrate, human menopausal gonadotropins and bromocriptine.

The recent publication by Whittemore et al (29) addressed the possible relation of fertiliy drugs and ovarian cancer. These authors interpret their findings to show that any increased risk of ovarian cancer associated with infertility may be due to use of fertility drugs.

Whittemore et al identified 12 case control studies of ovarian cancer performed between 1956 and 1986. Detailed information on fertility was obtained in only 3 of the 12 studies. They found that relative risk of ovarian cancer was increased in infertile women. Women with an ovulatory disturbance had a relative risk of 2.1. The relative risk in women who had used fertility drugs had a relative risk of 4.0 for borderline tumors.

Although Whittemore et al seem to have demonstrated an association between fertility drugs and ovarian cancer, there are several possible biases in the data that cause concern.

Because fertility drugs were more strongly related to borderline tumors, it is possible that diagnostic bias may explain some of the findings.

The findings by Whittemore et al (29) also may be biased because of inability to control for key confounding variables. Because only small number of patients were available for studying fertility drugs, the authors were not able to control for tubal ligation, hysterectomy, or a family history of ovarian cancer nor for other factors known to affect ovarian cancer risk.

Whittemore et al (29) provided no information on the age of the patients, diagnosis or time of drug administration in those patients taking fertility drugs. Such data would have made it possible to evaluate whether the findings were plausible in relation to latency, receny or dose response which are all important concepts in cancer epidemiology. Whittemore et al did not place sufficient emphasis on

the link between infertility per se and ovarian cancer. Previous studies have shown that infertile nulliparous women have between 2.8 and 6.5 times the risk of ovarian cancer compared with nulliparous women whose infertility has not been tested.

Whittemore et al again demonstrated that women with ovulatory abnormalities had an increased risk for the development of ovarian cancer. These are the population of women for whom infertility drugs would be prescribed. The only evidence the authors proposed to support that fertility treatment is implicated rather than the underlying ovarian disorder is that there is a higher risk associated with those diagnosed as infertile after 1970 compared with those diagnosed between 1961 and 1970. They suggest that this is beause fertility drugs were introduced into the USA in the 1960 s. The three studies in question, involved women with an average age of 53 years who had cancer diagnosed between 1977 and 1981. If we assume that they were treated with infertility drugs between the ages of 30 and 40, this meas that they were treated between 1954 and 1967. However, clomiphene citrate was registered in 1967, hMG in 1969, and bromocriptine in 1978. It is therefore logical to question how many of the patients in these studies were exposed to the 3 fertility drugs that were cited by Whittemore et al.

In summary, although a causal relationship between fertility drugs and ovarian cancer could not be excluded, it clearly has not been demonstrated at the present time. The International Federation of Fertility Society (IFFS) organized a task force representing clinical and epidemiological expertise. The IFFS task force proposes the following recommendations.

To request Whittemore et al, make available or publish the list of patients and controls who were exposed to fertility drugs, stating their epidemiological characteristics and giving as much clinical and drug information as is available. To evaulate whether a risk of ovarian cancer associated with the use of fertility drugs exists. Accurate and precise studies are needed.

To continue to reassure patients who received drug treatment for their infertility. Even if the results by Whittemore et al were to be confirmed by further studies, women who choose to use such drugs will be exposed to an annual added risk of <1 in 5000. Furthermore, this limited risk should be balanced against the benefit of achieving a birth.

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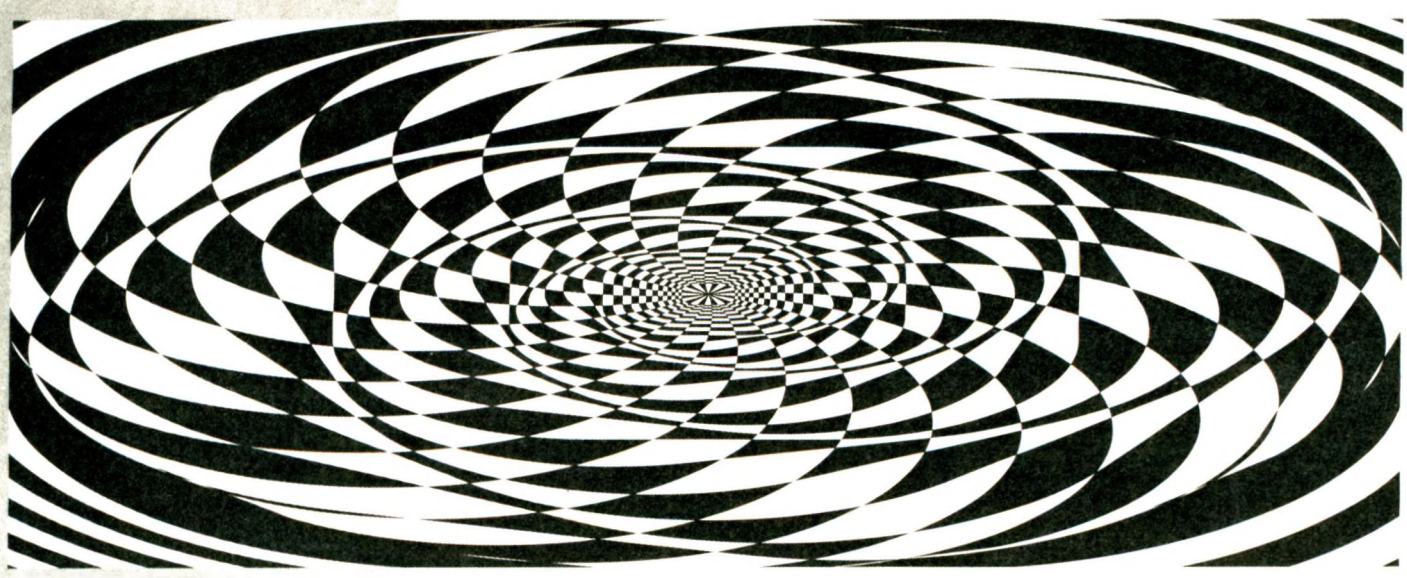

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